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PLASTICS IN MEDICAL DEVICES FOR CARDIOVASCULAR APPLICATIONS

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This work is dedicated to my family

About the Author

Ajay Padsalgikar graduated with a degree in Polymer Engineering from the University of Poona, India in 1990. He then completed a PhD from Clemson University, SC, USA in 1996. In his PhD, he worked on the microrheology of polymer blends and their resultant structure formation in the process of fiber spinning. His first work assignment after his education was at the Research & Technology Center in Everberg, Belgium at ICI Polyurethanes.

At ICI, Ajay worked mainly on the processing of polyurethanes, thermoplastic, as well as thermoset. In 1999, ICI Polyurethanes became Huntsman Polyurethanes. His work continued in the field of processing of polyurethanes but became more focused on computer modeling and simulation of the different processes including polyurethane synthesis.

In the middle of 2002, Ajay joined AorTech Biomaterials in Scotland from where he was transferred to Australia in late 2002. He served as the Chief Scientific Officer of the company and various projects that he was involved with included polyurethane bulk and solution synthesis, chemical engineering of the synthesis of raw materials for polyurethanes, processing of polyurethanes for medical devices. He was involved with various applications of medical devices and requirements of polymer properties in the particular application.

Ajay joined St Jude Medical in December 2012 as a Senior Principal Scientist and has been involved with material development, application, and characterization in the cardiac space. St Jude Medical was acquired by Abbott in January 2017.

Ajay is active with the Society of Plastics Engineers (SPE) at the national level with the Medical Plastics Division and at the local level in the Mid West regional section. He has more than 30 published scientific papers and 10 patents.

Preface

The rapidly increasing use of medical technology has resulted in the early diagnoses of various disease states. The advancement of medical science has allowed efficient treatment of various diseases which at one point of time were thought either difficult to treat or incurable. This advancement of medical science and technology is to a large extent the result of the development of newer medical devices that depend directly on plastics. The area of cardiovascular health and the treatment of cardiovascular diseases have shown tremendous advancement in the past few decades. There have been numerous books and texts written on the different aspects of both these topics; the science and technology of the cardiovascular system and plastics. This text attempts to bring these two diverse topics together.

This book is organized into three sections: Parts I, II and III. Part I comprises four chapters and deals with plastic materials that are found in cardiovascular devices. Chapter 1 in this section serves as an introduction to the nature and properties of plastic or polymeric materials. This introductory chapter summarizes many of the basic concepts of plastics; the application of this basic knowledge can be further expanded depending on the specific application. Chapters 2 and 3 in Part I deal with the specific kinds of plastics used in cardiovascular devices. A distinction here is made between device components made from materials available on a large scale or commodity plastics versus device components made from material formulations developed with greater emphasis toward medical applications or specialty polymers. Part I ends with Chapter 4, a chapter that deals with the biological properties of plastics and specifically answers the question as to what makes the plastic suitable for use in medical applications.

Part II deals specifically with the cardiovascular system of the human body and can be described as an introductory text on the cardiovascular system for nonmedical personnel. Part II goes on to describe the main diseases affecting the cardiovascular system and the diagnosis and treatment of these diseases with medical devices.

Part III brings plastics together with the cardiovascular space and talks about the applications of plastics in the medical devices used to diagnose and treat cardiovascular diseases. This section attempts to catalog different devices that are currently used or have been tried in the past with the kind of plastics that are part of the device.

In the preparation of this manuscript, discussions with several people over the years have enabled my greater exposure to new fields of knowledge and understanding. I am especially grateful to my current employer Abbott, formerly St. Jude Medical, my manager Dr. Chris Jenney and colleagues at the Materials Technology team and the Rogers, Minnesota site. My former colleagues at AorTech Biomaterials and Huntsman Polyurethanes have played a significant role in the development of my knowledge base. A couple of my teachers deserve special mention for sparking my interest in polymers, Dr. Rajeev Basargekar during my undergraduate years and my PhD advisor, Dr. Michael Ellison. I am indebted to Dr. Shekhar Hegde, Dr. Swati Dambal, Dr. Amar Mavinkurve, and Charles Christianson in thoroughly reviewing different parts of manuscript.

My family has been a great source of inspiration and support during the course of my entire life. I would like to acknowledge the role of my family members, my parents Devidas and Rekha, my parents-in-law Sharashchandra and Vandana, and my brother and sister-in-law, Dattatray and Aditee. Very special thanks go to my wife, Aparna, for her vast patience and faith in my abilities and my children Rutika and Rohan for their love and support.

PART I: PLASTICS MATERIALS IN MEDICAL DEVICES

1 Introduction to Plastics

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1 Introduction

The term plastic comes from the Greek word "plasticos," meaning capable of being molded or shaped. This property refers to the ability of these materials to be formed into a variety of shapes. Another commonly used term for plastics is polymers. Polymer is also derived from the Greek language where "poly" is many and "mer" is a unit or part. Therefore a material that can be shaped in various forms and is composed of a long chain of many repeating units is defined as a plastic.

All plastics are polymers and that term is used interchangeably in this text.

Polymers can be naturally occurring or synthetically manufactured. Naturally occurring polymers are biological materials within the human body, such as various proteins, the nucleic acids (DNA and RNA), hair, nails, etc. or within the plant and animal systems [1]. Cotton, rubber, starch, and silk are commercially used polymers with a natural source. Plastics usually refer to all man-made polymers that primarily use petroleum-based hydrocarbons as the raw materials.

The first commercial example of a synthetically manufactured plastic is that of phenol formaldehyde. It was developed by Belgian-born chemist Leo Baekeland in the early 1900s and known as Bakelite. Bakelite is a thermosetting plastic and the first commercially manufactured thermoplastic polymer followed 20–30 years later with companies such as BASF in Germany and ICI in the UK pioneering the introduction of polystyrene (PS) and polyethylene (PE), respectively [2,3].

Plastics can be manufactured with a range of properties and their ability to be shaped into a variety of forms has meant that plastic usage has soared in the last hundred years. The overall plastics production is over 200 million tons/year with a worldwide market of greater than $500 billion [4]. Mechanical, thermal, electrical, and chemical properties of plastics combined with their low density have created numerous new applications over the years. In medical applications, the mechanical properties have contributed to the durability of the medical device whereas the chemical properties ensure appropriate interaction with the biological environment. The contribution of plastics within the medical devices sector is relatively small and is said to be close to $3 billion [5]. However, with an increasingly aging population, greater government involvement and newer emerging markets there is expected to be strong growth in the general area of medical devices and the use of plastics within that sector.

The role of the nature and properties of plastics in the correct functioning of a medical device is critical. Very often the selection of the plastic can dictate the efficacy of the device and the treatment of the disease. There is a strong need for the amalgamation of plastics professionals, polymer scientists, and medical device design experts to exploit the full potential of plastics and facilitate effective treatment of medical conditions.

This chapter is an introduction to plastics; many of the aspects of plastics with respect to their usage in cardiovascular devices are covered in subsequent chapters. For details on the sections in this chapter, the reader is referred to many references in the following pages.

2 Chemistry

Polymers are long chain compounds composed mainly of organic chains, there are a few exceptions with the only one of relevance being the polymer formed from siloxane groups.

2.1 Nature of Polymerization

Polymer chains can be put together by two kinds of chemical reactions, Carothers in 1929 introduced the concept of addition and condensation polymerization [6]. Addition polymerization was defined as the reaction where small chain monomers are converted to long chain polymers without the elimination of any small atoms or molecules during the course of reaction. Condensation polymerization, on the other

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hand, was defined as the reaction of conversion from monomers to long chain polymers accompanied with the elimination of a small molecule such as water. This classification is not very accurate for polymers such as polyurethanes. Polyurethane chains grow with a reaction mechanism similar to condensation polymerization but without the elimination of any small molecule. Flory, in 1953, went on to classify polymers according to their growth mechanism, as chain growth polymers and step growth polymers [7]. Although most addition polymers grow by the chain growth process whereas most condensation polymers grow by the step growth mechanism, the use of these terms of classification synonymously can lead to confusion. The addition–condensation classification is primarily applicable to the composition or structure of polymers, whereas, the chain-step classification is based on the mechanism of polymerization reactions.

2.2 Chain Growth Mechanism

Chain growth polymerization proceeds by the formation of an active center of growth [8,9]. Monomers are added one by one to the active site on the growing polymer. Most chain growth polymers are formed from unsaturated hydrocarbons, with the unsaturation present as a double bond between carbon atoms (Table 1). The most common example of chain growth polymerization is the conversion of ethylene monomers to PE under the influence of heat (temperature T), pressure (P), and catalysis as shown in the following.

$$n(CH_2 = CH_2) \xrightarrow{T,P,\text{Catalyst}} —(CH_2 - CH_2)_n—$$

The active center can be formed as a result of various mechanisms, free radicals, ionic, or an organometallic complex. In the most common type of chain growth polymerization, a free radical molecule is generated and its presence initiates the polymerization of the monomer. A free radical is simply a molecule with an unpaired electron. The tendency for this free radical to gain an additional electron to form a pair makes it highly reactive so that it breaks the bond on another molecule by stealing an electron and in the process of doing so creates another free radical [9].

The process of polymerization in chain growth mechanism occurs in three distinct steps:

- Initiation
- Propagation
- Termination.

Initiation begins when an initiator decomposes, under the influence of heat or light, into free radicals in the presence of the monomers. The susceptibility of the double bond to the unpaired electrons in the radical breaks the unsaturation in the molecule and creates a new free radical. This is the step of initiation.

Once synthesis has been initiated, propagation proceeds. The growth of the chain due to the propagation of the active free radical center leads to the conversion of the monomer into a polymer as in Fig. 1.

The propagation reaction, in theory, can proceed till all the monomers are exhausted; however, this is rarely the case and the growing polymer chain is

Table 1 Examples of Polymers Formed Through Chain Growth Mechanism

Name	Formula	Monomer
Polyethylene Low density (LDPE) High density (HDPE)	$—(CH_2 - CH_2)_n—$	$CH_2 = CH_2$ Ethylene
Polypropylene	$—(CH_2 - CHCH_3)_n—$	$CH_2 = CHCH_3$ Propylene
Poly vinyl chloride	$—(CH_2 - CHCl)_n—$	$CH_2 = CHCl$ Vinyl chloride
Polystyrene	$—(CH_2 - CH[C_6H_5])_n—$	$CH_2 = CH(C_6H_5)$ Styrene
Polytetrafluoroethylene PTFE, Teflon	$—(CF_2 - CF_2)_n—$	$CF_2 = CF_2$ Tetrafluoroethylene
Polymethyl methacrylate PMMA, Plexiglas, Lucite	$—(CH_2C[CH_3]COOCH_3)_n—$	$CH_2 = C[CH_3]COOCH_3$ Methyl methacrylate

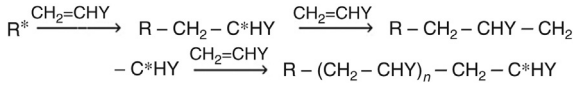

Figure 1 Depiction of the initiation and propagation steps for the polymerization of a vinyl polymer. Y depicts the vinyl group.

terminated. Termination can occur by two mechanisms, combination and disproportionation [8,9]. Combination occurs when two active free radical centers react with each other and two growing chains form one large chain. Disproportionation, on the other hand, occurs when instead of forming one chain, two reactive centers react with the result being the formation of hydrogen and double bond terminated chains, respectively. Disproportionation also occurs when the growing chain reacts with an impurity. Hence, it is critical to conduct addition polymerization reactions in very clean conditions else one could end up with too many incidences of disproportionation and consequently a low molecular weight.

Apart from free radical initiation, addition polymerization systems can also be initiated by ionic methods and coordination polymerization [8,9].

Ionic polymerization is the process where an ionic initiator transfers charge to a monomer which then becomes reactive and the growing active center. Ionic polymerizations are usually conducted in the presence of a solvent and the ability of the solvent to form free ions dictates the propagation of the ions. Cationic polymerization requires the presence of electron donating substituents and is usually limited to certain appropriate kinds of olefinic monomer systems. Anionic polymerization, on the other hand, requires strong electronegative groups and is used in the polymerization of certain styrene-based monomers.

In coordination polymerization, the active center is composed of an organometallic catalyst. The Ziegler–Natta heterogeneous catalyst system, based on titanium tetrachloride and aluminum cocatalyst, was developed in the 1950s in the polymerization of ethylene and propylene. The Ziegler–Natta catalysts had a great impact on the properties of the resultant polymer. Polymers thus formed were more linear and had a higher molecular weight. Spatial specificity or stereo tacticity could be imparted to the polymers and this tacticity implied polymers that were otherwise amorphous could transform to being crystalline.

2.3 Step Growth Mechanism

Step growth polymerization relies on the presence of reactive functional groups within a monomer; usually these functional groups form the end groups of the monomers [8,9]. The presence of at least two functional groups on the monomers is required to form a long polymer chain (Table 2). A functionality of greater than two results in the formation of a branched chain and can eventually lead to cross-linking and a thermoset polymer.

Table 2 Examples of Polymers Formed Through Step Growth Mechanism

Name	Linkage	Monomers
Polyester	—CO—O—	$C_6H_4(CO_2H)_2$ $HOCH_2CH_2OH$ Terephthalic acid and ethylene glycol (for PET)
Polyamide	—NH—CO—	$H_2N—(CH_2)_6—NH_2$ $HOOC—(CH_2)_4—COOH$ Hexamethylene diamine and adipic acid (for Nylon-6,6)
Polysiloxane (PDMS)	—Si—O—	$HO—Si(CH_3)_2—OH$ Dimethyl silanol
Polyurethane	—O—CO—NH—	$OCN—C_6H_4—CH_2—C_6H_4—NCO$ $OH—(CH_2)_4—OH$ $OH—((CH_2)_4—O)_n—H$ Methylene diphenylene isocyanate (MDI) Butane diol (BDO) Polytetramethylene oxide (PTMO) (for polyether-based thermoplastic polyurethane)

Monomer + monomer → dimer

Dimer + monomer → trimer

Dimer + dimer → tetramer

Trimer + monomer → tetramer

Trimer + dimer → pentamer

Trimer + trimer → hexamer

Etc.

Figure 2 Illustration of steps leading to a polymer in step growth polymerization [9].

The reactivity of the functional groups is relatively unaffected by the length of the molecular chain that it is attached to; however, the reactivity is more affected by the type of molecules on the chain and in particular the species that the functional group is joined to.

As the name suggests, step growth polymerization proceeds in a step wise fashion. The functional groups on two monomers react to form a dimer, the dimer reacts with another monomer to form a trimer, and these reactions lead to many monomeric units linked to form an intermediate molecular weight material, which is known as an oligomer, and eventually a polymer. The steps involved in the formation of a polymer in step growth polymerization are illustrated in Fig. 2.

A good example of a step growth polymerization that also follows the condensation polymerization route is the reaction of a diamine with a diacid with the elimination of water. Here the amide and acid end groups are the two functional groups. The reaction is as follows:

$$n\mathrm{H_2N-R-NH_2} + n\mathrm{HOOC-R'-COOH} \rightarrow \mathrm{H-(NH-R-NHCO-R'-CO)}_n\mathrm{-OH} + (2n-1)\mathrm{H_2O}$$

where R and R′ are aliphatic or aromatic groups. The unit in parentheses is the polyamide repeating unit. When $\mathrm{R} = (\mathrm{CH_2})_6$ and $\mathrm{R'} = (\mathrm{CH_2})_4$, that is, when hexamethylene diamine reacts with adipic acid, the result is poly(hexamethylene adipamide) or commonly known as Nylon-6,6.

The formation of polyurethanes is an example of step growth polymerization that proceeds without the elimination of any molecule therefore not following the route of condensation polymerization. In the case of polyurethanes, the functional groups are the isocyanate group (−NCO) and the hydroxyl group (−OH) and the reaction is as follows:

$$n\mathrm{OCN-R-NCO} + n\mathrm{OH-R'-OH} \rightarrow \mathrm{OCN-(R-NHCO-R')}_n\mathrm{-OH}$$

In many medical applications, R is aromatic, R′ is aliphatic and the reaction proceeds with different hydroxyl terminated compounds; this is explained in detail later.

The growth of molecular weight in chain growth reactions is almost instantaneous with the presence of high molecular weight polymers seen right from the start of the polymerization reaction independent of the level of conversion. In step growth polymerization, high molecular weight polymers are only formed only after high levels of conversion (>98%) and almost at the very end of reaction. The contrast of the molecular weight growth in the two reaction systems is shown in Figs. 3 and 4.

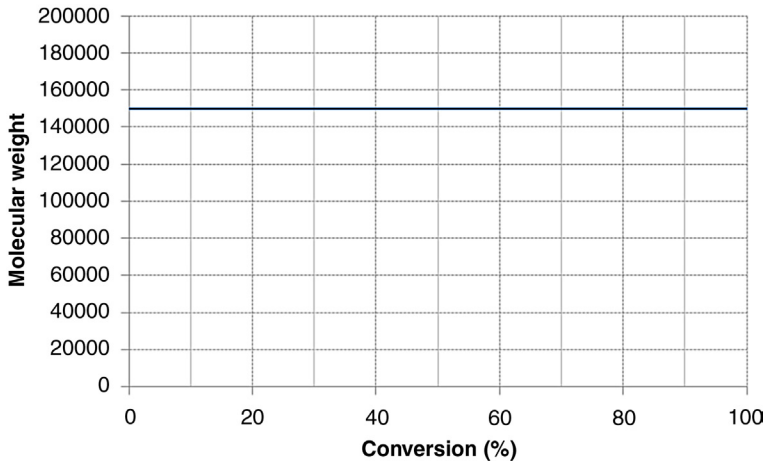

Figure 3 Illustration of variation of molecular weight with conversion in chain growth polymerization.

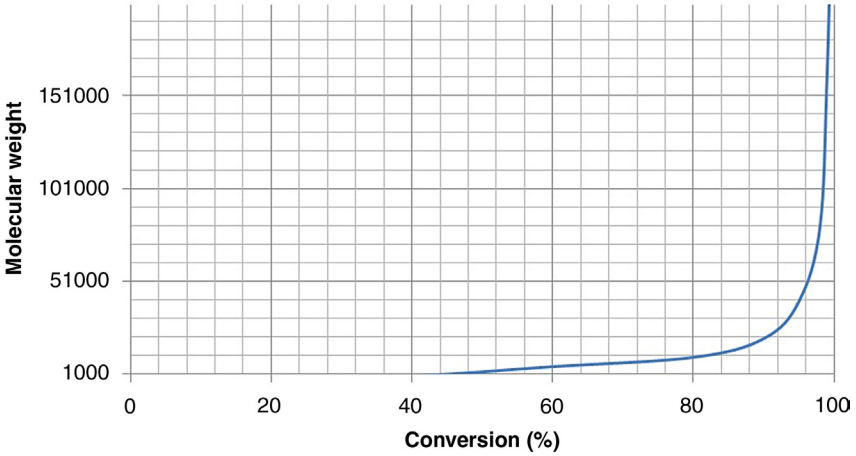

Figure 4 Illustration of variation of molecular weight with conversion in step growth polymerization.

One way of measurement of conversion is the degree of polymerization represented as DP or X_n. DP is defined as the number of monomeric units in a polymer [9]. The number average degree of polymerization is given by

$$\mathrm{DP} = X_n = \frac{M_n}{M_0} \tag{1}$$

where M_n is the number average molecular weight and M_0 is the molecular weight of the monomer

In step growth polymerization, X_n can be related to the fractional monomer conversion as follows:

$$X_n = \frac{1}{1-p} \tag{2}$$

where p is the fractional monomer conversion.

Eq. (2) shows that a high monomer conversion in step growth polymerization is required to achieve a high degree of polymerization.

From the preceding discussion it would be erroneous to conclude that chain growth reactions proceed faster than step growth polymerizations. The rate of disappearance of the monomer in step growth reactions can be as fast as or even faster than chain growth reactions, the difference in the two mechanisms lies in the time required for the growth of a polymer chain. In chain growth polymerization even when the total conversion is low, long polymer chains are present. At low conversions only a small amount of long chains are present; however, in chain growth reactions the size of the polymer chain is independent of the degree of conversion but the amount of long polymer chains is dependent on the conversion. In contrast, in step growth polymerizations both the size and the amount of polymer chains are dependent on the conversion degree.

3 Microstructure

3.1 Linear, Branched, and Cross-linked Chains

Polymers can be classified as linear (A), branched (B), or cross-linked (C) polymers depending upon their structure. The different structures are illustrated in Fig. 5. The structure of the polymer chains is governed by the nature of the monomers and the reaction conditions.

Linear polymers have chains linked to each other end to end. Branched polymers have side chain branching connected to the main chain. These branches can be of various types, short chains attached to the main chain, longer side chain branches, or extensive branching where branches protrude from other branches. The structure of a polymer, linear or branched, has a significant effect on the properties of the polymer. Linear polymers tend to pack easier and thus tend to have an ordered structure, higher melting point, and better mechanical properties than their branched counterparts.

When polymer chains are linked to each other at points other than their ends they are said to be cross-linked. Cross-linking can be made to occur during the polymerization process by the use of monomers with more than two functional groups. Cross-linking can be done after the main polymerization either by using a smaller "cross-linker" molecule or by formation of a functional group on the main chain by using

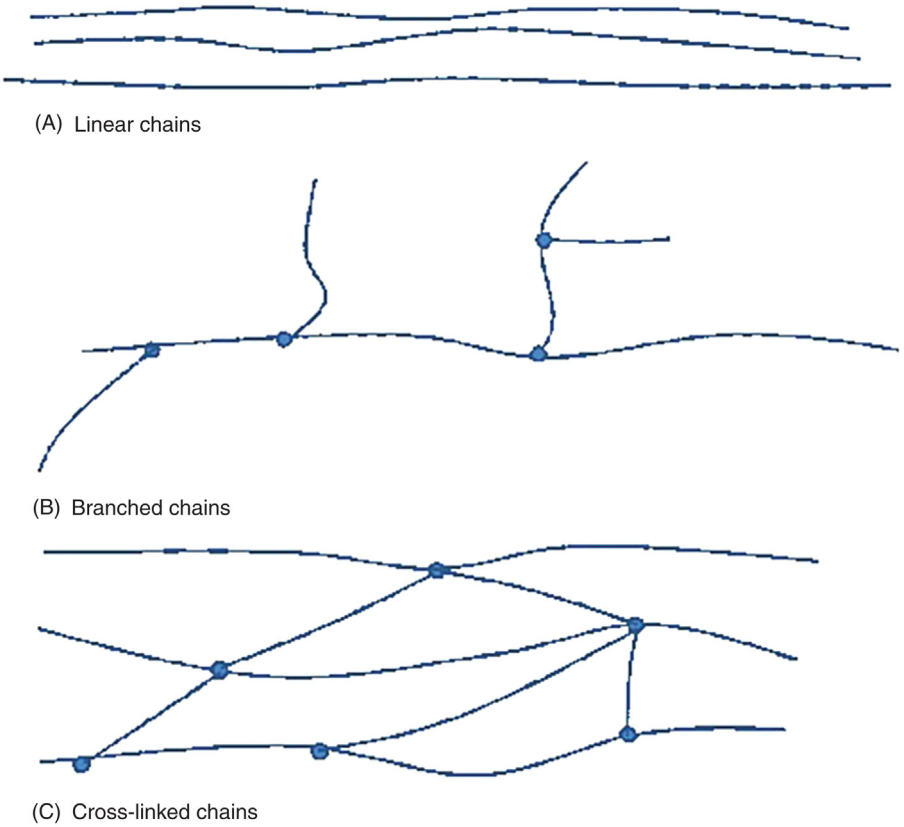

Figure 5 Structure of linear, branched, and cross-linked polymer chains.

techniques such as high energy radiation. The level of cross-linking can vary; light cross-linking is used to impart good elastic recovery properties in various elastomers, whereas a high degree of cross-linking is used to impart high rigidity and dimensional stability to polymers such as formaldehyde resins, epoxies and urethanes. At high levels of cross-linking, a level is reached when all chains are linked to each other; a three- dimensional network and a giant molecule is formed. Cross-linked polymers are also referred to as network polymers.

Cross-linking is the differentiator between thermoplastics and thermosets. The presence of the cross-links determines the thermal behavior of the material. Cross-links mean the polymer decomposes before it can melt and such polymers are classified as thermosets. Linear and branched polymers, without cross-links, have their melting points below their decomposition temperature and hence can be melted into liquids. Such polymers are called thermoplastics and they can be processed using a variety of melt processing techniques. Some examples of thermoplastic and thermoset polymers are listed in Table 3.

Table 3 Examples of Thermoset and Thermoplastic Polymers With Some General Class of Polymers Exist in Either Chemistry

Polymer	Nature
Epoxy	Thermoset
Silicone	Thermoset, also available as linear (thermoplastic) viscous fluids
Urethane	Available either in thermoset or thermoplastic chemistry Thermoplastic polyurethanes are refered to as TPUs
Polyester	Available either in thermoset or thermoplastic chemistry Poly(ethylene terephthalate) (PET) is a polyester thermoplastic
Teflon (PTFE)	Thermoplastic, however not easily melt processable
Polyolefins–Polyethylene, polypropylene	Thermoplastic
Polvinyl chloride (PVC)	Thermoplastic

3.2 Crystallinity in Polymers

Polymers in their solid state differ from low molecular weight compounds in terms of their physical microstructure or morphology. Depending on the chemical structure of the chains, the resultant polymer can have more or less ordered regions. Polymers can range from having highly ordered structures and termed crystalline to less ordered structures and amorphous polymers. In reality, no polymer is perfectly crystalline and even highly ordered polymers have amorphous phases, hence are only partly crystalline.

Two factors are primarily responsible for crystallinity in polymer systems; the conducive nature of the polymer chain structure to packing and the strength of the secondary forces within the chains. Both factors may play a role in the determination of the degree of crystallinity in polymer whereas in some polymers only one factor may dominate over the other. PE is a good example for where the conducive nature of the chains plays the major role in deciding the crystallinity of the polymer [9]. PE has low secondary forces within the chains but displays a high degree of crystallinity because of its simple and regular structure. Polycaprolactam or Nylon 6, on the other hand, displays very strong secondary forces within the chain as a result of hydrogen bond forces due to the presence of the amide (—NHCO—) group and even though the chemical structure is more complex, shows a high level of crystallinity. Hence, Nylon 6 is a good example of a polymer displaying high levels of crystallinity due to the action of secondary forces in the structure [10].

Polymers such as PS, poly(vinyl chloride) (PVC) and poly (methyl methacrylate) (PMMA) show very poor crystallization due to the structure of the monomers in their chains. The monomers are structurally complex and this leads to great difficulty in packing, even though there are clear secondary forces due the presence of polar molecules within the chain. These polymers are good examples of amorphous polymers. Amorphous polymers also occur when the polymers chains are too inflexible due to cross-linking [9]. All thermosets tend to be noncrystalline. Excessive chain flexibility can also act the other way as in the case of polysiloxane (PDMS) polymers, the packing conformation cannot be maintained due to the high flexibility of the chain and resultant polymer is amorphous.

Polymer crystallization can occur during cooling from a polymer melt, during the evaporation of the solvent in a polymer solution in both cases to form a solid or in the solid form as a result of a mechanical action. The essential aspect in all these processes is the ability of some action that drives the chains together and aligns them to enable ordering and crystallization. Crystallization can have significant impact on various polymer properties. With an increasing degree of crystallinity, a higher thermal stability results with better mechanical properties at higher temperatures, this is in contrast to amorphous polymers. Semicrystalline polymers also tend to be optically opaque; this is due to the light scattering on numerous boundaries between the amorphous and crystalline regions.

The nature of polymer crystallinity has been a subject of many investigations [10–12]. The folded chain lamella theory is generally established as the mechanism of the formation of crystalline regions [13]. Even though the most thermodynamically favored arrangement is the one involving completely extended chains, it appears that chain folding is the system's compromise in achieving a stable crystal with a macromolecular structure. Defects in the chain folding process such as imperfect folds, loose chain ends, chain entanglements, etc. mean that a perfect crystal structure in polymers is never obtained and polymer crystallinity is always less than 100%. In fact, the degree of crystallinity in various polymers is estimated as being between 10% and 80% [11] and thus crystallized polymers are often called semicrystalline. Table 4 gives the standard degrees of

Table 4 Degree of Crystallinity (*D*, %) and Densities of Crystalline (ρ_c) and Amorphous (ρ_a, g/cm^3) Polymers [11]

Polymer	Degree of Crystallinity (*D*)	Crystalline Density (ρ_c)	Amorphous Density (ρ_a)
Nylon (6 and 6,6)	35–45	1.24	1.08
Polyethylene terephthalate (PET)	30–40	1.5	1.33
Polytetrafluoroethylene (PTFE)	60–80	2.35	2.0
Polypropylene (isotactic)	70–80	0.95	0.85
High density polyethylene (HDPE)	70–80	1.0	0.85
Low density polyethylene (LDPE)	45–55	1.0	0.85

crystallinities of different polymers. The growth of crystal structures in such polymers follows a spherulitic form, where the crystal regions grow in spherical structures called spherulites. Spherulites are sized typically in the order of around 1 μm [14] and are initiated by the process of nucleation. The nucleation usually begins with nanometer-sized areas and is a result of homogeneous or heterogeneous nucleation. When cooling from a melt, polymer chains align to form thermally induced homogeneous nuclei that can grow into spherulites. Heterogeneous nucleation, on the other hand, can occur as a result of impurities in the system such as dyes, plasticizers, fillers, and other additives in the polymer.

The degree of crystallinity in a polymer can be measured using techniques such as density, X-ray diffraction, nuclear magnetic spectroscopy (NMR), and differential scanning calorimetry (DSC) [11]. The plot of temperature versus heat flow as generated in the DSC thermogram shows clear transition peaks for crystallinity. The area of this peak can be computed for the heat content and the ratio of heat content and the polymer's specific heat of melting can be used to calculate the level of crystallinity in the material.

4 Properties

4.1 Molecular Weight

The main distinguishing feature of a macromolecule over any normal molecule is its chain length or molecular weight. The molecular weight of a polymer is the main reason for the useful mechanical properties of polymeric materials. The mechanical properties of a polymer can vary considerably depending on its molecular weight. The dependence of the mechanical properties on the molecular weight of the polymer is illustrated in Fig. 6 [9]. There is a minimum molecular weight (A) above which any significant mechanical strength is obtained. From there on the mechanical strength rises rapidly with molecular weight till a critical molecular weight (B) is reached. This point B is also known as the threshold molecular weight of the material. After B the rise of the mechanical strength is much less appreciable and reaches a maximum at point C. All commercial polymers exist above the threshold molecular weight value.

The values and locations of A, B, and C vary with different polymers. The plot in Fig. 6 will be shifted to the right when the magnitude of intermolecular forces decreases as is the case with PE, polypropylene (PP), and PS. Apart from mechanical strength, many other polymer properties also show significant dependence on the material molecular weight. Not all properties show a linear dependence on the molecular weight, some properties may reach a maximum at a lower molecular weight and beyond that may actually decrease with increasing molecular weights. The viscosity of the polymer melt, for example, does increase with increasing molecular weight, however, beyond a certain viscosity; melt processing the polymer becomes difficult. In this case, it may be beneficial to limit the growth of the polymer molecular weight.

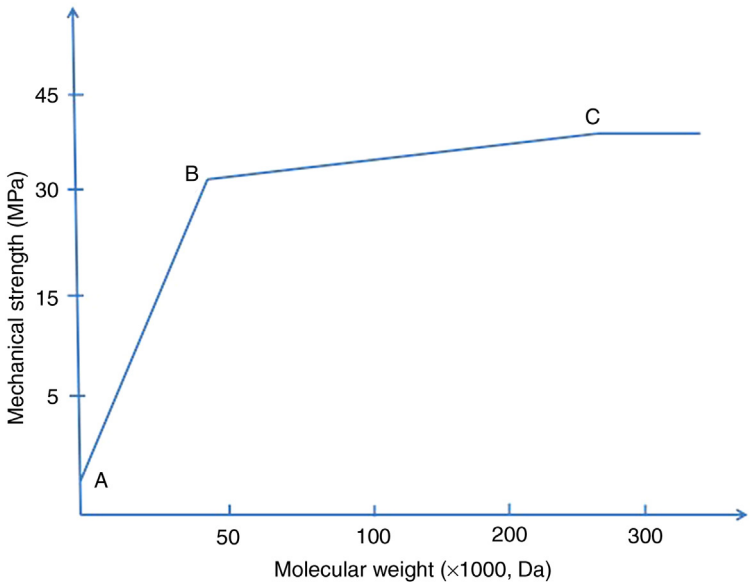

Figure 6 Dependence of mechanical properties on the polymer molecular weight.

The molecular weight of a polymer is different from the molecular weight of a low molecular weight material, polymers are heterogeneous in nature and the molecular weight of the polymer is always its average molecular weight. Polymers are mixtures of molecules of different molecular weights; they are polydisperse in molecular weight. This heterogeneity or polydispersity results from the statistical variations present in the polymerization process.

4.1.1 Gel Permeation Chromatography

Different methods are used for the detection of the molecular weight distribution of a polymer. These methods focus on the properties resulting from chain length differences such as refractive indices, light scattering intensities, and viscosity. The most common technique used in the industry is size exclusion chromatography (SEC) also termed gel permeation chromatography (GPC) and a refractive index detector. The technique is a variant of high performance liquid chromatography (HPLC), where a dilute polymer solution is forced through a series of columns composed of microporous polymer particles under high pressures. GPC separates the molecular chains on the basis of their dimensions or their radius of gyration. Mathematically, the radius of gyration is the root mean square distance of any point in the polymer chain from its center of mass. The longer molecules in the polymer solution have a lower tendency to be caught within the pores of the particles in the column and therefore emerge earlier in the elution curve. The shorter molecules tend to stay longer in the column and make up the end of the elution curve. The pore size distribution of the particles determines the size range within which separation occurs. The use of calibrated standards of known molecular weights, such as anionically polymerized PS, allows one to correlate between elution/retention times and molecular mass. A multidetector method can be used for greater accuracy [15] and without the need for a calibration standard. Low angle light scattering detectors permit direct measurement of the molecular weight of the sample eluting from the column without reference to a calibration curve. The use of multiangle light scattering detectors with SEC permits the measurement of the scattered intensity at as many as 15 angles as the sample elutes from the column, thus the root mean square radius of gyration as well as the molecular weight may be measured directly [15].

Two average molecular weights are commonly used: the number average molecular weight (M_n) and the weight average molecular weight (M_w). These are defined in Eqs. (3) and (4) as

$$M_n = \frac{\Sigma N_i M_i}{\Sigma N_i} \tag{3}$$

and,

$$M_w = \frac{\Sigma N_i M_i^2}{\Sigma N_i M_i} \tag{4}$$

where N_i is the number of moles of species i and M_i is the molecular weight of species i.

As can be seen, M_n is biased toward the shorter chain lengths whereas M_w is biased toward the longer chain lengths. As a result, M_w is always greater than M_n. The ratio M_w/M_n is referred to as the polydispersity index (PDI). A typical distribution of the polymer molecular weight is shown in Fig. 7.

The PDI values for commercial polymers lie between 1.1 and 50. In general, the greater the uniformity of the polymer, the lower the value of the PDI is and the closer it is to 1.1. For commercial polymers, specialized polymerization techniques, such as anionic polymerization, have to be used to reduce the PDI to values lower than 1.1.

4.1.2 Intrinsic Viscosity

Another technique used to measure the molecular chain length of polymers is the intrinsic viscosity (IV) technique. The IV is determined by the measurement of the viscosity of the dilute solution of the polymer in an appropriate solvent and then correlating it to the molecular weight of the polymer using the Mark–Houwink equation. The Mark–Houwink equation describes the relationship between the molecular weight of a polymer and IV of the solution as in Eq. (5):

$$[\eta] = kM^a \tag{5}$$

where $[\eta]$ is the polymer IV, M is the polymer molecular weight, and k and a are constants.

The constants, k and a, are known as Mark–Houwink parameters and the values of these constants are dependent on the polymer–solvent system. A value of $a = 0.5$, represents a theta solvent. A theta solvent is defined as the solvent that opens up the polymer chains to present the ideal configuration. Thermodynamically, for a theta solvent the excess chemical potential of mixing between the polymer

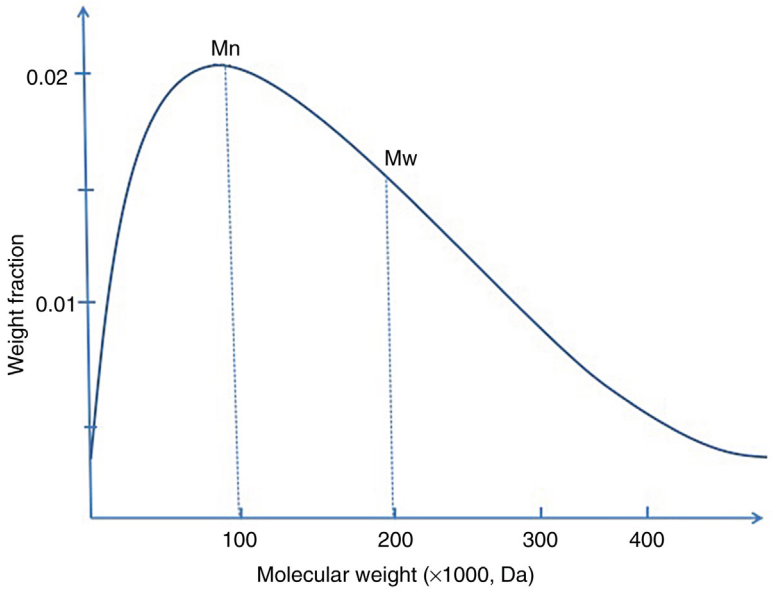

Figure 7 A typical distribution of the polymer molecular weight as represented by an elution curve from GPC.

and solvent is zero. For most polymer systems, the value of "*a*" lies between 0.5 and 0.8.

An ASTM document [16] describes the test method for the standard test method for dilute solution viscosity (DSV) of polymers. DSV is used for polymers that dissolve completely without chemical reaction or degradation into the solvent and this test can provide an excellent determination of lot-to-lot consistency of the synthesized polymer or can be used to compare molded parts to original resin for determination of degradation from molding.

From the flow time of the pure solvent mixture in a glass, Ubbelohde type, viscometer, and the corresponding flow times of known concentration polymers solutions, it is possible to obtain the relative (η_{rel}), inherent (η_{inh}), reduced (η_{red}), and intrinsic [η] viscosities by means of the following equations:

$$[\eta] = \lim_{\phi \to 0} \frac{\eta - \eta_{rel}}{\eta_0 \phi} \tag{6}$$

$$\eta_{rel} = \frac{t}{t_o} \tag{7}$$

$$\eta_{inh} = \frac{\mathrm{In}(\eta_{rel})}{c} \tag{8}$$

$$\eta_{red} = \frac{(\eta_{rel} - 1)}{c} \tag{9}$$

$$[\eta] = \frac{0.25\{(\eta_{rel} - 1) + 3\mathrm{In}(\eta_{rel})\}}{c} \tag{10}$$

where ϕ is the volume fraction of the solute in the solution, t is the flow time of polymer solution (s), t_o is the flow time of pure solvent (s), and c is the polymer solution concentration (g/dl).

4.2 Mechanical Properties

A perfectly elastic material follows Hooke's law of deformation, that is, the applied load is proportional to the deformation or the imposed stress is proportional to strain. A viscous material follows Newton's law of flow, that is, stress is proportional to the rate of change in strain. A polymer, owing to its network-like microstructure can behave as a high modulus, glassy solid, a low modulus, rubbery solid, or a viscous liquid depending on the temperature of application. Polymers are thus defined as intermediate, viscoelastic materials.

The mechanical properties of a polymer are very important in deciding the suitability of the material in any application. Fig. 8 shows a testing apparatus with different configurations of the specimen [17]. The mechanical properties of the polymer are usually determined by a uniaxial pull test, as depicted as grip configuration (A) in Fig. 8. In this test, the polymer specimen, with a defined geometry, is placed within the grips of a tensile testing machine. In the test, one grip is stationary whereas the other moves with a predetermined speed. The response of the material to this imposed elongation is recorded on stress–strain curve. The stress is defined as the ratio of imposed load in Newton over the area of the specimen in

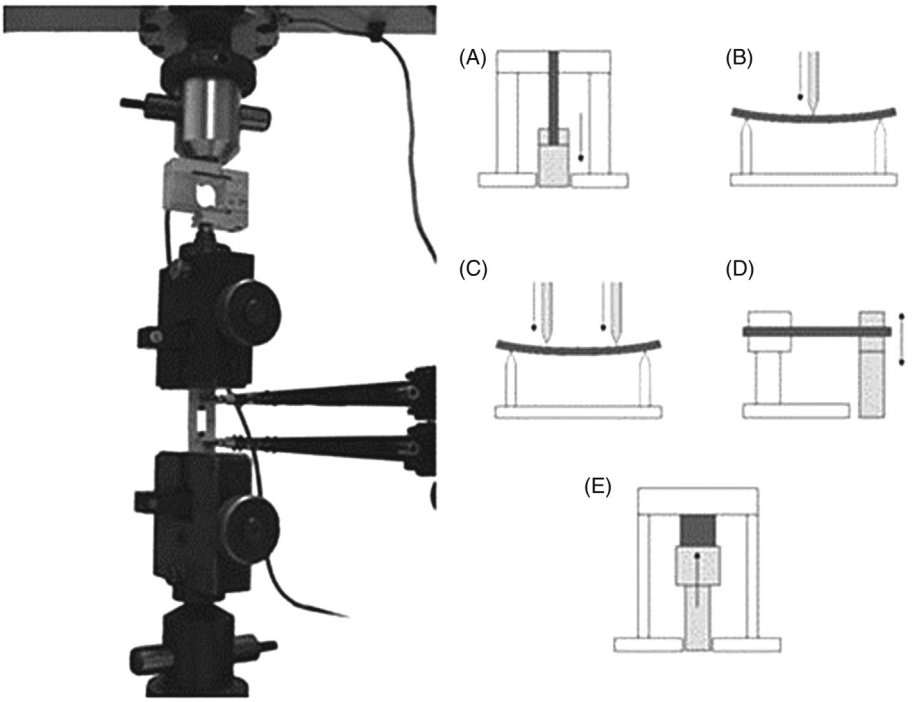

Figure 8 Simple tensile test configuration, along with different specimen geometries commonly used in solid-state testing. (A) Tension; (B) three-point bending; (C) four-point bending; (D) single cantilever; and (E) uniaxial compression [17]. *Courtesy: Elsevier Publications.*

square meters; it is therefore expressed as Newtons per square meter of the sample (N/m^2). The strain felt by the sample is the fractional increase in the length of the sample, that is, dL/L, where L is the original, unstretched sample length.

Three quantities are considered as the important representatives of the mechanical properties of the polymer:

- Ultimate tensile strength
- Elastic modulus
- Elongation at break

Ultimate tensile strength (UTS)—The stress required to break or rupture the sample is known as the UTS of the sample or simply as the tensile strength of the material. In simple terms, the UTS can be expressed as

$$\sigma_{UTS} = \frac{F}{A} \tag{11}$$

where F is the load required for sample rupture and A is the cross-sectional area of the sample.

Care is taken to ensure that this break occurs in the stressed region and not within the grips or the jaws of the test machine. If a sample breaks in the jaw, a jaw break is said to have occurred causing an erroneous measurement and therefore those samples are discarded. Frequently, stress-induced crystallization may occur in the later stages of the tensile test. This stress-induced crystallization significantly increases the stress required for sample rupture and as a result of the crystallization the sample, if initially transparent, turns opaque before rupture. Stress-induced crystallization is seen many times in multicomponent samples or blends; this is mainly due to one component of the sample being more sensitive to crystallization under stress.

Elastic modulus—Elastic modulus is the resistance to deformation as measured in the initial, linear portion of the curve. This initial portion, where polymer is perfectly elastic and follows Hooke's law, can be very small, as most polymers display a nonlinear response to applied stress. The modulus is expressed as the initial stress divided by the corresponding dL/L or ε value. The modulus can be expressed as

$$E = \frac{\sigma}{\in} \tag{12}$$

where E is the elastic modulus, σ is the stress, and ε is the elongation.

Since elongation is dimensionless, the modulus is expressed in the same units as tensile strength, that is, the units of pressure, such as in N/m^2 or Pascals (Pa).

It is important to note that the value of the elastic modulus is not constant with nonlinear viscoselastic materials that polymers are. The slope of the stress–strain curve changes with increasing stress; therefore the initial slope is taken as material's elastic modulus. In general, among polymers, fibers have the highest tensile moduli, elastomers have the lowest, and other plastics have tensile moduli somewhere in between fibers and elastomers.

Many times, compliance is another mechanical property used for a polymer and that can be described as the reciprocal of modulus:

$$D = \frac{1}{E} \tag{13}$$

where D is the material compliance that describes the ability of a material to deform and comply to the stresses in the application.

Elongation at break—Samples under uniaxial tension undergo deformation and this deformational strain recorded at the point of sample rupture is the ultimate elongation. The value is also referred to as % elongation and expressed as a percentage. It can be written as

$$\%\ \text{ultimate elongation} = \frac{L_f - L_0}{L_0} \times 100\% \tag{14}$$

where L_f is the sample length at break and L_0 is the initial sample length.

The % ultimate elongation is an important measure of the nature of polymer. Higher ultimate elongation is an indication of the ductility of the material; brittle polymers show low values of ultimate elongations and a brittle surface on the fractured sample. Elastic elongation is the level of elongation which does not induce the material to permanently deform. In other words, elastic elongation is that point on the stress–strain curve from where the material, on the release of the applied stress, can come back to the origin. Elastomers have a greater value of elastic elongation as compared to harder plastics.

The mechanical properties of polymers can be examined in a range of additional tests that go beyond a uniaxial tensile test; some of these variations are shown in Fig. 8. Many times these tests might correspond better with the stresses experienced by the polymer in the respective field of application. These tests include compression, flexure, and torsion. In compression, the polymer sample is compressed instead of being extended. The compression tests can be performed on the same equipment that is used for the tensile tests. In a flexural test, the polymer sample is bent with a defined stress at multiple points along the sample and the resulting deflection measured. The torsional strength is measured under twisting conditions.

An additional property of the polymer that describes mechanical behavior is its toughness. The toughness of material is the area underneath the stress–strain curve. Toughness is a measure of the energy a sample can absorb before it breaks. Hence, depending on the shape of the stress–strain curve, material may be strong but not tough at the same time. Toughness values are an effective measure of the brittle or ductile nature of the material; low toughness signifies high brittleness of the material.

The mechanical properties of a polymer can vary widely. This variation is dependent on a number of factors including the following:

- Chain organization—whether the material is amorphous or semicrystalline and the existence of intermolecular attraction
- Chain arrangement—whether the chains are linearly spaced or are branched
- Thermal nature—whether the material is a thermoplastic or a thermoset.

Depending upon the particular combination, a specific polymer can be used as a flexible plastic, a rigid plastic, or as an elastomer. Fig. 9 shows stress–strain plots for different kinds of polymers.

In summary, the moduli of elasticity for polymers tend to be in the range of ~5 Mega Pascal (MPa)–4 Giga Pascal (GPa), the tensile strengths are in the range of 5–100 MPa and the percentage elongation can be up to 1000% in certain cases. This can be compared to metals, their elastic moduli range from ~50 to 400 GPa, UTS can be several GPa and the ultimate elongations are usually less than 100%.

As depicted in Fig. 10, the mechanical properties of polymers change dramatically with temperature. Polymers can go from being glass-like brittle materials at low temperatures to rubber-like ductile materials at high temperatures. An increase in temperature can lead to a decrease in the elastic modulus, a reduction in the tensile strength, and an increase in the ultimate elongation of the material. The decrease in elastic modulus, as shown in Fig. 10, becomes more pronounced as the temperature approaches the glass transition temperature of the material. The glass transition temperature, T_g, is explained in the section on the thermal properties. The change is less dramatic with increasing crystallinity of the material and

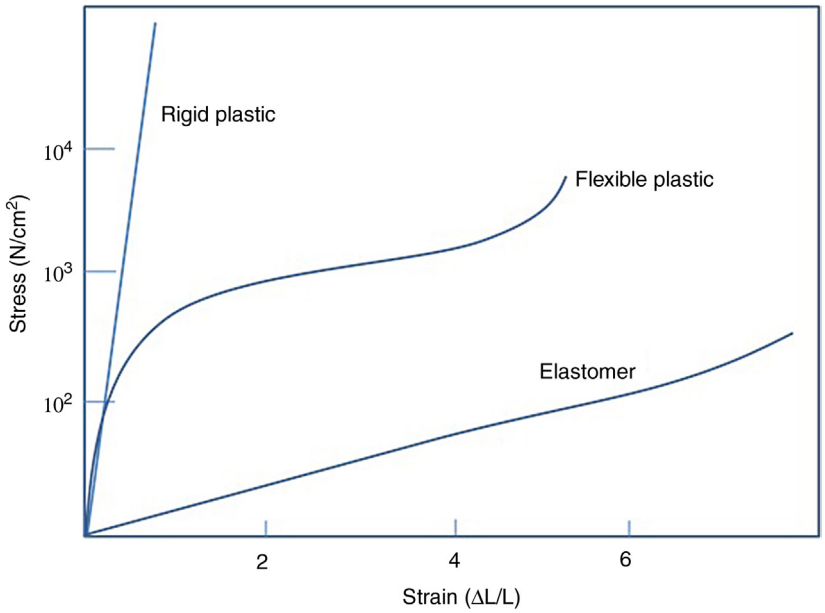

Figure 9 Stress–strain plots for typical polymers.

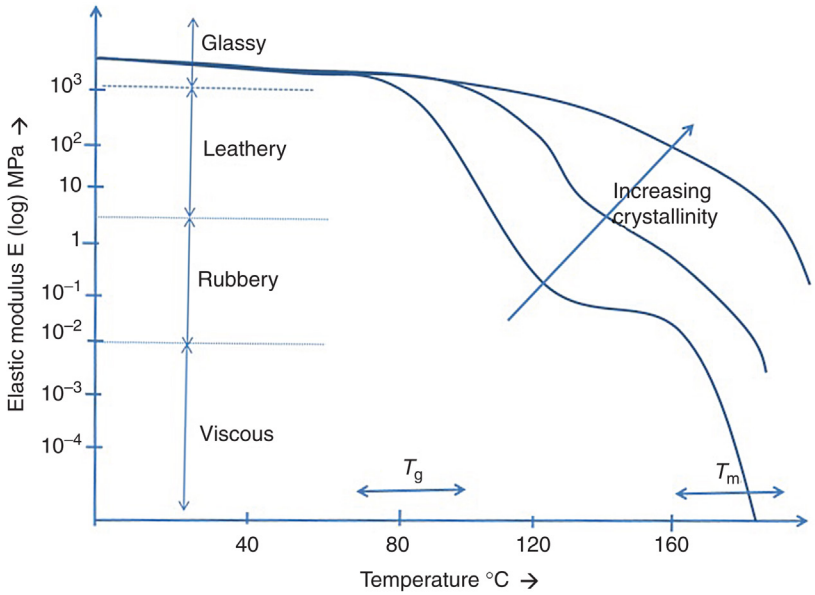

Figure 10 Illustration of the temperature effects on the elastic modulus of polymers.

eventually the temperature increases to a point where the polymer is completely transformed into a viscous melt. Another source of mechanical property variation is the rate of deformation or the strain rate of the sample, polymers are very sensitive to the rate of deformation, decreasing the rate of deformation has the same effect as increasing temperature. In other words, polymers tend to behave like elastic materials for rapidly applied stress and viscous materials for gradually applied stress.

Polymers are also susceptible to time dependent deformation under constant load. This phenomenon is known as viscoelastic creep. Creep may be significant even at room temperature and under moderately low stresses. The amount of creep tends to decrease as the crystallinity of the polymer increases.

4.3 Chemical Properties

The behavior of plastics with respect to the chemicals present in the environment of their applications determines to a large extent the suitability of the material to be used in a particular

application. The resistance of a plastic to the chemicals present in the environment is known as its chemical resistance.

The chemical resistance of a plastic depends on the nature of the monomer, chain structure, polarity, solubility, cohesive energy density (CED), and reactivity [18]. Cross-link density, for example, is one of the indicators of chemical resistance and thermosets, in general, are resistant to solvents and associated swelling. In general, plastics are resistant to weak acids, weak alkali, salt solutions, and water, although some polyesters and polyamides may hydrolyze in acid and alkali environments. Strong oxidizing acids may attack plastics, resulting in discoloration or embrittlement. Most plastics are affected by organic liquids; for example, fuels, oils, and various organic solvents may attack plastics, causing swelling, softening, and dissolution.

A number of factors can affect the rate and type of chemical attack that may occur [16] these are as follows:

Concentration— In general, the rate of attack increases with the concentration of the chemical in the environment, but in many cases there are threshold levels below which no significant chemical effect is noted.

Temperature— As with all processes, rate of attack increases as the temperature rises. Again, threshold temperatures may exist.

Period of contact—The time period that the polymer is in contact with the chemical has a profound impact on the resistance of the polymer to the particular chemical. In many cases, rates of attack are slow and of significance only with sustained contact.

Chemical immersion results are reported in terms of volume change, tensile strength retention, elongation retention; change in Shore A hardness and surface condition of the sample. A chemical resistance chart is shown in Table 5 [18].

Table 5 A Representative Chemical Resistance Chart for Certain Plastic–Chemical Combinations

Material	Acetone	Benzene	Diethyl ether	Glycerine	Heptane	Isopropyl Alcohol	Methyl Ethyl Ketone	Nitric Acid (10%)	Sulphuric Acid (10%)
Acrylics (PMMA)	D	D	[a]	A	[a]	C	D	[a]	[a]
Polyethylene (HDPE)	A	D	[a]	A	[a]	A	D	[a]	[a]
Nylon 6,6	A	A	A	A	A	B	A	D	D
Poly ether ether ketone (PEEK)	B	A	A	A	A	A	A	A	A
Polyethylene terephthalate (PET)	B	A	A	A	A	A	A	C	A
Polypropylene (PP)	A	D	[a]	A	[a]	A	D	[a]	[a]
PTFE	A	A	A	A	A	A	A	A	A
Polycarbonate	C	D	[a]	A	C	[a]	D	[a]	[a]
Silicones	B	D	C	A	D	A	D	C	C
Polyurethane (TPU–ether based)	D	C	B	A	B	C	D	C	B

A, no attack, possibly slight absorption. Negligible effect on mechanical properties is expected; B, slight attack by absorption. Some swelling and a small reduction in mechanical properties is likely; C, moderate attack of appreciable absorption. Material will have limited life; D, material will decompose or dissolve in a short period of time.

[a]*No data available.*

Where aqueous solutions are shown, the concentration as a weight % is given.

4.3.1 Polymer Solubility

The measurement of many polymer properties, such as molecular weight of a polymer, occurs with the material dissolved in a solvent. Here the assumption is that the solvent completely dissolves the polymer. The understanding of the dissolution characteristics of the polymer is important not only from a testing aspect but also as there are numerous processing methods such as dip molding and spray coating that utilize this property of polymer dissolution. The dissolution of polymers in a solvent depends upon many factors of the polymer structure including the following:

- Molecular weight and branching
- Degree of cross-linking
- Crystallinity
- Polarity

The molecular weight of a polymer plays an important role in its solubility, in a given solvent at a particular temperature, as the molecular weight increases, the solubility of the material decreases. Branching, on the other hand, generally increases solubility as the branched structure of the polymer increases regions of interaction with the solvent. Decreasing solubility behavior is also noted with increasing degree of cross-linking, as the thermoset nature of the material increases there is increased inhibition in the interaction between the polymer and solvent molecules. Increased crystallinity also decreases dissolution, for example with highly linear, crystalline polyolefins such as high density polyethylene (HDPE), dissolution in a solvent is only possible at high temperatures. These high temperatures are high enough to disrupt the crystalline structure of the polymer. In general, polymer solubility follows the like-for-like principle, that is, polar polymers tend to dissolve in polar solvents whereas nonpolar polymers tend to dissolve in nonpolar solvents. Thus, highly polar polymers such as poly acrylic acid and poly vinyl alcohol dissolve in water.

The solubility of a polymer can be expressed by the following equation [19]:

$$\Delta H = \varphi_s \varphi_p (\delta_s - \delta_p)^2 \tag{15}$$

where ΔH is the enthalpy of mixing, φ_s is the volume fraction of solvent, φ_p is the volume fraction of polymer, δ_s is the CED for solvent, and δ_p is the CED for polymer.

The CED is a measure of the strength of the intermolecular forces and is commonly known as the solubility parameter. The *like-for-like* principle can be applied to solubility parameters and it has been established that, for a polymer to be dissolved in a given solvent, the term $(\delta_s - \delta_p)^2$ in equation [19], must be smaller than 4.0. The solubility parameters of some common polymers and solvents are in Table 6 [19].

4.4 Electrical Properties

Most plastic materials are dielectrics or insulators, that is, they are poor conductors of electricity and resist the flow of electric current. This is one of the most useful properties of plastics and makes

Table 6 Hildebrand Solubility Parameters for Some Solvents and Polymers

Solvent	δ_s (MPa$^{1/2}$)	Polymer	δ_p (MPa$^{1/2}$)
Acetone	20.3	Polyethylene	15.8–18.0
Benzene	18.8	Polypropylene	18.9–19.2
Chloroform	19	Polymethyl methacrylate	18.4–26.3
n-Hexane	14.9	Poly vinyl alcohol	25.8
n-Pentane	14.3	Poly vinyl chloride	19.2–22.1
Toluene	18.2	Polystyrene	17.4–21.1
Water	47.9	Poly vinyl acetate	18.0–19.1
Tetrahydrofuran (THF)	18.5	Polyamide (Nylon 6,6)	27.8
Dimethyl acetamide (DMAc)	24.7	Polydimethyl siloxane (PDMS)	15.5

much of the current lifestyle possible through the use of plastics as wire coatings, switches, and the ever expanding usage of plastics in numerous electronic products. Despite this, dielectric breakdown of plastics can occur at sufficiently high voltages to give current transmission and possible mechanical damage to the material.

In general, the application of an electrical potential difference or voltage causes the movement of electrons. This movement of electrons occurs when the electrons are free to move and as a result there is a corresponding flow of electric current. For instance, metals can be thought of as a collection of atomic nuclei existing in a "sea of electrons" and when a voltage is applied the electrons are free to move and to conduct a current. Polymers and the atoms that make them up have their electrons tightly bound to the central long chain and side groups through "covalent" bonding. Covalent bonding makes it much more difficult for most conventional polymers to support the movement of electrons and therefore plastics act as insulators.

Not all polymers or plastics behave the same when subjected to voltage. Polymers are classified as "polar" or "nonpolar" to describe their variations in behavior. The polar polymers do not have a fully covalent bond and there is a slight imbalance in the electronic charge of the molecule. In polar polymers/plastics, dipoles are created by an imbalance in the distribution of electrons. In the presence of an electric field, the dipoles will attempt to move to align with the field. This will create "dipole polarization" of the material. As movement of the dipoles is involved, there is a time element to the movement. Examples of polar polymers are polyurethanes (PU), polymethyl methacrylate (PMMA), PVC, nylon (PA), polycarbonates (PC), etc. The nonpolar plastics are truly covalent and generally have symmetrical molecules. In these materials there are no polar dipoles present and the application of an electric field does not try to align any dipoles. The electric field does, however, move the electrons slightly in the direction of the electric field to create "electron polarization". In this case the only movement is that of electrons and this is effectively instantaneous. Examples of nonpolar plastics are fluoro polymers (PTFE), PE, PP, and PS. These materials tend to have high resistivity and low dielectric constants.

The alternating current (AC) electric breakdown strength of thin polymer films as a function of sample thickness with the sphere-plane electrode configuration was investigated by Yilmaz and Kalenderli [20] at various temperatures. The electric strength of the polymer film is reduced with increasing thickness of the film and temperature. The thickness of thin films needs to be controlled to get a necessary dielectric strength, thus in the device in which a high voltage is applied, the film needs to be made thick. For example, a thickness of approximately 10 μm is necessary to get a dielectric strength of 100 V.

The dependence of the dielectric constants on film thickness was explained by the orientation of polymer chains by Liang et al. [21]. Thickness dependent soft-breakdown phenomena of low dielectric constant thin films and corresponding activation energy were studied by different researchers [22,23]. The dielectric constant was decreased with the decrease of thickness; however, the frequency dispersion of the dielectric constant which is characteristic for the relaxation was observed.

Dielectric strength is a measure of the electrical strength of a material as an insulator. Dielectric strength is defined as the maximum voltage required to produce a dielectric breakdown through the material and is expressed as volts per unit thickness. The higher the dielectric strength of a material, the better is its quality as an insulator. Dielectric strength is calculated by dividing the breakdown voltage by the thickness of the sample. The data are expressed in volts/mil. The location of the failure is also recorded. A higher dielectric strength represents a better quality of insulator.

$$\text{Dielectric Strength} = \frac{\text{Breakdown voltage (volts)}}{\text{Film thickness (mil)}}$$

Dielectric constant is used to determine the ability of an insulator to store electrical energy. The dielectric constant is the ratio of the capacitance induced by two metallic plates with an insulator between them to the capacitance of the same plates with air or a vacuum between them. Dissipation factor is defined as the reciprocal of the ratio between the insulating materials capacitive reactance to its resistance at a specified frequency. It measures the inefficiency of an insulating material. If a material were to be used for strictly insulating purposes, it would be better to have a lower dielectric constant. When a material is to be used in electric applications where high capacitance is needed, a higher dielectric constant is required. The test can be conducted at different frequencies, often between the 10 Hz and 2 MHz range—the specific frequency is determined by the application. Table 7 lists electrical properties for some polymers.

Table 7 Dielectric Properties of Various Polymers

Polymer	Dielectric Strength (Kv/cm)	Dielectric Constant (50 Hz/1 Mhz)	Dissipation Factor, *D* 50 Hz/1 Mhz ($\times 10^{-3}$)
Polytetrafluoroethylene (PTFE)	480	2.1/2.1	0.2/0.2
Low density polyethylene (LDPE)	370	2.29/2.28	0.15/0.08
High density polyethylene (HDPE)	—	2.35/2.34	0.24/0.20
Polypropylene (PP)	240	2.27/2.25	0.40/0.50
Poly vinyl chloride (PVC)-plasticized	270	4-8/4-5	80/120
Polystyrene (PS)	200–300	2.5/2.5	0.1–0.4/0.05–0.4
Poly methyl methacrylate (PMMA)	140	3.3–3.9/2.2–3.2	40–60/4–40
Polyamide-6	400	3.8/3.4	10/30
Polyamide-66	600	8/4	140/80
Polycarbonate	380	3.0/2.9	0.7/10
Polyethylene terephthalate (PET)	420	4.0/4.0	2/20
PUR-thermoset	240	3.6/3.4	50/50
Polyurethane–thermoplastic (average)	300	6.6/5.6	30/60
Silicone	200	3.6	5–13/7

4.5 Thermal Properties

As a polymer is heated, the energies stored in the molecules increase in their intensities. These increases cause the polymer to go through different transitions. There are two primary transitions of interest, the crystalline melting temperature T_m and the glass transition temperature T_g. The T_m is the melting temperature of the crystalline portion of the polymer whereas T_g is the temperature below which the amorphous regions of the polymer display glassy properties such as brittleness, stiffness, and rigidity [24].

When a polymer is cooled down, for example, from a molten state, at a certain temperature, the translational and rotational energies of the molecules reduce to point where ordered packing of the molecules is possible. If the structure of the chains is such that crystallization is possible then crystallization begins at this temperature that also is the T_m. However, if the structural requirements for crystallization are not possible then crystallization does not take place and the polymer does not display a T_m. Upon further cooling down, a temperature is reached where no further bond rotation is possible; this temperature T_g is the glass transition temperature.

The values of T_g and T_m are dictated by the molecular structure of the polymer. A completely amorphous material displays only a T_g whereas a semicrystalline material displays both T_g and T_m. The values of T_g and T_m for different polymers are listed in Table 8.

The two thermal transitions are conveniently measured by the changes in polymer properties such as specific volume and heat capacity. DSC is a common technique used widely to determine thermal transitions in a polymer. DSC is a thermo-analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The difference in the heat requirement for the pans is measured and constitutes the DSC curve. On the DSC curve, the temperature is plotted on the *x*-axis and on the *y*-axis, the difference between the heat outputs between the two pans is plotted.

Changes in the specific heat denote changes in the mobility of the polymer chains. DSC thermograms can be used to identify the glass transition temperature (T_g) of a polymer. The glass transition temperature is identified by the change in the heat capacity that appears as a baseline shift. Above the

Table 8 Thermal Transitions of Polymers [20]

Polymer	Formula	Glass Transition Temperature (°C) (T_g)	Crystalline Melting Temperature (°C) (T_m)
Polyethylene	$(CH_2–CH_2)_n$	−125	137
Polypropylene	$(CH_2–CHCH_3)_n$	−13	176
Poly vinyl chloride	$(CH_2–CHCl)_n$	81	273
Polystyrene	$(CH_2–CH[C_6H_5])_n$	100	240
Polytetrafluoroethylene PTFE, Teflon	$(CF_2–CF_2)_n$	127	327
Polymethyl methacrylate PMMA, Plexiglas, Lucite	$(CH_2C[CH_3]COOCH_3)_n$	105	200
Polyester (PET)	$(CO–C_6H_4–CO–O–CH_2–CH_2–O)_n$	69	270
Polyamide Nylon 6,6	$[OC–(CH_2)_4–CO–NH–(CH_2)_6–NH]_n$	52	223

glass transition temperature the polymer chains have increased mobility; this mobility allows chains to fall in order and form crystalline domains. During the formation of these crystalline structures there is an evolution of heat and this is measured as the crystallization temperature of the polymer (T_c). Crystallization is an exothermic process. Heating the polymer beyond the temperature of crystallization, one reaches the melting point or the melting temperature of the crystals. The melting temperature denotes the temperature at which the disordering ordering off the crystalline regions occurs. A representative DSC curve is shown in Fig. 11. Obviously an amorphous polymer such as atactic PS will not show any transition to denote crystallization.

4.6 Rheology

"Rheo" is Greek for flow so polymer rheology is the study of the flow properties of a polymer liquid. A polymer is flowable when the response of the material to any externally imposed stress is no longer elastic deformation but predominantly plastic flow. The condition of plastic flow occurs in polymers is either above a certain temperature, a molten polymer for example, or when the polymer is dissolved in a solvent to form a solution.

The resistance to deformation to an applied stress is defined as the viscosity of a liquid. When a liquid is deformed, the rate of change of strain is defined as the shear rate (Fig. 12).

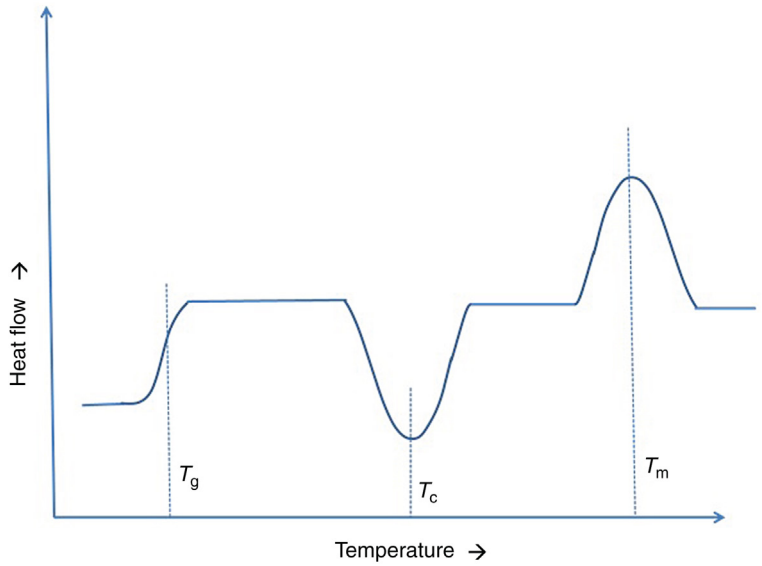

Figure 11 A representative thermogram of a polymer as recorded with the differential scanning calorimeter.

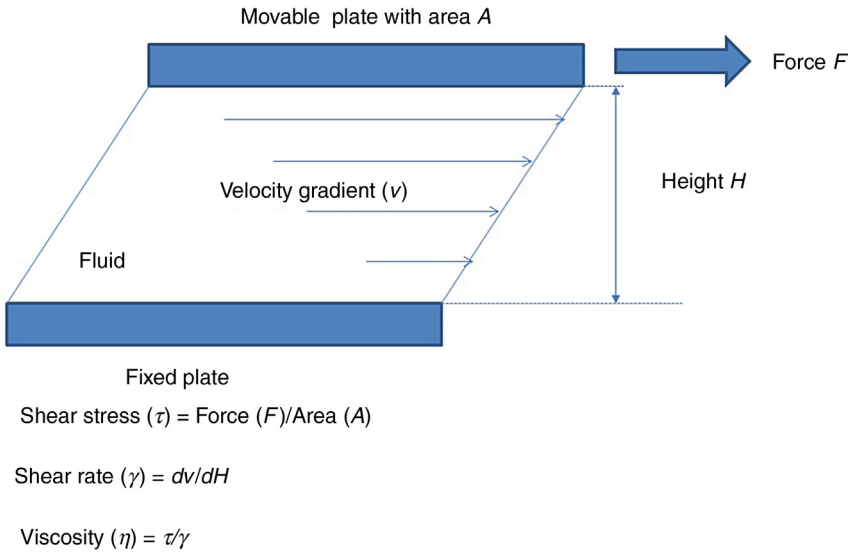

Figure 12 Depiction of fluid motion and the resultant viscosity.

A plot of stress versus the strain rate is shown in Fig. 13. The ratio of stress and shear rate is the viscosity of the system, this is the same as the slope of the stress–shear rate curve. A constant value for this slope indicates that the viscosity is independent of the shear rate and the resultant fluid is called a Newtonian liquid. When the viscosity of the liquid is dependent on the shear rate, the liquid is termed non-Newtonian. When the viscosity decreases with increasing strain rate, the liquid is shear thinning whereas if viscosity increases with increasing shear rate the liquid is shear thickening. Polymer liquids, melts, and solutions are shear thinning fluids also known as pseudoplastic fluids.

4.6.1 Viscoelasticity

Apart from being shear thinning the polymer liquids are also elastic [25,26]. Examples of their elastic behavior are apparent in phenomena such as rod climbing behavior and extrudate or die swell. In the rod climbing effect, a polymer solution stirred by a rod tends to be drawn toward the rod as opposed to being pushed away and starts rising up the rod. The effect is also known as the Weissenberg effect after Karl Weissenberg, an Austrian physicist who first observed the effect in the 1940s. Extrudate swell or die swell is another phenomenon peculiar to viscoelastic fluids. When a viscoelastic fluid is forced

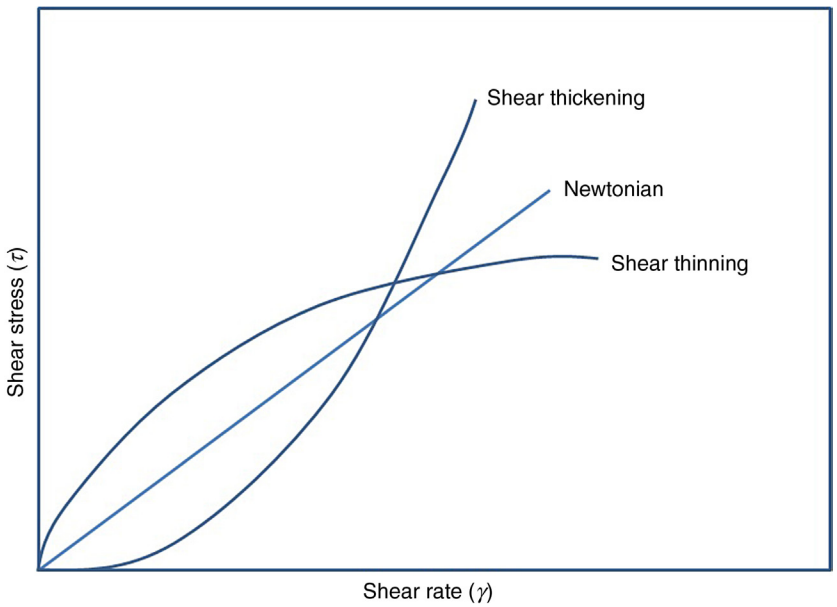

Figure 13 Illustration of different rheological behaviors.

through a narrow channel such as a die or a nozzle, the fluid swells to several times the diameter of the channel as it exits the channel. This is in contrast to a viscous fluid that demonstrates a maximum of ~13% increase in the diameter of the fluid emerging from a die [27]. The degree of swelling is dependent upon the conditions of extrusion and the molecular structure of the polymer liquid. One of the reasons for the viscoelastic nature of polymer liquids is the development of normal forces during the flow of polymer melts and solutions. When polymer melts or solutions are subjected to shearing flows, stresses perpendicular to the direction of flow are generated, these are called normal forces. Normal forces arise due to the anisotropies in the microstructure of the long molecular chains in polymers. Normal stresses can be measured by the first normal stress difference N_1, which is defined as the normal stress in the direction of flow (τ_{xx}) minus the perpendicular (τ_{yy})

$$N_1 = \tau_{xx} - \tau_{yy} \tag{16}$$

The second normal stress difference is

$$N_2 = \tau_{yy} - \tau_{zz} \tag{17}$$

Experiments show that N_1 is positive for most polymers; N_2 is negative and usually 20% of N_1 for most common polymers [25]. The positive value of N_1 as compared to the negative value of N_2 is an expression of the fact that extensive forces are positive whereas compressive forces are negative.

The viscoelastic nature of polymers also shows up in their extensional or elongation viscosity values. The extensional viscosity is the resistance of a fluid the extensional flow. For a Newtonian fluid the extensional viscosity is 3 times the shear viscosity, this relationship can be derived from the continuity equation, has been observed in many studies and is known as Trouton's law [25]. For polymeric fluids, the ratio of elongation viscosity to shear viscosity follows the Trouton's law for very small elongational shear rates. A deviation from the Trouton ratio is observed at higher shear rates usually found in polymer fluid flow situations.

The macromolecular structure is the origin of the different rheological behavior of polymers to low molecular weight fluids. Increasing shear rate allows for the longer molecules to progressively align with the direction of flow and this result in the shear thinning effects. Chain entanglement leads to the elastic effects that are visible in the flow of polymer liquids. At high shear rates, as all the chains are aligned and disentangled, the flow of the liquids tends toward a more Newtonian nature [28]. Studies [24] have indicated the different dependencies of polymer rheology on molecular structure.

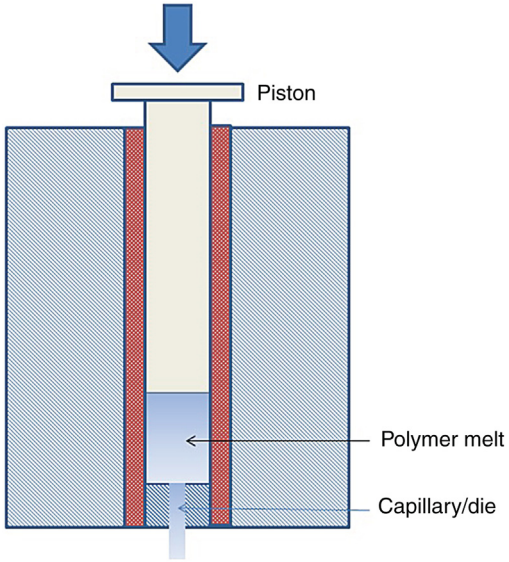

Figure 14 A capillary rheometer.

4.6.2 Rheological Measurement

Depending upon the level of shear rate of interest and the viscosity of the liquid, different techniques can be used to measure polymer rheology. Capillary rheometry involves melting polymer pellets and compacting them into a heated barrel. The melt is then pushed by a piston, descending at a controlled speed, and forced through an orifice of a defined geometry (Fig. 14). The ratio of the stress imposed by the piston and shear rate, which is a function of the speed at which the piston is traveling, is the resistance to deformation of the melt or its viscosity. The speed of the piston is usually varied in steps to obtain a shear rate dependence of the melt viscosity. A variation of the test is very common in the industry and that is melt flow index (MFI). In the MFI measurement, a fixed weight is used on the piston so only one stress and one shear rate is used and one point on the curve is obtained and reported as the MFI value of the material. The MFI value can be useful in setting the temperature on an extruder for example, but since it does not give any indication as to the shape of the curve, one cannot predict what will happen when different dies, screw speeds, etc. are used.

Another technique useful in the measurement of polymer rheology is cone–plate (or plate–plate) rheometry (Fig. 15). The polymer liquid is placed in between the cone and plate and the cone is rotated

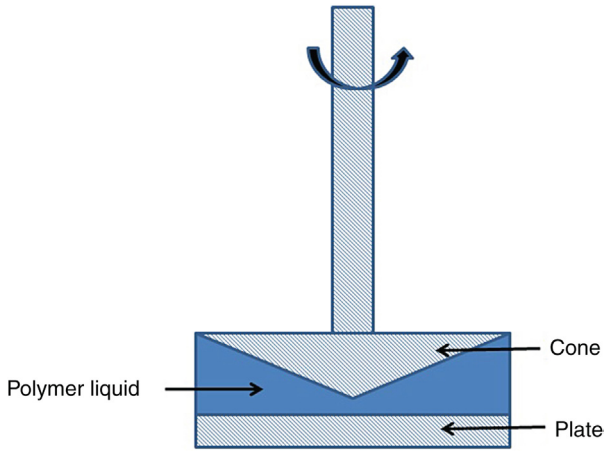

Figure 15 Cone and plate rheometer.

at a fixed speed. The torque measured as the cone is turning gives the value of the stress whereas the speed at which the cone is turning together with the cone angle is used to calculate the shear rate. The cone–plate rheometry is suitable for low shear rates whereas the capillary rheometer measures higher shear rate viscosity data. Often cone and plate rheometers are equipped with sensors to measure the normal force. The normal force during the shear flow of the rheometer produces an axial thrust pushing the cone and plate of part with the force this can be measured. The second normal stress difference can also be measured by measuring the distribution of pressure over the surface of the cone.

The measurement of elongational viscosity is considerably more difficult than the measurement of viscosity. Different devices have been developed for the measurement of elongational viscosity [17,29]. One of the devices used involves extrusion from a capillary and subsequent testing with the help of a pair of rollers (Fig. 16). Depending upon the temperature between the capillary exit and the rollers, the measurement can be true elongational viscosity if the temperature is maintained at the level where the polymer remains in a molten state or if the temperature is not maintained at the melting point, the measurement is referred to as melt strength. Melt strength is more of an engineering measure of resistance to extension. Cogswell [29] developed a method for the measurement of elongational viscosity from the excess pressure drop in a capillary rheometer.

4.7 Surface Properties

The composition of the surface of materials very often differs significantly from the make-up of the

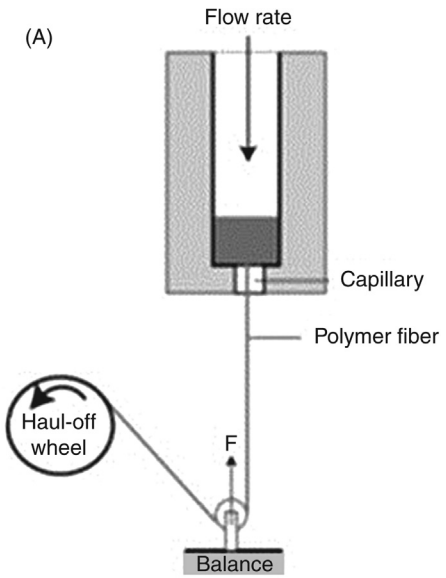

Figure 16 A haul off device connected to a capillary rheometer for extensional viscosity measurement [17]. *Courtesy: Elsevier Publications.*

bulk of the material. In many instances, the interaction of the surface of the polymer with the environment it is placed in determines its performance. This is especially true in biomedical applications where the interaction happens at the tissue–biomaterial interface and the nature of the polymer surface plays an important role in influencing this interaction. The compatibility of a polymer with the biological environment or its biocompatibility is determined by the nature of its surface. The characterization of the surface is thus an important facet of the overall testing of polymers in establishing the suitability of the material for a particular application.

Surface characterization techniques provide information on the topmost layers of the surface of the polymer. These techniques provide information on the chemical structure, chain orientation and the group mobility comprising the atomic layers of the surface of the polymer. There are limitations as to the depth and resolution of different techniques and as a result a combination of these techniques is used to obtain a complete picture of polymer surface.

The most commonly used surface characterization techniques used for polymers are based on surface microscopy including scanning electron microscopy (SEM) and atomic force microscopy (AFM), contact angle measurements and spectroscopic techniques such as attenuated Fourier transform infrared spectroscopy (ATR-FTIR), X-ray photo-electron spectroscopy (XPS), and secondary ion mass spectroscopy (SIMS) [30].

SEM is a well-known electron microscopy technique that uses electron scattering to assess and quantify the topography of the surface of any material. In this technique, the material under investigation is made a conductor through different coating techniques. The electron beam is made incident on the surface of the material and scattering of these electrons is picked up with an electron detector. SEM has potential to magnify images with a great deal of resolution measuring up to a few nanometers, the images in many cases can have resolutions more than 100 times that of an optical microscope.

In AFM, generally known as scanning probe microscopy, a finely pointed probe is attached to a cantilever and this scans the surface and picks up very small surface forces, for example molecular forces associated with chemical bonds. AFM is able to achieve very high resolutions, in the vertical plane AFM can achieve atomic level resolutions, and in the horizontal plane a resolution of 0.01 nm can be achieved.

XPS is a surface sensitive analytical technique with a depth of analysis of the order of 5–10 nm. XPS instruments operate in ultrahigh vacuums to minimize any undesirable surface contamination from occurring. X-ray photons irradiate the samples surface and cause emission of photoelectrons from near the surface region. The kinetic energy of these emitted electrons is determined and the corresponding binding energy of the electrons is calculated. From the calculated binding energies the elements present near the surface region can be determined. This can allow effective determination of the surface composition of a material.

Similar to the XPS systems, time-of-flight secondary ion mass spectrometry (ToF-SIMS) instruments also require to be operated under the clean and ultrahigh vacuum conditions. The material under investigation is irradiated with a pulsed, highly focused primary ion beam causing the emission of charged and neutral fragments from the surface and near surface region of the material. The secondary ions are mass analyzed using a time-of-flight analyzer. The resulting mass spectrum plot provides elemental, isotopic, and molecular formation of the surface of the material.

Attenuated total reflectance infrared spectroscopy (ATR-IR) is conducted by passing infrared radiation over the material's surface. ATR-IR is very sensitive to the presence of chemical bonds in the structure of the surface.

In optical contact angle (OCA) analysis, a drop of a known liquid is dispensed on to the surface of the sample being tested. The angle that the liquid makes with the surface is accurately recorded. Smaller contact angles indicate a better wettability of the surface with a higher surface energy whereas a larger contact angle indicates a lower energy surface of the material.

Table 9 Surface Measurement Techniques and Their Capabilities

Technique	Analysis Depth	Lateral Resolution
Contact angle	3–20 Å (Angstrom)	1 mm
X-ray photo-electron spectroscopy (XPS)	10–250 Å	10–150 μm
Secondary ion mass spectroscopy (SIMS)	10 Å (static) to 1 μm (dynamic)	500 Å
Scanning electron microscopy (SEM)	5 Å	1 μm
Attenuated Fourier transformed infrared spectroscopy (ATR-FTIR)	1–5 μm	10 μm

Table 9 shows the different characterization methods and a comparison of the surface depth of analysis of each method [30].

4.7.1 Polymer Adhesion

The adherence of polymers to themselves, to other polymers or to nonpolymer substrates is of primary importance in many applications. The efficiency of adhesion can be the determining factor in the use of certain polymers within different applications. Adhesion can be defined as the interaction at the interface of two surfaces at the atomic and molecular levels. There are many factors that affect this interaction; these factors include surface chemistry, surface physics, rheology, polymer chemistry, stress analysis, polymer physics, and fracture analysis [31]. The range of adhesion mechanisms that include diffusion, mechanical, molecular, chemical, and thermodynamic-based mechanisms are currently the focus of investigation in various studies [31–34]. It has been recognized that adhesion is dependent on surface characteristics of the materials in question. Research has focused on the characterization of surfaces to explain the mechanisms involved in adhesion. The surface characterization techniques have included time of flight secondary ion mass spectrometry (ToF-SIMS), XPS, AFM, SEM, ATR-IR, and other microscopic techniques (Table 9).

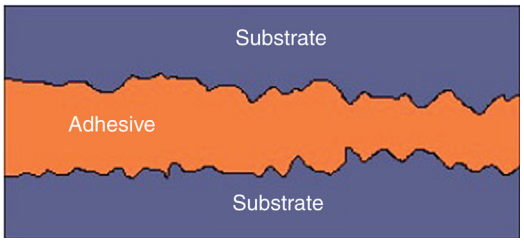

Figure 17 Illustration of mechanical coupling between two substrates [27]. *Courtesy: Elsevier Publications.*

Three main adhesion mechanisms have been identified as playing a key role in the adhesion of polymer surfaces. These three adhesion mechanisms are as follows: mechanical coupling, molecular bonding, and thermodynamic adhesion. The mechanical coupling concept is based on surface irregularities present for the interlocking between the two materials to occur. Fig. 17 illustrates the mechanical coupling concept. Several studies have shown that mechanical coupling is an important adhesion mechanism [32], however, some other studies have argued that increased surface roughness only results in the increase of surface area for other adhesion mechanisms such as molecular bonding [33]. Molecular bonding, on the other hand, is the most widely accepted mechanism for explaining adhesion in polymer surfaces. This mechanism uses dipole to dipole interactions, van der Waals forces, and chemical interactions of the ionic or covalent nature. The molecular bonding mechanism is illustrated in Fig. 18. The exact nature of the molecular bonding mechanism is not fully understood; however, the development of surface measurement techniques combined with adhesion strength measurement tests has allowed the generation of several correlations and contributed to the understanding of the molecular bonding mechanism. There has been considerable work into thermodynamic adsorption model of adhesion. The advantage of the thermodynamic mechanism over the other mechanisms is that it does not require a molecular interaction for good adhesion only equilibrium processes at the interface.

In many cases, adhesion between two surfaces is improved with the use of adhesion promoters. Chemical treatments are frequently used with the aim to create new functional groups at the interface of the two materials undergoing adhesion. Many nonpolar polymer surfaces are treated with reagents such as acids and oxidizers and these treatments increase surface polarity. The increase in surface polarity causes an increase in the molecule or forces between the substrates and hence an increase in the strength of the adhesive bond. In many cases, the surface formation of a material is dynamic, such as polyurethanes where depending on the surface environment the polar hard domains or the nonpolar soft domains can come to the surface. Generally, the nonpolar soft domain polyurethanes dominate surface when exposed to air. In such cases, a solvent of increased polarity such as dimethyl acetamide (DMAc) is used to force the hard domains to come to the surface providing polar surface for adhesion. Treatment of the material surface using plasma is a very effective way of increasing the inherently poor surface properties of polymers. It has been observed that only short plasma treatment times are required to increase the adhesion strength between two materials. Plasma treatment of surfaces induces the formation of oxygen containing

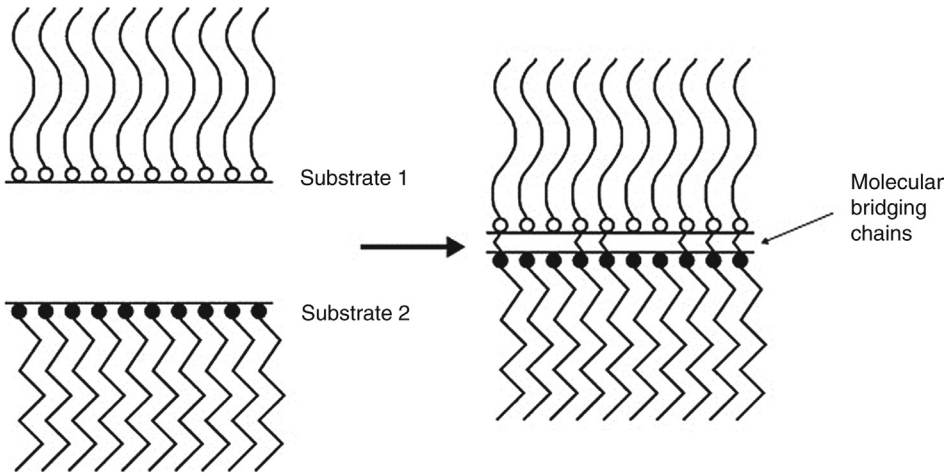

Figure 18 Schematic of the molecular bonding between substrates [27]. *Courtesy: Elsevier Publications.*

functional groups resulting in increased surface wetting and improved adhesion [34].

5 Polymer Processing

Different processing techniques are possible to fabricate the desired object. The techniques could either be based on the polymer melt or on the dissolved polymer in a solvent. The data obtained from the rheometry study can be utilized to construct a flow model of the polymer and a constitutive equation can be used to represent its flow. This constitutive equation relates the viscosity of the polymer to the shear stress, shear rate, and the temperature of operation. The constitutive equation can be more simplistic such as a power-law model [35]:

$$\tau = K\dot{\gamma}^n \tag{18}$$

$$\eta = K\dot{\gamma}^{n-1} \tag{19}$$

where τ is the shear stress in N/m^2, $\dot{\gamma}$ is the shear rate in 1/s, K is known as the flow consistency index, n is the dimensionless power-law constant, and η is the viscosity, the SI unit of which is Pascal $\times$ seconds (Pa.s).

Using the power-law model for $n = 1$, the fluid is Newtonian, for $n < 1$, the fluid is shear thinning and for $n > 1$, the fluid is shear thickening.

Or various more complicated forms that model the flow behavior more accurately, such as a Carreau model [35,36];

$$\eta = \eta_\infty + (\eta_0 - \eta_\infty)(1 + (\lambda\dot{\gamma})^2)^{\frac{n-1}{2}} \tag{20}$$

where η is the viscosity, $\dot{\gamma}$ is the shear rate, λ is the relaxation time of the fluid in s, n is the dimensionless power-law constant, η_∞ is the value of viscosity at an infinite shear rate, and η_0 is the viscosity at zero shear rate.

These equations can be used in combination with the basic equations of flow to simulate the processes of polymer processes. The simulations [37,38] are very helpful in determining the design of the processing equipment and the processing conditions to be used for a plastic to obtain the desired product.

5.1 Melt Processing

Melt processing techniques are primarily based on variations of extrusion and molding. Extrusion is a two-dimensional manufacturing operation where the output is a continuous profile. In extrusion, plastic pellets or granules are loaded into a hopper, then fed into a metallic, cylindrical, heated chamber, in the chamber or the barrel, a continuously rotating screw pushes the plastic forward (Fig. 19).

The plastic is melted by a combination of heat from heaters on the barrels and the mechanical work done due to the rotating screw. At the end of the extruder, the molten polymer is forced out through an orifice or a die to shape the finished product. As the plastic product exits from the die, it is cooled by air or water. Many plastic products requiring a continuous form such as pipes, tubes, fibers, and films are made by extrusion processing. Extrusion of plastics to convert them to fiber is achieved by a process termed melt spinning. In melt spinning, the molten plastic is forced through narrow die holes called spinnerets, cooled by a blast of air as they emerge from the spinneret and subsequently drawn over heated rolls to produce fibers.

Molding, on the other hand, is a three-dimensional manufacturing operation that transforms plastic pellets into discrete articles. As opposed to extrusion, molding is not a continuous operation and the output is limited to a number of articles per unit time. The most commonly used molding technique is the injection molding operation. Just like in extrusion, injection molding involves feeding plastic pellets into a

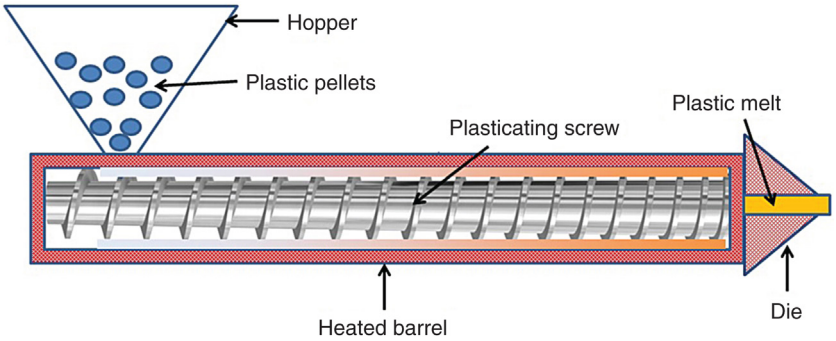

Figure 19 Plastic extrusion process.

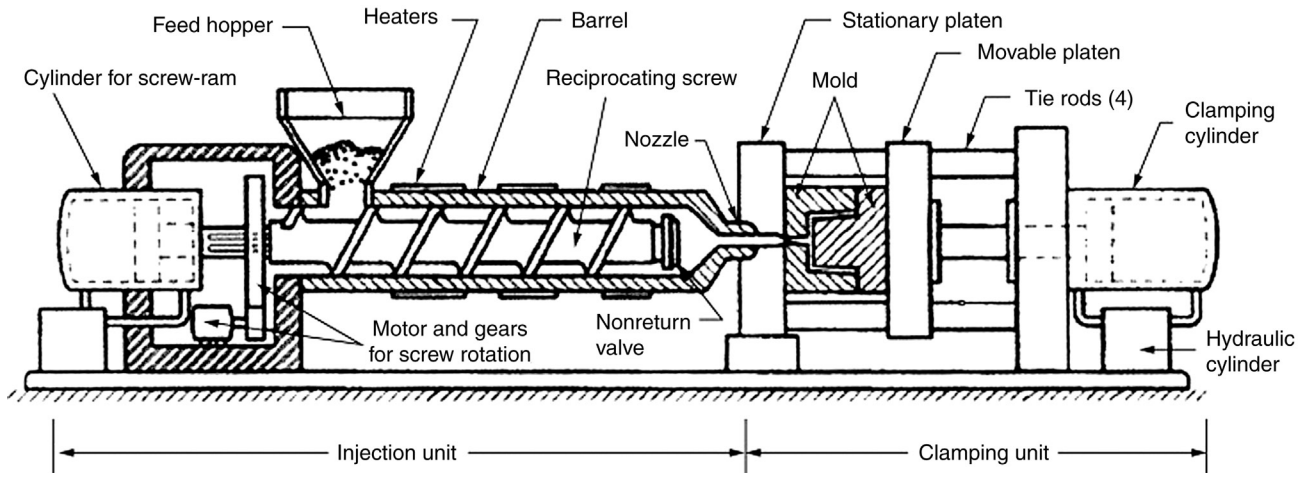

Figure 20 Plastic injection molding process [38]. *Courtesy: Elsevier Publications.*

barrel-screw arrangement where the solid plastic is converted to a melt with the action of heat coming from the barrel walls and mechanical action. In contrast to extrusion, the screw is reciprocating (Fig. 20) and that enables the machine to force the molten polymer into a mold.

The mold is shaped in the form of the article desired and the molten polymer takes the form of the mold. The mold is also equipped with a cooling circuit that cools the molten material to a solid and subsequently the solid is ejected from the mold in the shape of the final article. Injection molding pushes the melt into the mold through narrow channels consisting of a sprue, runner, and gate arrangement. This forcing of the melt happens with a high shear rate and the values measured in the high shear rate regime in rheometry are very relevant for injection molding. Extrusion, on the other hand, utilizes lower shear rates so the data at lower shear rates are more relevant for extrusion.

5.2 Solution Processing

Polymers are soluble in certain solvents. The solubility of a particular polymer in a solvent depends upon the chemical nature of the polymer as described earlier. This property is used in solvent processing. The solution viscosity is dependent on the concentration of the polymer in the solvent as well as the molecular weight of the polymer. The fabrication of a component occurs by processes such as dip coating, casting, or spraying. Solvent processing also occurs at low shear rates; here the plastic dissolved in an appropriate solvent is fabricated into the right shape. The part is then placed in an oven to flash off the solvent and obtain the final article.

In the use of solvent coating for the production of coated surfaces or thin films, the most important dimension is usually the thickness of the coating; this process can therefore be looked upon as a one-dimensional process. The first step in solvent coating is the preparation of the substrate. The surface of the substrate to be coated needs to be treated to both clean the surface and improve the wettability by the polymer solution [30]. The quality of the surface of the substrate directly affects the efficiency of the coating operation. Treatment of the surface with chemical etching [30] may be required prior to coating. The subsequent step in the coating process is the actual application of the polymer solution to the substrate. The coating process could be a static contact of the solution or involve a flow of the solution over the substrate. The thickness of the coating is determined by factors such as:

- Concentration of the polymer in the solvent
- Contact time of the solution and substrate
- Process temperature

The coated product is then placed in an oven to remove the solvent. The time of evaporation of the solvent is dependent on the solvent concentration, temperature of the oven, pressure or vacuum applied in the oven, and the thermal properties of the solvent including its boiling point.

Solvent processing can also be used to produce polymeric fibers, a two-dimensional product. The polymer solution can be forced through a spinneret

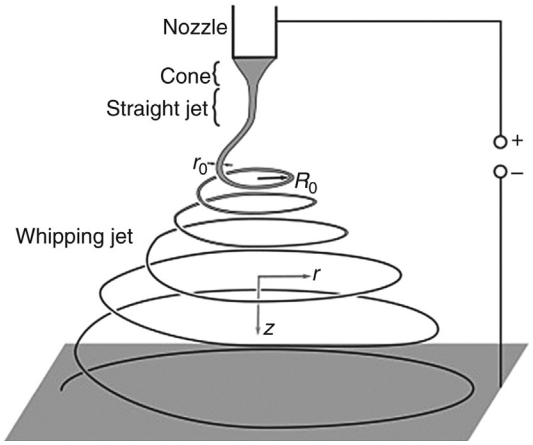

Figure 21 Schematic representation of an electrospinning device and a polymer jet [39]. *Courtesy: Elsevier Publications.*

and form fibers. As the polymer solution emerges from the spinneret, the solvent can be removed either by submerging the solution in a bath of nonsolvent or by achieving solidification by evaporating the solvent in a stream of inert, heated gas. The process of submerging the solution in a nonsolvent bath to precipitate the polymer is known as wet spinning whereas the process where the solvent is evaporated is known as dry spinning. A process that is used to produce nanometer sized fibers is electrospinning (Fig. 21). Electrospinning uses electric force to draw charged threads of polymer solutions [39]. When sufficiently high voltage is applied, the liquid droplet becomes charged to the extent that it can counteract the forces of surface tension and form a continuous fiber. As the liquid stream travels to the fiber collection point, the solvent is evaporated. The fiber diameters produced in the electrospinning process are in the order of 10 nm [39]. Electrospinning can be used for polymer melts as well, especially for polymers that are hard to dissolve such as PP and PE terephthalate. However, due to the high viscosity of polymer melts, the size of the electrospun fibers is larger than with polymer solutions.

6 Medical Devices and Plastics

Plastics have an inherent advantage over traditionally used materials, such as glass and metals, in medical devices. Plastics are lightweight, inexpensive, and often compatible with bodily fluids. Most plastics are also comparable in density to the body and thus are easier to be incorporated into the body. They, for the most part, also have a high degree of resistance to chemicals, both natural and synthetic, that make them suitable to be used in medical applications.

Plastics can also be formulated with a myriad of different chemistries. They can be soft or hard, elastomeric or rigid, thermoplastic or thermoset, etc.

They can also be formulated as biologically stable or degradable. A stable formulation is one that can resist the action of body fluids and can be inert, making them suitable for the construction of long-term implants. A degradable formulation, on the other hand, can be broken down into easily digestible and harmless elements over time. The degradation can be programmed to occur either at a specific time or upon a specific action. This makes biodegradable plastics attractive options in areas such as drug-device combinations and regenerative medicine.

The use of plastics in medical applications spans a wide spectrum of applications. Many plastics form a part of medical disposables such as wipes, bandages, syringes, tubes, blood bags, packaging materials, etc. As the name suggests, these are discarded after a single use in a medical procedure. They do come in short-term contact with medicines and/or the human body.

The use of plastics has revolutionized the area of medical diagnostics. Whether it be in simple blood pressure measurement devices or the much more complex magnetic resonance imaging (MRI) machines, plastic materials offer many advantages in the construction of this equipment such as design flexibility, light weight, robustness, etc., this has enabled the doctors to diagnose the patient's condition accurately and monitor the progress of any condition. Often these diagnostic equipment work outside the body and remain external. However, there are diagnostic systems that work inside the body; these are usually introduced inside the body with the aid of plastic tubes known as catheters. Internal devices used in the area of cardiovascular diagnostics are described later in the chapter on the applications of plastics in cardiovascular devices.

The majority of medical devices are made to be implantable systems. These devices are implanted inside the human body and perform critical functions either in the area of drug delivery or regulation of some bodily function. Plastics form the core of many of these devices, and the properties of the plastic material allow greater functionality of the device.

The implantable devices are further divided into short-term implantable and long-term implantable devices depending on the duration of the dwell time of

the implantable device inside the body. Most devices shorter than a 90 day dwell time are classified as being short-term implants. Biological stability becomes an important consideration for long-term implantables.

6.1 Biocompatibility

A material is said to be biocompatible when the material does not elicit any undesirable response from the body upon coming in contact with the elements of the body. By generating a beneficial response from the cellular or tissue structures, the material allows the appropriate function of the implanted device that the material either makes up or supports.

Depending on the duration of the implant and its function different demands are placed on the characterization techniques for biocompatibility. The details are given in the international standards document ISO 10993 [40]. Some of the basic tests of biocompatibility include quantification and identification of any leachables from the material, the response of the cells in contact with the material (cytotoxicity) and the response of the genes in contact with the material (genotoxicity). These tests are described in more detail in the chapter on the biological properties of plastics.

6.2 Biostability

The ability of a material to withstand the biological environment within the human body is termed as the biostability of the material. Upon implantation of a medical device inside the body, the body's immune system immediately responds to the new object and treats it as a foreign object [41]. As a result, different active species aided by enzymes attack the foreign object. In addition, the material also has to withstand the hydrolytic environment within the body. The response of the material to these environments determines the degree of biostability of a material. The biostability of a plastic determines the suitability of a material to be used in implantable devices.

The best measure of biostability for a plastic is the actual data coming from clinical studies. However, there needs to be an indication of how the plastic will behave under the conditions of the bodily environment especially with a new material. Animal trial is one method to ascertain material performance in in vivo conditions. An appropriate animal model is chosen for the trial and either the finished device or the plastic on its own is implanted.

Several researchers [41–45] have also worked on the development of a representative laboratory or in vitro test to replicate the in vivo conditions. Many methods also try to accelerate the tests to get confidence of the long-term performance of the material in the body [41,44–50]. It has been frequently noted that in vitro tests in general and accelerated in vitro tests in particular do not correspond to results from in vivo conditions and this has been attributed to the complexity of body environment and the inadequacy of in vitro models in successful replication. The biostability tests are further described in the chapter on the biological properties of plastics.

References

[1] A. Ravve, Principles of Polymer Chemistry, Springer, 2000.
[2] A.L. Andrady, M.A. Neal, Applications and societal benefits of plastics, Phil. Trans. R. Soc. Lond. B 364 (1526) (2009) 1977–1984.
[3] R.C. Thompson, S.H. Swan, C.J. Moore, F.S. vom Saal, Our plastic age, Phil. Trans. R. Soc. Lond. B. 364 (1526) (2009) 1973–1976.
[4] Plastics Fact Sheet, Society of Plastics Industry (SPI), 2012.
[5] Plastics News, Plastics and Rubber World (PRW), September 2013.
[6] W.H. Carothers, Studies on polymerization and ring formation. I. An introduction to the general theory of condensation polymers, J. Am. Chem. Soc. 51 (8) (1929) 2548–2559.
[7] P.J. Flory, Principles of Polymer Chemistry, Cornell University Press, (1953) p.39.
[8] J.M.G. Cowie, Polymers: Chemistry and Physics of Modern Materials, CRC Press, (1991).
[9] G. Odian, Principle of Polymerization, John Wiley and Sons, (1981).
[10] C.E. Carraher, R.B. Seymour, Seymour/Carraher's Polymer Chemistry. CRC Press. pp. 43–45.
[11] G.W. Ehrenstein, R.P. Theriault, Polymeric Materials: Structure, Properties, Applications, Hanser Verlag, (2001) pp. 67–78.
[12] W. Weissbach, Materials Science and Materials Testing, Vieweg+Teubner Verlag, (2007).
[13] N.A. Plate, Problems of polymer modification and the reactivity of functional groups of macromolecules, Pure Appl. Chem. 46 (1) (1976) 49–54.
[14] L.C. Sawyer, D.T. Grubb, G.F. Meyers, Polymer Microscopy, Springer, (2008) p. 5.

[15] D. Lee, T.A. Speckhard, A.D. Sorensen, S.L. Cooper, Methods for determining the molecular weight and solution properties of polyurethane block copolymers, Macromolecules 19 (9) (1986) 2383–2390.
[16] ASTM D2857: Standard Method of Test for Dilute Solution Viscosity of Polymers, 21 CFR 177.2210(b).(3).
[17] S. Hashmi, G. Batalha, C. Van Tyne, B. Yilbas, Comprehensive Materials Processing, Elsevier, Oxford, (2014) vol. 1, pp. 35-70.
[18] W. Woishnis, S. Ebnesajjad, Chemical Resistance of Thermoplastics, Elsevier, 2011.
[19] J. Brandrup, E. Immergut, Polymer Handbook, Wiley, New York, (1989).
[20] G. Yilmaz, O. Kalenderli, Turk Siemens Kablo ve Elektrik Sanayii AS, Bursa, Electrical Insulation Conference, and Electrical Manufacturing & Coil Winding Conference Proceedings, 1997.
[21] T. Liang, Y. Makita, S. Kimura, Effect of film thickness on the electrical properties of polyimide thin films, Polymer 42 (11) (2001) 4867–4872.
[22] S.-W. Lee, H. Kim, F.G. Shi, B. Zhao, Thickness dependent soft-breakdown phenomena of low dielectric constant thin films and corresponding activation energy, Microelectron. J. 33 (8) (2002) 605–608.
[23] T. Alfrey, Jr, H.C. Haas, C.W. Lewis, The dehalogenation reaction. I. dechlorination of vinyl chloride/vinyl acetate copolymers 1. J. Am. Chem Soc., 73 (6) (1951) 2851–2853.
[24] N. Wakiya, J-W Moon, T. Kiguchi, K. Shinozaki, N. Mizutani, Applications of Ferroelectrics, ISAF 98. Proceedings of the Eleventh IEEE International Symposium, 1998, pp. 97–100.
[25] J.D. Ferry, Viscoelastic Properties of Polymers, John Wiley & Sons, (1980).
[26] M.A. Meyers, K.K. Chawla, Mechanical Behavior of Materials, Cambridge University Press, Cambridge, 1999, pp. 98–103.
[27] P.C. Hiemenz, T. Lodge, Polymer Chemistry, second ed., CRC, Boca Raton, (2007).
[28] S.A. Baeurle, A. Hotta, A.A. Gusev, Polymer 47 (2006) 6243–6253.
[29] F. Cogswell, Polymer Melt Rheology, G. Godwin in association with Plastics and Rubber Institute, London, (1981).
[30] N. Lamba, K. Woodhouse, S. Cooper, Polyurethanes in Biomedical Applications, CRC Press, (1998).
[31] F. Awaja, M. Gilbert, G. Kelly, B. Fox, P. Pigram, Adhesion of polymers, Prog. Polym. Sci. 34 (9) (2009) 948–968.
[32] W. Wake, Adhesion and the Formulation of Adhesives, Applied Science Publishers, London, (1982).
[33] G. Akovalı, The Interfacial Interactions in Polymeric Composites, Kluwer Academic, Dordrecht, (1993).
[34] J. Rivière, S. Myhra, Handbook of Surface and Interface Analysis, Marcel Dekker, New York, (1998).
[35] J.-M. Piau, J.-F. Agassant (Eds.), Rheology for Polymer Melt Processing, Elsevier, Amsterdam, 1996.
[36] J.L. White, Principles of Polymer Engineering Rheology, John Wiley & Sons, (1990).
[37] Moldflow Design Guide: A Resource for Plastics Engineers, vol. 10, Jay Shoemaker Hanser, 2006.
[38] W.G. Frizelle, Injection Molding Technology. Applied Plastics Engineering Handbook, second ed., Oxford, UK, (2016) pp. 191–202.
[39] R. Stepanyan, A. Subbotin, L. Cuperus, P. Boonen, M. Dorschu, F. Oosterlinck, M. Bulters, Nanofiber diameter in electrospinning of polymer solutions: model and experiment, Polymer 97 (2016) 428–439.
[40] ISO 10993-1:2009 Biological evaluation of medical devices—Part 1 Evaluation and testing within a risk management process.
[41] J.M. Anderson, A. Hiltner, M.J. Wiggins, M.A. Schubert, Recent advances in biomedical polyurethane biostability and biodegradation, Polym. Int. 46 (1998) 163–171.
[42] K. Stokes, A. Coury, P. Urbanski, Auto-oxidative degradation of implanted polyurethane devices, J. Biomater. Appl. 1 (1987) 411–448.
[43] M.J. Wiggins, B. Wilkoff, J.M. Anderson, A. Hiltner, Biodegradation of polyether polyurethane inner insulation in bipolar pacemaker leads, J. Biomed. Mater. Res. A 58 (2001) 302–307.
[44] Q.H. Zhao, A.K. McNally, K.R. Rubin, M. Renier, Y. Wu, V. Rose-Caprara, J.M. Anderson, A. Hiltner, P. Urbanski, K. Stokes, Human plasma α2-macroglobulin promotes in vitro oxidative stress cracking of Pellethane 2363-80A: in vivo and in vitro correlations, J. Biomed. Mater. Res. A 27 (1993) 379–389.
[45] E.M. Christenson, J.M. Anderson, A. Hiltner, Biodegradation mechanisms of polyurethane elastomers, Corros. Eng. Sci. Technol. 42 (2007) 312–323.

[46] G. Gallagher, R. Ries, K. Cobian, M. Ebert, R. McVenes, Biostability of a new cardiac lead insulation material: PurSil 35, The Materials and Processes for Medical Devices (MPMD) Conference and Exposition of the ASM 2011. Online abstract. Available from: https://asm.confex.com/asm/mpmd11/techprogram/paper_28242.htm

[47] B. Ward, J.M. Anderson, R. McVenes, K. Stokes, In vivo biostability of polysiloxane polyether polyurethanes: resistance to biological oxidation and stress cracking, J. Biomed. Mater. Res. A 77 (2006) 580–589.

[48] K.A. Chaffin, A.J. Buckalew, J.L. Schley, X. Chen, M. Jolly, J.A. Alkatout, J.P. Miller, D.F. Untereker, M.A. Hillmyer, F.S. Bates, Influence of water on the structure and properties of PDMS-containing multiblock polyurethanes, Macromolecules 45 (2012) 9110–9120.

[49] C.D. Han, J.K. Kim, On the use of time-temperature superposition in multicomponent/multiphase polymer systems, Polymer 34 (1993) 2533–2539.

[50] A. Padsalgikar, E. Cosgriff-Hernandez, G. Gallagher, T. Touchet, C. Iacob, L. Mellin, A. Norlin-Weissenrieder, J. Runt, Limitations of predicting in vivo biostability of multiphase polyurethane elastomers using temperature-accelerated degradation testing, J. Biomed. Mater. Res. B 103 (1) (2015) 159–168.

2 Commodity Plastics in Cardiovascular Applications

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1 Introduction

The commodity plastics used in cardiovascular applications that are considered in this text are as follows:

- Polyolefins
  - Polyethylene
  - Polypropylene
- Polyethylene terephthalate (PET)
- Polyamides (PAs)
  - Nylons
  - Polyether block amide

Polyolefins have a long history of study and usage [1–4]. Polyolefins can be further divided into the most frequently used individual plastics of polyethylene and polypropylene. Polyethylene themselves are available in different structural forms and varying densities as high density polyethylene (HDPE), low density, and linear low density polyethylene (LLDPE) [5]. Polyolefins in general are the most widely used plastic and hence the materials right from their manufacturing to their structure, properties, and processing have been widely researched [1–10]. Polyolefins are used in numerous applications within the medical field, in the disposable devices and outside the body applications such as syringes, containers, and packaging [11,12]. In the cardiovascular area, polyolefins are used in introducers, catheters, catheter linings, and permanent sutures [12–15]. PET is the most common thermoplastic resin of the polyester family and finds varied usage in the areas of textiles, films, and packaging and are well studied plastics [16–18]. In the cardiovascular field PET is used in vascular grafts and sutures [14,19]. PAs are plastics with the basic amide linkage and can have a range of properties and applications based on the components of the chains preceding and following the amide linkage [20,21]. A range of different polymers both natural and synthetic are possible with the amide linkage [21,22]. A series of nylon blends and block copolymer formulations can be generated from the PA linkage having varied properties and applications [20–25]. In the cardiovascular area PAs find use as catheters, balloon catheters, and sutures [14,19]. As would be expected there are a number of suppliers that manufacture and supply these commodity plastics; however, many of them have restrictions for medical usage, especially usage inside the body. Careful evaluation of these plastics is necessary using the techniques described in Chapter 4 to determine the biological properties of plastics. The evaluation will obviously depend on the application of the plastic, that is, the location and duration of the device containing the plastic in the body.

There are other plastics that are also used in certain medical applications; poly vinyl chloride (PVC) is widely used and within the cardiovascular sector it is used as catheters, luers, connectors and disposables. Concerns about the use of PVC are primarily based on the additives, especially plasticisers, that are used in the formulation of PVC. These additives tend to leach out during the application period and have been shown to be toxic under certain circumstances. As a result the use of PVC within the medical devices area is decreasing and alternative materials for replacement are being considered. Styrenic polymers are also used for different applications, in some cases as polystyrene but usually as co-polymers of styrene with butadiene and ethylene.

2 Polyolefins

An olefin is a hydrocarbon that is unsaturated or contains at least one carbon–carbon double bond. An olefin is also known as an alkene or an olefin and these terms are used interchangeably. Acyclic olefins with only one double bond and no other functional groups form a series of hydrocarbons with the general formula C_nH_{2n}, ethylene is the simplest olefin with the formula C_2H_4, and propylene has the formula C_3H_6. Polymerization of olefins leads to the formation of polyolefins, ethylene can be polymerized to polyethylene, and propylene can be polymerized to polypropylene. Polymerization of olefins follows an addition, chain growth mechanism, and either through a free radical or ionic mechanism.

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2.1 Polyethylene

Polyethylene is the most common plastic with its annual usage in the excess of 80 million metric tons [26]. Polyethylene is made with different processes and produces different polymeric chain structures and their associated densities of packing.

The main raw material for the manufacture of all polyethylenes is ethylene. The molecular formula for ethylene is shown in Fig. 1.

The angle between the carbon and hydrogen atoms in ethylene is 121.3°. The distance between the carbon atoms is 133.9 pm (1 pm = 1×10^{-12} m) and the distance between the carbon and hydrogen atoms is 108.7 pm. The double bond in ethylene is a region of high electron density and thus is susceptible to attack by electrophilic compounds. Electrophilic addition is the main reaction pathway for ethylenes [4].

Ethylene is a colorless, flammable gas with the faint sweet odor. The raw material for the manufacture of ethylene is petroleum. The industrial route to make ethylene comprises steam cracking of hydrocarbons and subsequently separating ethylene through a series of compression and distillation steps.

The conversion of ethylene to polyethylene was first discovered in the 1930s by chemists at the Imperial Chemical Industries (ICI) in England. A high-pressure process was developed to convert ethylene into a white, waxy substance. This became the basis for the process of making low density polyethylene (LDPE) on an industrial scale. Work in the 1950s focused on the development of catalysts for this process of conversion of ethylene to polyethylene at more favorable conditions [4,7]. Chemists at Phillips Petroleum developed a chromium-based catalyst that worked in the conversion of ethylene to polyethylene at pressures and temperatures lower than what was developed by the ICI chemists. A few years later a German chemist, Ziegler, developed another catalyst based on titanium halides and organo-aluminum that worked at even milder conditions than the Phillips catalyst [27]. Both the Ziegler and the Phillips catalysts are used in the industrial production of polyethylene on a wide scale. The development of soluble catalysts known as Metalocenes in the 1970s has expanded the range of polyethylenes in terms of their densities and copolymerizations with other olefins [1,27].

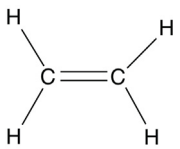

Figure 1 Molecular formula for ethylene.

2.1.1 Synthesis of Polyethylene

Polyethylene is made by the addition polymerization of ethylene as depicted in the following equation [4]:

$$n\mathrm{C_2H_4} \rightarrow [\text{—}\mathrm{CH_2}\text{—}\mathrm{CH_2}\text{—}]_n \quad \Delta H = -92\ \mathrm{kjmol^{-1}}$$

There are two traditional routes to manufacture polyethylene: a high-pressure route and the low-pressure route. In the high-pressure process, a lower density product is formed whereas the lower pressure process leads to the manufacture of a higher density product. Therefore, LDPE is formed with the high-pressure process and HDPE is formed using the low-pressure process. The difference between these two processes is outlined as follows.

In the high-pressure process, ethylene of >99% purity is compressed and added to the reactor with an initiator. The initiator used is either small amount of oxygen and/or organic peroxide. Radical polymerization proceeds and converts ethylene to polyethylene. The process is operated at very high pressures of 1000–3000 atm and at temperatures of between 150 and 300°C [28–30].

The reaction scheme and the resulting kinetics of the high-pressure process is a series of reaction steps, namely,

- Initiator decomposition
- Radical chain propagation
- Chain transfer to monomer and to modifier
- Intra- and intermolecular chain transfer
- Scission of secondary radicals, and
- Chain termination

These steps can be depicted as a series of reactions as shown in the following where I is the initiator, R is the radical, M is the monomer which in this case is ethylene, and P is the polymer or polyethylene.

$$\mathrm{I} \xrightarrow{k_d} 2.\,\mathrm{R_I}\ \text{Initiator decomposition}$$

$$\mathrm{R_I} + \mathrm{M} \xrightarrow{k_I} \mathrm{M_I}\ \text{Initiation}$$

$$\mathrm{M_I} + \mathrm{M} \xrightarrow{k_p} \mathrm{M_{I+1}}\ \text{Propagation}$$

$$\mathrm{M_I} + \mathrm{M_{I+N}} \longrightarrow \mathrm{M_{N'}}\ \text{Termination}$$

Two differently operated high-pressure processes, the autoclave and tubular reactors are used in the synthesis of LDPE [31]. A higher conversion rate can be achieved in tubular reactors as compared to the autoclave process. The conversion in tubular reactors is around 40% in contrast to around 25% in autoclave

reactors. Molecular weight of the resultant LDPE chains can be controlled by adding chain transfer agents such as saturated hydrocarbons, α-olefins, ketones, or aldehydes to the reaction [28–31]. At the end of the process the molten polyethylene is fed into an extruder and pelletized. The unreacted ethylene is recycled back. The resultant product contains anywhere between 4000 and 40,000 ethylene units and many attached branches.

A lower pressure in the process of making polyethylene is essentially achieved by the use of an appropriate catalyst system. The lower pressure enables the production of a higher density product as the material has much less branches attached to the main chain and HDPE is the result of a low-pressure process. The Phillips catalyst and the Ziegler catalyst are typically used in the manufacturing process [29]. An inorganic compound such as chromium oxide on a silica bed is an example of a Phillips catalyst system, the Ziegler catalyst is an organometallic compound and an example is a titanium halide with an aluminum alkyl. Using pressures in the range of 10–80 atm, temperatures in the range of 70–300°C, and in the presence of either catalyst systems three different kinds of processes are used to produce HDPE [4]. The slurry process, the solution process, and the gas phase process are the three different kinds of processes that are used to produce HDPE. In the slurry process, the Ziegler catalyst is mixed with the liquid hydrocarbon; this mixture forms a slurry. Gaseous ethylene is then pumped under pressure into the slurry; ethylene is polymerized to polyethylene in the slurry. Subsequently the hydrocarbon solvent is evaporated and HDPE is recovered. Similar to the slurry process is the process where the catalyst system is soluble in a solvent. The catalyst system is soluble in a higher molecular weight hydrocarbon solvent as compared to the hydrocarbon used for the slurry process. The reaction in a solvent system proceeds similarly to a slurry process and at the end of the reaction the solvent is evaporated and the polymer recovered. In a gas phase process, a mixture of ethylene and hydrogen is passed over a Phillips catalyst in a fixed bed reactor [4]. Ethylene polymerizes to form grains of HDPE, suspended in the flowing gas, which pass out of the reactor when the valve is opened. The HDPE powder coming out of any of the reactors discussed previously is separated from the diluent or solvent (if used) and is extruded and cut up into pellets. A process where a small amount of a different monomer is mixed with ethylene during polymerization can lead to the production of branching in the polymer chains. This comonomer process can result in the manufacture of lower density polymer using a low-pressure process and as a result lower densities than HDPE can be obtained. The comonomers typically used are butene and hexene. This process produces branches that are much smaller in length than the high pressure process and therefore are much more linear structure results. The polymer produced in this process is known as linear low density polyethylene (LLDPE). LLDPE is more resilient, tear resistant, and flexible compared to the low density system and is preferred in many applications. A newer process to produce LLDPE is by use of metallocene catalysts; these catalyst systems are more specific than the older systems [3]. These specific systems are more efficient in control of the chain length and chain structure. The materials produced with metallocene catalysts are superior in their properties and preferred for some applications especially packaging.

2.1.2 Properties of Polyethylene

The properties of polyethylenes are controlled by average molecular mass, molecular mass distribution, the degree of short chain branching, and comonomer composition distribution. These are directly a reflection of the technique used for polymerization, catalyst system employed, and the process reaction conditions [3].

The molecular weight distribution of polyethylene polymers is dependent on the catalyst system used during the manufacturing process. Chromium-based Phillips and titanium-based Ziegler catalysts are multisite catalysts, whereas metallocene catalysts are referred to as single-site catalyst systems. Standard multisite catalysts generate polyethylene with narrow to broad molecular mass distributions. The polydispersity index, that is, the ratio of weight average molecular weight to number average molecular weight $M_w/M_{n,}$ of polyethylenes produced by Phillips- and Ziegler-type catalysts vary between the values of 4 and 12. In contrast, metallocene catalysts produce PE with a narrow molecular mass distribution with a polydispersity index values less than 4 [3,4].

LDPE has a density range of 0.910–0.940 g/cm^3. Owing to its high degree of short and long chain branching, the polymer chains do not pack into the crystal structure as well. It has therefore weaker intermolecular attractive forces as the instantaneous-dipole induced-dipole attraction is less. This results in a lower tensile strength and increased elongation at break. The properties of LDPE are characterized by its molecular morphology specifically its molecular weight and branching structure. The short and long chain branches formed on the main chain of LDPE have a statistical distribution formed during the intra- and intermolecular radical transfer reactions. The high degree of branches with long chains gives molten LDPE unique and desirable flow properties.

Table 1 Physical Properties of Low Density Polyethylene

LDPE Physical Properties	Value
Tensile strength	12–15 MPa
Notched impact strength	No break
Thermal coefficient of expansion ($\times 10^{-6}$ K^{-1})	100–220 $\times$ 10^{-6}
Max. continued use temperature	65°C (149°F)
Melting point	110°C (230°F)
Glass transition temperature	−125°C (−193°F)
Density	0.910–0.940 g/cm^3

LDPE, low density polyethylene.

Polymer properties are correlated to the temperature and pressure during polymerization and by controlling these values the molecular structure and the resultant polymer properties can be tuned.

The main properties of LDPE can be summarized as; semirigid, translucent, tough, good chemical resistance, low water absorption, thermoplastic, and easily processed by most methods. Some representative values are given in Table 1.

HDPE is defined by a density of greater than or equal to 0.941 g/cm^3. HDPE has a low degree of branching and thus stronger intermolecular forces than LDPE. This results in higher tensile strength as compared to its lower density counterparts.

The main properties of HDPE can be summarized as: flexible, translucent/waxy, weatherproof, good low temperature toughness (to −60°C), easy to process by most methods, low cost, and good chemical resistance (Table 2).

Table 2 Physical Properties of High Density Polyethylene

HDPE Physical Properties	Value
Tensile modulus (MPa)	750–1500
Tensile strength at yield (MPa)	18–28
Thermal coefficient of expansion (x10^{-6} K^{-1})	100–220 $\times$ 10^{-6}
Max. continued use temperature	65°C (149°F)
Melting point (°C)	128–135
Density	0.941–0.965 g/cm^3

HDPE, high density polyethylene.

To a great extent the length of the polymer chains and their organization, that is, the molecular weight and the % crystallinity, play the most significant roles in the determination of the properties of HDPE [3]. Typical for all HDPE resins are opposite dependencies in the mechanical properties. Material stiffness or Young's modulus, and tensile strength are opposite to environmental stress crack resistance (ESCR) and material toughness or impact properties. The challenge of product development is to achieve the best balance of properties meeting all the needs of the application the material is subjected to.

2.2 Polypropylene

The molecular formula for propylene is shown in Fig. 2.

The difference between ethylene and propylene is the presence of the additional methyl group. Similar to ethylene, propylene is a colorless gas at room temperature and atmospheric pressure; however, the presence of the methyl group gives propylene additional molecular mass and it has a higher boiling point than ethylene in its liquid form.

Propylene, like ethylene, is a by-product of oil refining [1,2]. A major source of propylene is naphtha cracking; during the cracking process, ethylene, propylene, and other compounds are produced as a result of refining larger hydrocarbon molecules to produce lower molar mass hydrocarbons. Propylene can subsequently be separated by fractional distillation from hydrocarbon mixtures obtained from cracking. Owing to the presence of the methyl group, the double bond present between the carbon atoms is especially weak and relatively easy for the polymerization into polypropylene.

2.2.1 Synthesis of Polypropylene

Polymerization of propylene to polypropylene was first attempted in the 1950s by different chemists at Phillips Petroleum, Italian chemist Giulio Natta

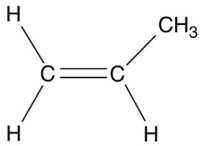

Figure 2 Molecular formula for propylene.

and German chemist Karl Rehn. First commercial production of polypropylene was started by the Italian firm Montecatini in 1957 [1,9]. Traditionally, two main processes are used for the conversion of propylene into polypropylene; these are the bulk or bulk slurry process and the gas phase process. The development of a combination catalyst, the Ziegler–Natta catalyst, was essential for the progress of the industrial application of the polymerization of propylene to polypropylene. The Ziegler–Natta catalyst is formed by the interaction of titanium chloride and alkyl aluminum such as triethyl aluminum [29]. The bulk process occurs without a solvent, in liquid propylene. The pressures and temperatures required to maintain propylene in liquid form are kept throughout the process. The temperatures used are between 70 and 80°C and the pressures are in the range of 30–40 atm [9]. At the end of polymerization polymer particles are separated from the liquid and the unreacted propylene is cycled back into the process. The use of liquid propylene as the solvent for the polymer means that there is no requirement for the use of higher hydrocarbons as the solvent. In the gas phase process, a mixture of propylene and hydrogen is passed over a bed containing the Ziegler–Natta catalyst at temperatures of 50–80°C and a pressure of 8–35 atm. At the end of the process, the polymer is separated from the gaseous propylene and hydrogen using cyclones and the unreacted gas is recycled back into the process [29]. Metallocene catalysts are also being increasingly used for the production of polypropylenes. Metallocene catalysts offer some distinct advantages over traditional catalyst systems. The main advantage is in the control of the structure of polypropylene. The structure of the polypropylene is dictated by tacticity or its stereo arrangements.

2.2.2 Structure and Properties of Polypropylene

An important concept in defining the structure of polypropylene is the understanding of its tacticity [9]. The orientation of the methyl group on the monomer with respect to the orientation on the other or the neighboring monomers controls or defines the tacticity of the polymer chain. When the orientation of all the methyl groups is the same, polymer is said to be isotactic. In a syndiotactic polymer, alternate methyl groups are on different sides of the chain. The tacticity of the chain plays a critical role in determining the extent of crystallinity of polypropylene. The catalyst used in the process to make polypropylene plays a very important role in deciding the tacticity of the material. Ziegler–Natta catalysts are very effective in the production of isotactic polymer chains. The newer metallocene catalysts have been shown to produce syndiotactic materials reproducibly. When the methyl groups in a polypropylene chain exhibit no preferred orientation, the polymers are called atactic. Atactic polypropylene is an amorphous rubbery material.

The properties of polypropylene are in many respects similar to that seen with polyethylene, both LDPE and HDPE [1]. The presence of the additional methyl group improves certain mechanical properties including material toughness, creep, and fatigue. The presence of the methyl group also enhances thermal resistance; however the chemical resistance decreases as a result of the increased chemical activity around the carbon bond. Equal balance is noted with polyethylene especially in solution behavior and electrical properties. Overall the properties of polypropylene depend on the molecular weight and molecular weight distribution of the polymer chain, degree of crystallinity, the tacticity type, and any proportion of comonomer if used.

The density of PP is between 0.895 and 0.92 g/cm^3, making PP the commodity plastic with the lowest density. The lower density is a result of lesser density difference between the amorphous and crystalline regions of the polymer; this density difference is lower than polyethylene and hence a polymer density lesser than LDPE is observed [1,9].

The ultimate tensile strength of polypropylene is in the range of 4000 and 5000 psi, the Young's modulus of PP is between 1300 and 1800 N/mm^2, and the % elongation at break ranges from 10% to 30%. Polypropylene is normally tough, fatigue resistant, and flexible; these properties are enhanced when propylene is copolymerized with ethylene [32]. The range of mechanical properties allows polypropylene to be used as an engineering plastic in numerous applications [9], competing with other thermoplastic materials.

The thermal properties of polypropylene are strongly dependent on its structure, specifically on its tacticity [33]. PP with a perfectly isotactic structure has a melting point of 171°C (340°F); however there is always a certain amount of impurity in the structure and commercially available isotactic PP has a melting point that ranges from 160 to 166°C (320–331 °F). Syndiotactic PP with a crystallinity of 30% has a melting point of 130 °C (266 °F). It has

been noted that at low temperatures (below 0 °C) PP has a tendency to become brittle. The coefficient of thermal expansion of polypropylene is seen to be similar to polyethylenes [1].

2.2.2.1 Chemical Properties

The chemical resistance of polypropylene at room temperature conditions is one of its outstanding properties; in spite of this high chemical resistance it is less resistant than the polyethylenes mainly due to the tertiary carbon atom in its structure [9]. This property makes it suitable for polypropylene to act as storage containers and these containers are suitable to store many different kinds of chemicals. At room temperature PP is resistant to polar and nonpolar substances alike, all fats and almost all organic solvents do not attack PP, the exception is strongly oxidizing solvents such as peroxides and perchlorates. Nonoxidizing acids and bases can be stored in containers made of PP. At temperatures above 100°C, PP can be dissolved in low polarity solvents such as xylene. *p*-Xylene (PX) is a known solvent for PP and commercial grades are fully dissolvable in PX at temperatures of 140°C [9]. It is seen that the atactic portion of the material remains dissolved in the solvent even as the solution is cooled down from 140°C to room temperature. The isotactic portion, which is the majority of all commercial grades, precipitates out of the solution as the temperature falls below 100°C [33].

The presence of the methyl group and the associated tertiary carbon atom imparts a certain degree of chemical instability to polypropylene's structure. Polypropylene is susceptible to chain degradation when exposed to heat and ultraviolet (UV) radiation, this susceptibility is a source for concern in outdoor applications as sunlight can act as a potential degradant for polypropylene [34,35]. Oxidation usually occurs at the tertiary carbon atom that is present in every repeat unit. A free radical is formed at this site and then reacts further with available oxygen, followed by chain scission to yield aldehydes and carboxylic acids. UV absorbing additives such as carbon black are used as a filler in outdoor applications, otherwise degradation leads to the formation of a network of cracks that grow deeper and more severe with increasing time of exposure. Polypropylene can also be oxidized at high temperatures; therefore antioxidants are added to prevent oxidation occurring in thermoplastic processing operations [34]. Polypropylene degradation has also been noted in biological conditions. Microbial communities isolated from soil samples mixed with starch have been shown to be capable of degrading polypropylene [34]. Polypropylene has been reported to degrade while in human body as implantable mesh devices. The degraded material is seen to form a tree bark-like layer at the surface of mesh fibers [36].

The melt flow rate (MFR) or melt flow index (MFI) is a measure of molecular weight of polypropylene. The measure helps to determine how easily the molten raw material will flow during processing. Polypropylene with higher MFR will fill the plastic mold more easily during the injection or blow-molding production process. As the melt flow increases, however, some physical properties, like impact strength, will decrease.

There are three general types of polypropylene: homopolymer, random copolymer, and block copolymer. The comonomer is typically used with ethylene. Ethylene–propylene rubber or EPDM added to polypropylene homopolymer increases its low temperature impact strength. Randomly polymerized ethylene monomer added to polypropylene homopolymer decreases the polymer crystallinity, lowers the melting point, and makes the polymer more transparent. PP can be made translucent when uncolored but is not as readily made transparent as polystyrene, acrylic, or certain other plastics. It is often opaque or colored using pigments.

The various properties of PP are listed in Table 3.

2.3 Medical Applications of Polyolefins

Polyethylene and polypropylene are the two important polymers of the polyolefin family with a wide range of medical applications because of their biocompatibility and chemical resistance [12]. In cardiovascular arena, both low-density polyethylene and high-density polyethylene are utilized in making tubings and housings for blood supply. They are also utilized in production of blood bags to store blood. Polypropylene is also used for making heart valve structures [12,14].

Its most common medical use is in the synthetic, nonabsorbable suture [37]. Polypropylene also has been used in hernia and pelvic organ prolapse repair operations to protect the body from new hernias in the same location. A small patch of the material is placed over the spot of the hernia, below the skin, and is painless and rarely, if ever, rejected by the body [38]. However, a polypropylene mesh will erode the tissue surrounding it over the uncertain period from days to years. Therefore, the Food and Drug Adminstration in the USA (FDA) has issued several warnings

Table 3 Properties of Polypropylene

	Property	Homopolymer	Copolymer
D792	Density (lb/in^3) (g/cm^3)	0.033 0.905	0.033 0.897
D570	Water absorption, 24 h (%)	<0.01	0.01
D638	Tensile strength (psi)	4,800	4,800
D638	Tensile modulus (psi)	195,000	—
D638	Tensile elongation at yield (%)	12	23
D790	Flexural strength (psi)	7,000	5,400
D790	Flexural modulus (psi)	180,000	160,000
D695	Compressive strength (psi)	7,000	6,000
D695	Compressive modulus (psi)	225,000	—
D785	Hardness, Rockwell R	92	80
D256	IZOD notched impact (ft-lb/in)	1.9	7.5
D696	Coefficient of linear thermal expansion ($\times 10^{-5}$ in./in./°F)	6.2	6.6
D648	Heat deflection temp (°F/°C) at 66 psi at 264 psi	 210/99 125/52	 173/78 110/43
D3418	Melting temperature (°F/°C)	327/164	327/164
—	Max operating temp (°F/°C)	180/82	170/77
C177	Thermal conductivity (BTU-in/ft^2-h-°F) ($\times 10^{-4}$ cal/cm-s-°C)	 0.76–0.81 2.6–2.8	 — —
UL94	Flammability rating	HB	n.r.
D149	Dielectric strength (V/mil) short time, 1/8″ thick	500–660	475
D150	Dielectric constant at 1 kHz	2.25	2.2–2.36
D150	Dissipation factor at 1 kHz	0.0005–0.0018	0.0017
D257	Volume resistivity (Ω-cm) at 50% RH	8.5×10^{14}	2×10^{16}
D495	Arc resistance (s)	160	100

on the use of polypropylene mesh medical kits for certain applications in pelvic organ prolapse, specifically when introduced in close proximity to the vaginal wall due to a continued increase in number of mesh-driven tissue erosions reported by patients over the past few years [39]. Initially considered inert, polypropylene has been found to degrade while in the body. The degraded material forms a bark-like shell on the mesh fibers and is prone to cracking [36].

3 Polyethylene Terephthalate

PET is a thermoplastic polymer of the polyester family. The common chemical group in the polyester family is the ester group. The ester group is highly susceptible to hydrolysis; in many studies it has been seen to be easily cleaved by the presence of moisture. It is noteworthy that despite belonging to the polyester family, PET is considered extremely biostable [14,19]. This biostability is a result of the structure of PET and its molecular organization or its crystallinity [18].

PET consists of long chains of the polymerized monomer ethylene terephthalate, with repeating ($C_{10}H_8O_4$) units as shown in Fig. 3.

3.1 Synthesis of PET

The monomer of PET can be synthesized in either of the two ways; by esterification or transesterification

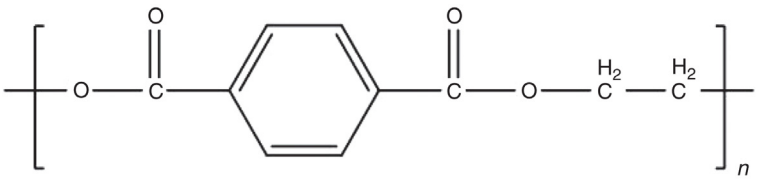

Figure 3 Structure of polyethylene terephthalate (PET).

[40,41]. Esterification is the reaction of an alcohol with an acid leading to the formation of esters with the elimination of water. Transesterification, on the other hand, is the transfer of the ester group in the reaction between an ester compound and an alcohol replacing the alkoxy group. The esterification reaction proceeds by the reaction between terephthalic acid (TA) and ethylene glycol with water as a by-product, the transesterification reaction proceeds by the reaction between ethylene glycol and dimethyl terephthalate with methanol as a by-product. Subsequent polymerization is through a condensation reaction and a step growth process of the monomers immediately after esterification/transesterification with water as the by-product.

PET was first patented in the 1940s in the United Kingdom. Its first commercial use occurred in the 1950s throughout the world [42].

The common substance in the production process of PET is ethylene glycol. In the transesterification process ethylene glycol is reacted with dimethyl terephthalate, in the esterification process ethylene glycol is reacted with TA.

Ethylene glycol is produced from ethylene (ethene), via the intermediate ethylene oxide. Ethylene oxide reacts with water to produce ethylene glycol according to the following chemical equation:

$$C_2H_4O + H_2O \rightarrow HO — CH_2CH_2 — OH$$

The ethylene glycol reaction can be catalyzed by the use of either acids or bases, or can occur at neutral pH under high temperatures. The highest yields of ethylene glycol are seen to occur at acidic or neutral pH conditions with a large excess of water in the system [41]. Under these conditions, ethylene glycol yields of 90% can be achieved.

Dimethyl terephthalate (DMT) can be produced in a few different ways [40]. There are two conventional methods that are frequently used on an industrial basis to produce DMT. One common method for the production of DMT is from para-xylene (PX) and methanol. In this process, a mixture of PX and p-Toluic ester (PT) is oxidized with air in the presence of a heavy metal catalyst such as a cobalt-based catalyst. This is the oxidation step and the acid mixture resulting from this oxidation is esterified with methanol (CH_3OH) to produce a mixture of esters. The crude ester mixture is distilled and the raw DMT is then sent to the crystallization section to remove DMT isomers, residual acids, and aromatic aldehydes. This process is known as the Witten process. Another method is the direct esterification of TA with methanol.

The other raw material for PET synthesis, TA can be produced in several ways. The basic principle is oxidation of PX into TA. One example as shown in the following is the Amoco process [40].

In the Amoco process, TA is produced by oxidation of PX by oxygen in air as in Fig. 4.

The process uses a cobalt–manganese–bromide catalyst, where bromine functions as a regenerative source of free radicals. In this process, acetic acid is the solvent and oxygen from compressed air is the oxidant. In variations of this basic concept of PX oxidation, there have been different catalyst systems, different sources of free radicals, and different oxidants. These variations have given rise to different reaction schemes and processes.

The process of PET manufacture can proceed by either esterification or transesterification. DMT is used in reaction with mono ethylene glycol (MEG) as the reaction process in transesterification. In the DMT process (Fig. 5), this compound and excess MEG are reacted in the molten form at 150–200 °C with a basic catalyst and under atmospheric pressure. Methanol (CH_3OH) is removed by distillation to drive the reaction forward in accordance with the

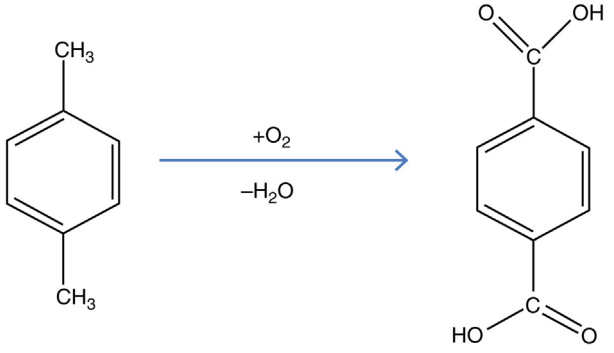

Figure 4 The process to manufacture TA.

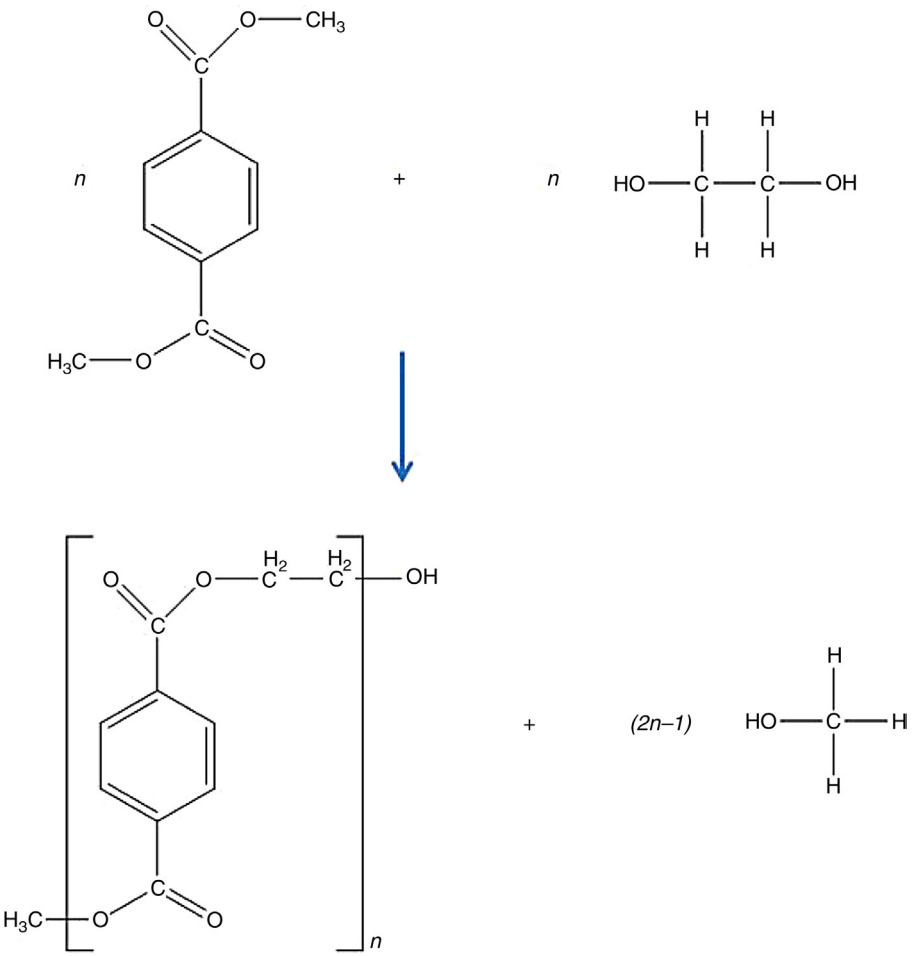

Figure 5 DMT process for the synthesis of PET.

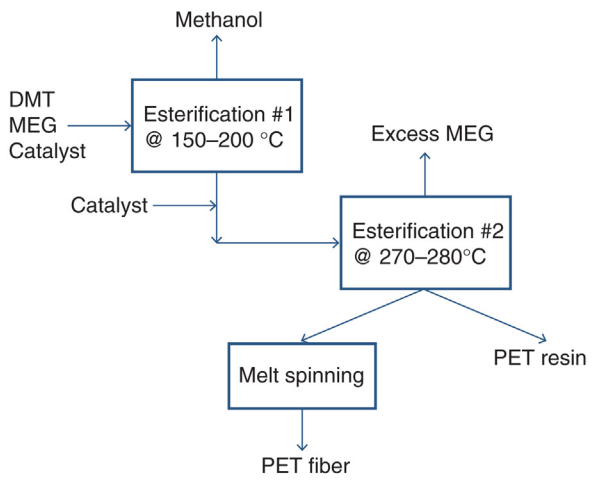

Figure 6 DMT process for the synthesis of PET as a block diagram.

Le Chatelier principle. Excess monomer MEG is distilled off at higher temperature with the aid of vacuum. The second transesterification step proceeds at 270–280°C, with continuous distillation of ethylene glycol as well [40,41].

The DMT process can be depicted by the block diagram in Fig. 6.

In the esterification-based process TA is used (Fig. 7). The TA process has many advantages over the DMT process and is widely used in the production of PET. The advantages include easier handling of TA over DMT as a result of the higher bulk density of TA, more robust process with TA, no requirement of catalyst during the esterification process of TA, and the by-product of easier to handle water in the TA process as compared to methanol in the DMT process. In the TA process, esterification of ethylene glycol and TA is conducted directly at moderate pressure (2.7–5.5 bar) and high temperature

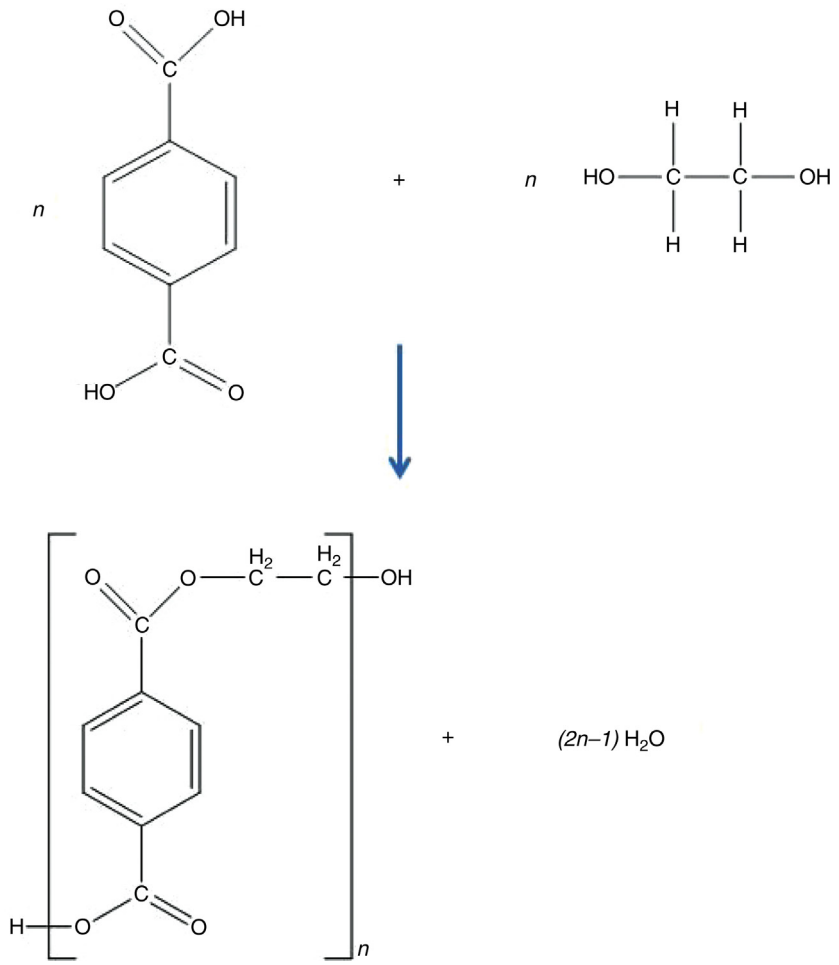

Figure 7 The TA process for the synthesis of polyethylene terephthalate (PET).

(220–260°C). Water is eliminated in the reaction, and it is also continuously removed by distillation.

The TA process is depicted in Fig. 8.

3.2 Structure and Properties of PET

The level of crystallinity in PET affects the material properties quite significantly; PET is inherently crystallizable due to its regularity in chemical and geometric structures [43–45]. Polymers with greater degree of crystallinity have a higher glass transition temperature T_g, (T_g is 67°C for amorphous PET and 81°C for crystalline PET) show a higher modulus, stiffness, tensile strength, hardness and more resistance to solvents, but a lower impact strength [43]. Crystallinity in PET is usually induced by thermal- or stress-induced processes. Thermally induced crystallization occurs when the polymer is heated above its glass transition temperature (T_g), in this condition

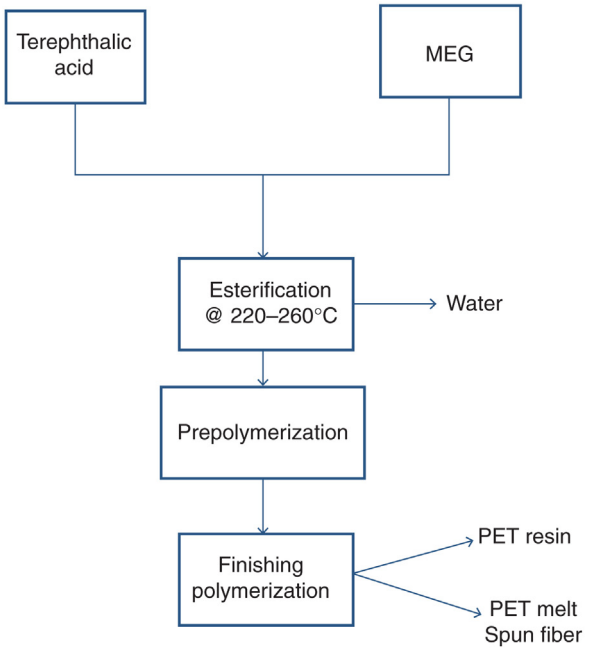

Figure 8 The TA process for the synthesis of polyethylene terephthalate (PET) as a block diagram.

the chains are mobile enough to allow them to be arranged in an orderly fashion and form crystals. The crystallized polymer tends to be opaque due to the spherulitic structure generated by crystallite aggregates [46]. In stress-induced crystallization, stress is applied usually in addition to the thermal effects, stretching or orientation is applied to the heated polymer and that allows the polymer chains to rearrange and pack into crystals [47]. The stress-induced crystallization process is used during fiber drawing. PET fibers are heated past their glass transistion temperatures and subjected to high levels of uniaxial stress. The combination of heat and stress results in molecular orientation and subsequent crystallization. The process of fiber drawing can achieve high levels of crystallinity in PET. The crystallization process comprises nucleation and spherulitic crystallization and is said to occur at temperatures above T_g and below the melting point T_m [48]. Crystallization may be curbed by quenching the melt quickly after heating resulting in a completely amorphous structure. When the molecules of any polymer are not given enough time to arrange themselves in an orderly, crystalline fashion as the melt is cooled an amorphous polymer results. Rapid quenching can lead to formation of transparent PET, clear products are produced by this rapid cooling process bringing the molten polymer to temperatures below T_g. When allowed to cool slowly, the molten polymer forms a more crystalline material. The spherulites in the material mean that all the crystallites that it contains form an optical boundary. As light crosses the boundary between the crystalline and amorphous regions, it scatters and therefore crystalline PET has an opaque and almost white appearance. Crystallized commercial PET is usually capped at an upper limit of about 60% crystallization; fibers are an exception as they can have significantly higher values due to stress-induced crystallization in the fiber drawing process. In PET a phenomenon known as solid state crystallization is observed; in this process crystallization can occur by heating the polymer up past its glass transition but not going to the polymer's melting point and cooling it down slowly. At room temperature the molecules are frozen in place, but, if enough heat energy is put back into the molecules by heating above T_g, they begin to move again, allowing crystals to nucleate and grow. In addition to time and temperature, many other factors such as pressure, the degree of molecular orientation and environment have influence on crystallization mechanism, morphology, and final properties of PET [43,46]. Nucleating agents also affect the crystallization of PET. Some studies have investigated the effect of the additives on crystallization behavior [41,48]. Moisture and molecular weight have a great effect on crystallization. It is found that the kinetics of crystallization depends on molecular weight and that with increasing percentage of moisture, the half-time of crystallization and induction time of crystallization decrease. Spherulite growth rate was observed to be independent of water absorbed [43].

3.2.1 Intrinsic Viscosity

The final molecular weight of the PET is an important determinant of polymer structure and properties. One of the most important ways to measure the molecular weight of PET is by the use of the intrinsic viscosity (IV) technique [49]. Molecular weight determination of PET by the use of size exclusion chromatography or gel permeation chromatography methods may be expensive and hazardous due to the high cost and toxicity of the solvents involved. In the determination of IV of PET, a solvent mixture of phenol and tetrachloroethane in the ratio of 60/40 is used, solutions are prepared after dissolution of the polymer at 120°C for 3 h and an Ubbellodhe type viscometer is used for the actual measurement [17]. The IV of the material is found by extrapolating to zero concentration of relative viscosity to concentration which is measured in deciliters per gram (dl/g). IV has no units of its own as it is being extrapolated to zero concentration. The longer the polymer chains the more are the entanglements between chains and therefore the higher the IV. The average chain length of a particular batch of resin can be controlled during the synthesis process.

The IV of PET affects its subsequent properties of molecular weight, tensile strength, toughness, and crystallization. The properties decide the applications that the polymer can be used in. The IV ranges and the corresponding applications that PET is used in are shown in Table 4 [17].

Table 4 IV Ranges and Applications for Polyethylene Terephthalates

Application	Intrinsic Viscosity
Textile fiber	0.40–0.70
Technical fiber	0.72–0.98
Film–Biaxially oriented	0.6–0.7
Sheet–for thermoforming	0.7–1.00
Bottle	0.7–0.85
Engineering plastic	1.0–2.0

Table 5 Typical Property Values of PET

Physical Properties	**ASTM Test Method**	**Units**	**PET**
Density	D792	lbs/cu in.^{3}	0.0499
Water absorption, 24 h	D570	%	0.10
Mechanical Properties	**ASTM Test Method**	**Units**	**PET**
Specific gravity	D792	g/cu cm.^{3}	1.38
Tensile strength at break, 73°F	D638	psi	11,500
Tensile modulus, 73°F	D638	psi	4×10^5
Elongation at break, 73° F	D638	%	70
Flexural strength, 73°F	D790	psi	15,000
Flexural modulus, 73°F	D790	psi	4×10^5
Izod impact strength, notched, 73°F	D256	ft-lbs/in.	0.7
Rockwell hardness	D785	—	R117
Coefficient of friction @ 40 psi, 50 fpm	—	Static/dynamic	0.19/0.25
Thermal Properties	**ASTM Test Method**	**Units**	**PET**
Heat deflection, 264 psi	D648	°F	175
Melting point	—	°F	490
Coefficient of linear thermal expansion	D696	in./in./- °F	3.9×10^{-5}
Applicable temp. range for thermal expansion	—	°F	50–250
Max. serving temperature for long term	—	°F	230
Flammability	UL94	—	HB
Electrical Properties	**ASTM Test Method**	**Units**	**PET**
Volume resistivity, 73°F	D257	Ω-cm	10^{16}
Dielectric constant @ 60 Hz, (73°F, 50% RH)	D150	—	3.4
Dissipation factor, @ 60 Hz, 73°F	D150	—	0.002
Dielectric strength	D149	V/mil	400

The general properties of PET are listed in Table 5. PET exists as a colorless and semicrystalline resin. The specifics of the properties of PET are dependent on the manner and the degree of processing steps the polymer has undergone. The degree of crystallization is significantly affected by the processing steps and based on that PET can be semirigid to rigid, enhancements can be made to the polymer's toughness and barrier properties. In general, PET demonstrates good gas and fair moisture barrier properties, as well as good barrier properties in relation to alcohol and other solvents. PET is an unreinforced, semicrystalline thermo-plastic polyester derived from PET. Its excellent wear resistance, low coefficient of friction, high flexural modulus, and superior dimensional stability make it a versatile material for designing mechanical and electro-mechanical parts. As PET has no centerline porosity, the possibility of fluid absorption and leakage is virtually eliminated.

3.3 Processing of PET

PET can be processed into its final form using a variety of different thermoplastic processing techniques. The molecular weight of the polymer and its subsequent IV value determines, to a certain extent, the technique that is most applicable for the polymer. When processing PET, the challenge of coping with its various possibilities of degradation has to be met [50]. Mechanical, thermal, oxidative, and especially hydrolytic degradation can cause significant damage to the molecular structure of the PET and can have a negative influence on the resulting properties of the

product. Therefore, it is imperative that these degradative influences are kept within certain limits. PET has to be processed applying a low shear stress and temperature level, exposure to oxygen must be minimized, and the PET pellets used for melt processing have to be dried thoroughly to achieve a sufficiently low water content prior to melting [50].

3.3.1 Drying of PET

Drying PET pellets is essential for successful conversion of PET pellets to the final article in melt processing applications. PET is extremely hygroscopic, meaning that it absorbs water from its surroundings. Water molecules can hydrolyze PET at high temperatures and that can lead to chain scission and a loss in polymer properties. If PET is melted with the pellets that are not well dried, the water can hydrolyze the PET, causing a significant decrease in its molecular weight. Drying is achieved through the use of a desiccant or vacuum drying systems before the PET is fed into the processing equipment. Typically, residual moisture levels in the resin must be less than 50 parts per million (parts of water per million parts of resin, by weight) before processing. Dryer residence times are not recommended to be shorter than about 4 h. This is because drying the material in less than 4 h would require a temperature above 160 °C, at higher temperatures hydrolysis can be initiated before the material is completely dry. PET can also be dried in compressed air resin dryers. Compressed air dryers do not reuse drying air. Dry, heated compressed air is circulated through the PET pellets as in the desiccant dryer, then released to the atmosphere.

4 Polyamide

The linking together of an amide (—NHCO—) bond leads to the formation of the macromolecule generically referred to as a polyamide (PA). The amide link is produced from the condensation reaction of an amino group (—NH—) and a carboxylic acid group (—COOH), in the condensation reaction water is the by-product. The amino group and the carboxylic acid group can be on the same monomer, or the polymer can be constituted of two different bifunctional monomers, one with two amino groups, and the other with two carboxylic acid groups. PAs are present abundantly in nature, in living organisms, amino acids are condensed with one another with the catalytic activity provided by an enzyme [20,21]. Amino acids react together to form amide groups; the resulting macromolecules are known as polypeptides or proteins. The PAs most commonly used on a commercial basis are derived from aliphatic compounds and the resultant PAs are termed Nylon 6 and Nylon 6,6 [22]. PAs derived from fully aromatic compounds are termed Aramids and a common example of that is Kevlar. PAs can also be copolymerized and many mixtures of monomers are possible which can in turn lead to numerous PA-based copolymers [23].

Nylon 6 and Nylon 6,6 were among the first thermoplastic materials to be introduced on a commercial basis. The first introduction was in applications such as bristles in toothbrushes and yarn for women's stockings. The silky nature of nylons was considered one of its greatest attributes and thus was intended to be a synthetic replacement for silk and substituted for it in many different products in the years of the Second World War as the scarcity of silk increased [20]. It replaced silk in many military applications such as parachutes and flak vests, and was used in many types of military vehicle tires. Nylon polymers can be mixed with a wide variety of additives to achieve many different property variations above the silkiness properties. After initial applications of nylon as a fiber, improvements in the synthetic process lead to further applications in the form of shapes and films. Currently, the main market for nylon parts is in the automotive sector [21].

The first commercialization of the PA formulations occurred in the 1930s. Wallace Carothers at DuPont worked on many aspects of condensation reactions formed from step growth polymerization. He developed the Carothers equation where the degree of polymerization is related to the conversion of the monomer in step growth polymerization [51]. His work with the use of hexamethylenediamine and adipic acid and their subsequent polymerization lead to the development of the patent for the PA formulation that came to be known as Nylon 66 [52]. A few years after Carother's work, Paul Schlack at a German chemical company I G Farben (predecessor of Bayer and BASF) developed a route where a cyclic amide compound, caprolactam, was ring opened at high temperatures exposing functional groups for polymerization. This route led to the development of the PA formulation known as Nylon 6 [20].

4.1 Raw Materials

The formulation of Nylon 6,6 is based on two raw materials: hexamethylenediamine and adipic acid. As the name suggests, hexamethylenediamine is

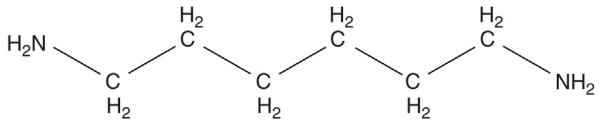

Figure 9 Structure of a diamine.

made from a core hydrocarbon hexamethylene and terminated by amino functional groups (Fig. 9).

Hexamethylenediamine is produced by the hydrogenation of adiponitrile:

$$NC(CH_2)_4CN + 4\,H_2 \rightarrow H_2N(CH_2)_6NH_2$$

The hydrogenation is conducted on molten adiponitrile diluted with ammonia with the aid of metallic catalysts based on cobalt and iron.

Adipic acid belongs to the family of dicarboxylic acids. Commercially it is the most widely used of the dicarboxylic acids [53]. It has a chemical formula as in Fig. 10.

Adipic acid is produced from the general process of the cleavage of double bonds of alkenes by oxidation to form acids [53]. In one industrial process, a mixture of cyclohexanone and cyclohexanol is oxidized with nitric acid in a multistep pathway.

Caprolactam is a cyclic organic compound with the formula:

$$(CH_2)_5C(O)NH.$$

Caprolactam is a colorless solid that melts at around 70°C [54]. Chemically it is a cyclic amide (lactam) of a linear caproic acid. There are different ways to synthesize caprolactam, with the increasing significance of Nylon 6 as a polymer; various routes to industrial production of caprolactam have been developed. In one of the production routes (Fig. 11), cyclohexanone (**1**), is first converted to its oxime (**2**). Treatment of this oxime with acid induces a structural rearrangement known as the Beckmann rearrangement to give caprolactam (**3**) [54].

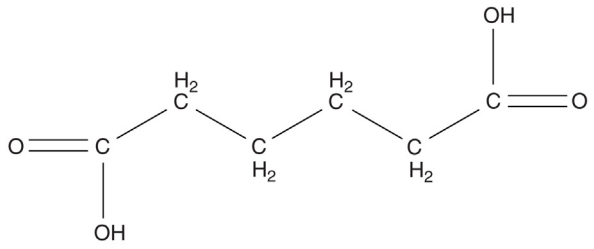

Figure 10 Structure of adipic acid.

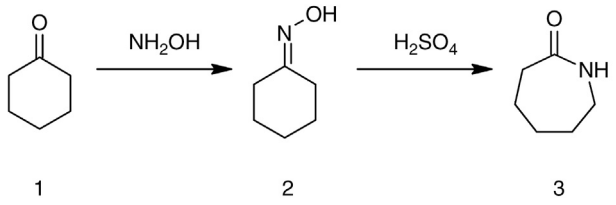

Figure 11 Caprolactam.

4.2 Synthesis of Polyamides

PAs are prepared by a stoichiometric step growth polymerization and belong to the group of condensation polymers. The polymers are formed by successive reactions between a difunctional reactant A–A with a difunctional reactant B–B or by the reaction of the difunctional monomer A–B with itself. The reaction of a dicarboxylic acid with a diamine to form Nylon 6,6 is an example of a difunctional reactant A–A reacting with a difunctional reactant B–B whereas a caprolactam reacting with itself to form Nylon 6 is an example of an A–B type monomer reaction. To obtain high molecular weight polymers, these two functional groups must be present in stoichiometric amounts [22]. Of course, the stoichiometry is automatically obtained with a difunctional monomer of the type A–B.

Nylon 6 or polycaprolactam is a PA developed in the late 1930s at German chemical firm of IG Farben. The objective of the development was to reproduce the properties of Nylon 6,6 without violating the existing intellectual property in terms of the granted patent on its chemistry, formulation, and production. The difference between the two PAs, Nylon 6 and Nylon 6,6 was the nature of chain growth [22]. The Nylon 6 PA used caprolactam as the starting material in contrast with Nylon 6,6 using hexamethylene diamine and adipic acid as the starting materials. The Nylon 6 process utilized the ring-opening polymerization of caprolactam. This meant that it was not based on condensation polymerization chemistry like that of Nylon 6,6 was based on. Caprolactam has six carbons, hence "Nylon 6" [21,22].

Three reversible reactions, hydrolysis, polycondensation, and polyaddition, are the main steps in the formation of Nylon 6 [22,55]. The overall reaction can be illustrated as follows (Fig. 12).

The first step is hydrolysis reaction to open the caprolactam ring, forming e-aminocaproic acid (Fig. 13).

The hydrolysis reaction proceeds with the caprolactam in a molten state and the presence of a small

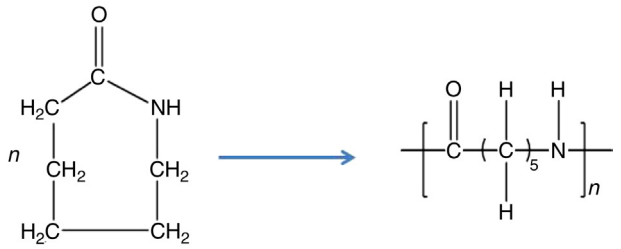

Figure 12 Conversion of caprolactam to Nylon 6.

amount of water. A material such as phosphoric acid is sometimes used as a chain length stabilizer as it helps to achieve the desired final molecular weight. Polyaddition follows hydrolysis and is primarily responsible for chain growth of the polymer. It occurs as soon as a certain amount of end groups have been made available through the hydrolysis reaction of caprolactam.

Polycondensation is the last step in the formation of Nylon 6. Polycondensation is used to further increase the molecular weight of the chains and fix the molecular weight distribution. In polycondensation, the reactive end groups condense forming linear chain molecules and the by-product of water. Organic acids such as acetic acid can be added as chain stabilizers, mono-functional organic amines can also be added for the same purpose. The industrial process for the production of Nylon 6 follows the previously described mechanism [21].

The polymerization process using the hydrolytic mechanism can be batch or continuous. As described so far, the hydrolytic process for the production of Nylon 6 can be divided into the following steps [56]:

- Caprolactam and additives addition
- Hydrolysis
- Addition
- Condensation
- Pelletizing
- Monomer extraction
- Drying and packaging

In one industrial process [20] the reaction to make Nylon 6 is carried out at temperatures between 220 and 280°C. The process is acid catalyzed and uses a simple tubular reactor where caprolactam and water are added continuously to the top at atmospheric pressure under reflux conditions. A balance of water content at the start and the temperature of the reaction significantly affect the molecular weight of the product as well as the rate of production. This effect on the molecular weight is addressed in different ways depending on the type of process involved. In a batch process, fairly large amounts of water are used in the initial stage of production. In the continuous process, subsequent water removal steps are incorporated within the system. A significant amount of unreacted monomer present at the end of the process necessitates extraction as a process step. In many cases, especially when a high molecular weight product is desired, solid phase polymerization may be carried out at the end of the process. The solid phase postcondensation may be carried out for 5–20 h at 160–180°C under vacuum [20].

Nylon 6 can be modified using comonomers or stabilizers during polymerization to introduce new chain end or functional groups, which changes the reactivity and chemical properties. It is often done to change the color dye acceptance ability of the material or its flame retardance properties [57].

Nylon 6,6, as explained earlier, is made from two monomers in contrast to the single monomer used in Nylon 6 synthesis. The two monomers each contain six carbon atoms, hexamethylenediamine and adipic acid, which give Nylon 6,6 its name. Nylon 6,6 is synthesized by polycondensation reaction of the terminal amine groups present in hexamethylenediamine and the carboxylic acid groups present at the ends of adipic acid. The reaction forms a AA–BB type polymer with even–even numbers of methylene units; this structure gives Nylon 6,6 a high chain regularity and interesting properties as a result [20,56].

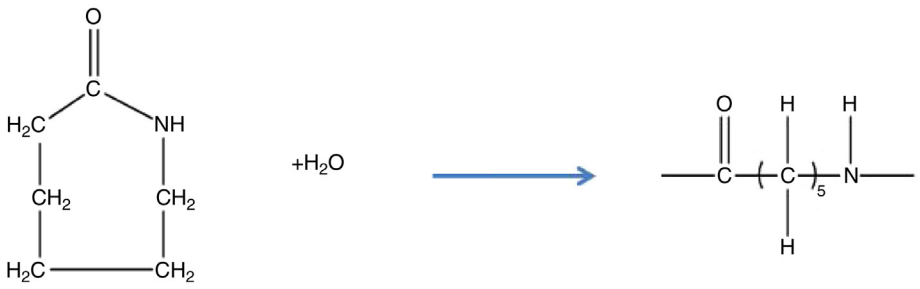

Figure 13 Hydrolysis in Nylon 6 formation.

The process for Nylon 66 synthesis begins with the formation of a PA salt in water. Equivalent amounts of hexamethylenediamine and adipic acid are combined with water in a reactor as seen in the following equation:

$$n\text{HOOC—(CH}_2\text{)}_4\text{—COOH} + n\text{H}_2\text{N—(CH}_2\text{)}_6\text{—NH}_2 \rightarrow [\text{—OC—(CH}_2\text{)}_4\text{—CO—NH—(CH}_2\text{)}_6\text{—NH—}]n + 2n\text{H}_2\text{O}$$

This is crystallized to make nylon salt, which has precise stoichiometric equivalents of the two reactants. The nylon salt is then added into a reaction vessel where polymerization process takes place either in a batch process or continuously. In a typical industrial process the following steps are followed [20]:

- Prepolymerization at 210–275°C and 1.8 × 10^6 Pa pressure
- Flashing stage, reducing the pressure to the atmospheric value
- Polymerization at 275–290°C and 1 × 10^5 Pa pressure

These steps can be followed by postcondensation to increase the molecular weight further if desired. Postcondensation can be achieved either by the melt finishing or solid-state postcondensation method.

Removing water drives the reaction toward polymerization through the formation of amide bonds from the acid and amine functional groups. Thus molten Nylon 66 is formed. It can either be extruded and granulated at this point or directly spun into fibers by extrusion through a spinneret (a small metal plate with fine holes) and cooling to form filaments. A representative block diagram is shown in Fig. 14.

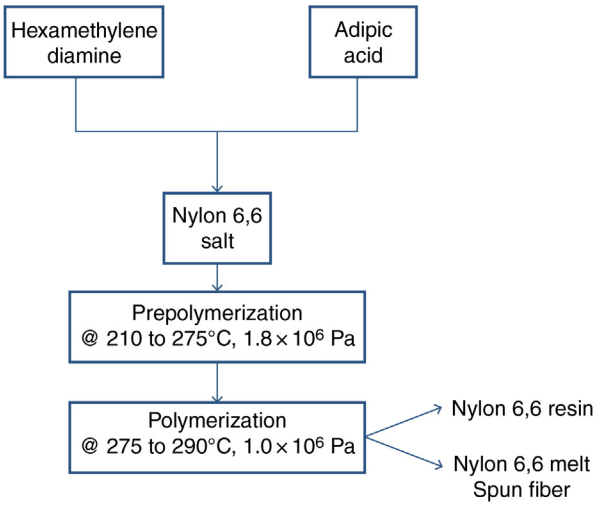

Figure 14 Production process for Nylon 6,6.

4.3 Structure and Properties of Polyamides

Above their melting temperatures, T_m, thermoplastics such as all PAs are amorphous in nature or they are viscous fluids in which the chains have no order and can be approximated as random coils. Below the melting temperature, amorphous regions in the polymer tend to alternate with regions which are more ordered and crystalline in nature [58]. In general, in this "two phase" arrangement, the amorphous regions contribute to the material's elasticity and the crystalline regions contribute to the material's strength and rigidity. The amide (—CO—NH—) groups are extremely polar and this leads to nylons forming multiple hydrogen bonds among adjacent chains. The regularity of the structure of nylons means the degree of crystallinity is high as well the polarity of the amide groups gives rise to numerous hydrogen bonded sites, the level of order and attraction among the adjacent chains make the material very suited for making fibers. The actual amount of crystallinity depends on the details of the polymerization process, as well as on the kind of PA formulation; however, a completely amorphous nylon cannot be manufactured even with rapid quenching from the molten form [58].

The hydrogen bonding is a feature of all PAs regardless of the actual formulation. Nylon 6,6, for example, can have multiple parallel chains aligned with their neighboring amide bonds at coordinated separations for considerable lengths, so the carbonyl oxygens and amide hydrogens can line up to form interchain hydrogen bonds repeatedly, without interruption (Fig. 15). Other formulations can form the hydrogen bonding sequence in different ways, Nylon 5,10 can have coordinated runs of 5 and 8 carbons, Nylon 6 will form uninterrupted H-bonded sheets with mixed directionalities [56].

In the process of melt spinning, PAs are extruded into fibers, the fiber formation occurs as the PA melt is forced through the die holes of a spinneret. During fiber formation and the melt flow through the spinneret, the melt is exposed to a combination of shear and elongational forces. This combination acts on the individual polymer chains and they tend to align or orient in the flow direction. If subjected to cold drawing afterwards, the molecular chains orient further, increasing the order of the chains and therefore its crystallinity. The increased crystallinity leads to the

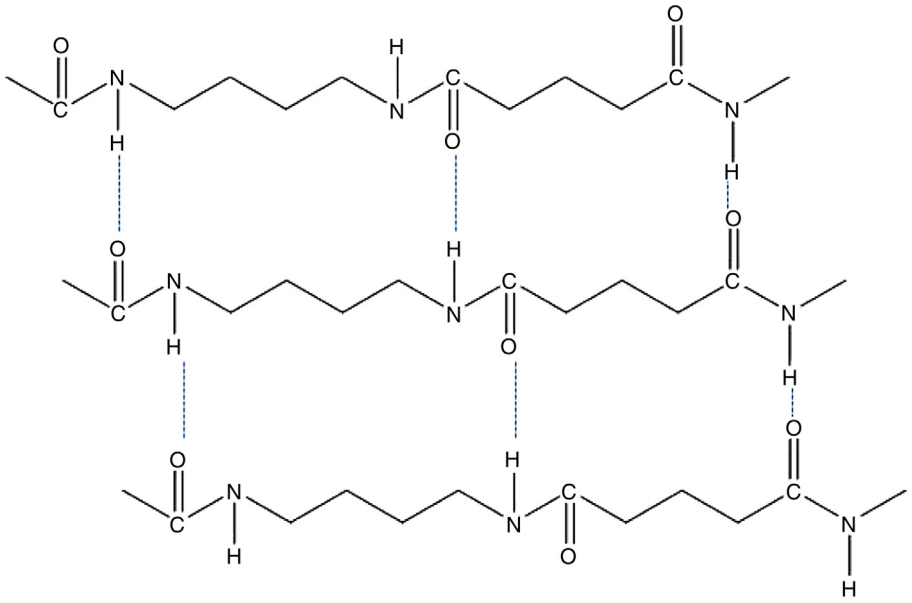

Figure 15 Hydrogen bonding in PAs.

material acquiring additional tensile strength especially in the direction of the stretching. In practice, nylon fibers are most often drawn using heated rolls at high speeds [58].

Nylon is clear and colorless, or milky, but is easily dyed using pigments. Multistranded nylon cord and rope is slippery and tends to unravel; however, the ends of the rope or cord can be melted and fused with a heat source such as a flame or electrode to prevent this.

Due to the polar nature of the amide linkage, all nylons tend to be highly hygroscopic, that is, they will absorb moisture as a function of the ambient humidity. In a solid form, the hygroscopic nature and the atmosphere nylons are exposed to lead to variations in the level of the moisture absorbed by the material. These variations in moisture content can have several important effects on the solid polymer. Moisture can affect the dimensions of the article and the absorption of moisture can act as a plasticizer and the plasticizer effect can lower the glass transition temperature, affect the degree of crystallinity, and thus significantly affect the physical properties of the material [59]. The moisture absorption can also affect the electrical properties of the material; greater moisture will mean lower effectiveness of the material as an insulator [59]. In the molten state the presence of moisture can lead to hydrolysis of the PA chains and significantly affect the molecular weight of the material and consequently the physical properties of the material [58–60]. Drying the resin before melt processing is an essential part of the handling steps with nylons. Nylons are usually dried to below 0.02% in moisture levels and this is achieved by a drying cycle at ~80°C (176°F) [56,59].

All nylons are susceptible to hydrolysis in the solid state, especially by strong acids; hydrolysis leads to a reaction that is essentially the reverse of the synthetic reaction. As a result, the molecular weight of nylon products drops during hydrolysis and visible cracks can form quickly in the affected zones. This limits the use of nylons in applications that come in contact with strong acids, for example nylon parts cannot be used as the electrolyte in lead–acid batteries.

Due to the presence of multiple hydrogen bonds per molecule, PAs exhibit strong interchain interactions. Owing to the hydrogen bonding effect the molecular weight of PAs does not need to be very high to obtain optimal thermal and mechanical properties. Typical molecular weight values of PAs are significantly lower than many other commercial polymers [59]. The biggest advantage of this low molecular weight is the fact that the melt viscosity is quite low. The melt viscosity, as described in an earlier section, can be related to the molecular weight raised to the power of ~3.4. The lower melt viscosity results in easier melt processing of the polymer especially in injection molding applications. In injection molding it is also possible to mold thin walled sections not easily possible with other polymers. Extrusion grades do require a higher melt viscosity to prevent extrudate sagging and as a result higher molecular

Table 6 Properties of Nylon 6 and Nylon 6,6

Property	Nylon 6	Nylon 6,6
Optical	Translucent to opaque	Translucent to opaque
Thermal melting point	210–220°C	255–265°C
% Moisture absorption	8.5–10	8.5
Oxidation resistance	Good	Good
Ultraviolet resistance	Poor	Poor
Solvent	Phenol and formic acid	Phenol and formic acid
Alkaline resistance	Good	Good
Acid resistance	Poor	Poor
Density (g/cc)	1.13–1.15	1.13–1.15
Ultimate tensile strength (psi)	6000–24,000	14,000
% Elongation at break	30–100	15–80
Tensile modulus	300,000	250,000–550,000
Hardness (Rockwell scale)	80–102	120

weight grades of nylons are required for extrusion applications [21].

Table 6 shows the representative properties of Nylon 6 and Nylon 6,6.

4.4 Polyether Block Amide

A combination of polyether- and PA-based segments can result in the ideal mix of properties. The amorphous, soft, polyether blocks with a low temperature of glass transition can provide the low-temperature toughness and the elastomeric properties, whereas the semicrystalline, hard PA blocks can provide the higher chemical resistance and strength. The PA blocks can form a kind of a cross-linked network that is thermally reversible, that is, can be molten and processed at temperatures above the melting point of the semicrystalline PA blocks. The polyether blocks can be regarded as internal plasticizers in the flow of the polymer during processing. This results in the synthesis of a block copolymer and in this manner, a thermoplastic elastomer can be manufactured. These block copolymers are called polyether block amides (PEBA) [60]. The polyether blocks in PEBAs are composed usually of polytetrahydrofuran (PTHF), polyethylene oxide (PEO), or polypropylene oxide (PPO), and the PA blocks, could be either PA6, 66, 11, or 12. The PEBAs are chemically linked by either ester or amide bonds, furnishing poly(ether ester amide)s and poly(ether amide)s, respectively.

4.4.1 Chemistry and Chemical Structure of PEBAs

There are different ways to manufacture PEBA. One of the ways that has been the most widely used is the two-step process. In the two-step process, the polyether block amide is first made into a carboxylic acid end capped oligoamide. The oligoamide is a short chain PA, with a typical molecular weight between 500–2000 g/mol [60]. A complete description of the process and formulation is given in the reference by Baumann et al. [61] for the manufacture of a PA 12-based poly(ether ester amide). According to that process, in the first step, a dicarboxylic acid such as 1,12-decanedicarboxylic acid and laurolactam are reacted at a temperature of 250–290°C and at pressure between 1 and 20 bar. The first step results in the formation of a prepolymer that is terminated by a difunctional carboxylic acid. This acid terminated PA or oligoamide PA 12 with the structure:

$$\mathrm{HO[OC(CH_2)_{11}NH]}x\mathrm{—CO(CH_2)_{10}CO}$$
$$\mathrm{—[NH(CH_2)_{11}CO]}y\mathrm{—OH}$$

The amount of carboxylic acid used in the process determines the length of the chain formed (x and y values) of the prepolymer or the oligoamide. The oligoamide has a molar mass range of 500–2000 as mentioned previously. In the second step, the prepolymer is further reacted with a difunctional polyether diol such as poly THF, to form the PEBA. The second step reaction is carried out in the melt stage

and under vacuum, the temperature utilized is usually between 200 and 270°C.

The connection between the PA chain and the polyether chain is an ester bond. The structure is as follows:

$$H — \{[O(CH_2)_4—]_zO — [OC(CH_2)_{11}NH]_x — CO(CH_2)_{10}CO — [NH(CH_2)_{11}CO]_y\}_n — OH$$

The stoichiometry of the components decide the values of the subscripts x, y and z. The requirement for this bond to form is the presence of a suitable esterification catalyst. Several catalysts for this esterification coupling reaction have been mentioned in the literature, these include dialkyl tin(IV) compounds, phosphoric acid, tetraalkyl titanates, tetraalkyl zirconates, tin(II) salts, antimonium trioxide, and combinations of antimonium trioxide and tin and phosphorous compounds [60,61].

The process of the formation of the prepolymer in the first step and subsequently the block amide in the second step can be problematic and has to be handled carefully. This can be especially the case when both the preformed PA and polyether segments have a relatively high molecular mass, and when the oligoamide segments are relatively polar. High polarity of the oligoamide blocks can lead to difficulties in compatibilizing the amide blocks with the relatively nonpolar polyether blocks. The problems of high molecular weights of the individual blocks and the polarity manifest themselves in premature phase separation during synthesis of the PEBA compounds. The premature phase separation can limit the molecular weight buildup of the final product. It has been observed that this premature phase separation can be avoided with the use of oligoamide 11 or 12 with the ether segment of poly THF. The compatibility between the oligoamide and the polyether phase has also been observed to be enhanced by the introduction of water vapor.

Another form of polyether block amide synthesis is using an one-pot synthesis method. In this method, the oligoamide-forming monomers are reacted with the dicarboxylic acid and the polyether diol in one step. Polyethers are susceptible to high temperatures and therefore the ring-opening reactions in the formation of oligoamides are limited to the ROPs occurring at lower temperatures. This is true when reactive lactams such as laurolactam (dodecalactam $(CH_2)_{11}C(O)NH$) are used as these can be ring opened at relatively low temperatures. In this case, at elevated pressures, the laurolactam ring-opening polymerization is initiated [62–64]. The one-pot synthesis process has also been successful several other formulations, such as the ones based on caprolactam, aminocarboxylic acids, and equimolar formulations of aliphatic diamines and dicarboxylic acids. Amine terminated polyethers such as α,ω-diaminopolyethers have been used in different studies as an alternative for polyether diols, and can be used for the synthesis of polyetheramides. The use of amine terminated polyethers leads to the formation of hydrolytically stable amide bonds between the oligoamide and the polyether segments. These α,ω-diaminopolyethers, such as poly(propylene oxide)diamine, can, for example, be mixed with caprolactam and a dicarboxylic acid, after which the corresponding PEBA is formed in a one-pot synthesis. In the synthesis with the amine terminated polyether, the amine end groups of the polyether can initiate the ring-opening polymerization of the caprolactam obviating the need for an esterification catalyst in the process. Premature phase separation is not an issue with all the different one-pot synthesis formulations.

4.4.2 Morphology of PEBAs

PEBA consists of two distinct phases, a highly ordered, semicrystalline PA region and a less ordered, amorphous polyether region. The morphology of final PEBA polymer is, thus, determined by its composition, and the amount of PA versus the amount of polyether. The phase separated structure can either be cocontinuous or have a dispersed phase in matrix structure. In general, materials exhibiting continuous or cocontinuous polyether phase are considered thermoplastic elastomers. In the two phase structure of the PEBA thermoplastic elastomer, the PA phase shows a spherulitic, lamellar structure, which contributes to the physical strength of the material. The elastomeric characteristics of the material arise from polyether phase in the phase separated structure of the material. In a traditional thermoplastic elastomer terminology, the spherulitic phase can be termed as the hard block whereas the polyether phase can be called the soft block. In high polyether contents, the spherulitic structure of the PA is lost and for very high polyether contents, the polyether segment becomes the matrix phase with the PA blocks forming a ribbon-like structure, the polyether rich material itself exhibits two glass transitions [61].

4.4.3 Physical Properties and Processing of PEBAs

The properties of PEBA are determined, to a large extent, by its morphology and composition. As explained earlier, PEBAs are phase separated structures

where the crystalline phase is made up of PA blocks whereas the polyether blocks occupy the amorphous phase. The properties of PEBA can be summarized to depend on the following:

- The nature of the PA blocks or the crystalline phase
- The composition of the polyether blocks or the amorphous phase
- The ratio of the PA to polyether in the formulation

4.4.3.1 PA Blocks

The PA blocks of the commercial PEBAs may consist of PA 6, 66, 612, 11, or 12. The semicrystalline phase formed by PA blocks takes a certain amount of heat to break them apart. This amount of heat determines the melting point of the material. The PA block type also determines the integrity of the crystalline regions and its susceptibility to diffusion and reaction with chemicals. Therefore the properties of water absorption, chemical resistance, stress cracking resistance, and density are determined by PA type and block length.

The polyether type, being either poly THF, polyethylene glycol (PEG), or polypropylene glycol (PPG), also plays a role in the determination of water absorption, chemical, and thermal resistance of the material. In addition, the glass transition temperature of the polyether block can decide the low temperature properties of the material. Finally, the mass ratio of the two blocks, that is, semicrystalline PA/amorphous polyether determines the rigidity, hardness, and flexibility. In PEBAs, it is clear that with increasing soft block or polyether content, the softness of the material increases and the elastic modulus decreases, whereas increasing PA content or hard block increases the elastic modulus and material hardness. With such a large variety in all the three factors defining the properties of the PEBAs, the PA type and block length, the polyether type and block length, and the mass ratio PA/polyether, a very broad range of physical properties can be obtained. Some examples of the property variation are given later.

The type of soft block or the polyether segment used significantly affects the water absorption properties of PEBAs. PEBAs that contain polyethylene–oxide-based soft blocks have a much higher water absorption value as compared to PEBA that has poly THF as the soft polyether block. PEO-based PEBAs absorb up to 120% by weight of water as compared to a poly–THF-based PEBA that absorbs only 1.2% by weight of water [65]. The higher water absorption in the PEO-based PEBAs is accompanied by a higher level of water permeability and a better antistatic behavior compared to the corresponding poly–THF-based PEBA. Material based on PA 12 as the hard block and poly THF as the soft block exhibit the lowest possible density of PEBAs [60] (1.01–1.03 g/cm^3). The PA block has a less significant effect on moisture absorption as compared to the polyether soft blocks. However, it is observed that PA 6-based PEBAs have higher moisture absorption than the corresponding PA 11- and PA 12-based PEBAs, having polyether blocks of the same type and molecular mass.

A range of hardness between 60 Shore A and 75 Shore D can be obtained with PEBAs [65]. For a PEBA based on the PA block, PA 12 and the polyether block of poly THF of molecular mass of ~1000 g/mol, the bending modulus varies from 500 N/mm^2 for the hardest types to ~20 N/mm^2 for the softest types [61]

With respect to thermal properties, depending on the molecular structure, the DSC-determined melting points of the physical network can vary between 122°C for the softer TPEs and 205°C for the harder TPEs.

The range of mechanical and thermal properties combined with their biocompatibility make the use of PEBAs attractive for the medical device sector. Within the cardiovascular area, PEBAs are extensively used for catheters for diagnostic purposes or for the delivery of implantable devices. The variation is hardness of the grades of PEBA has been used to manufacture catheters with varying stiffness, stiffer proximal end versus flexible distal end, using the reflow technique to bond the materials together. Melt processing of PEBAs is easy, for the similar reason to Nylons, as they tend to have a low melt viscosity. Drying of pellets prior to processing is a must and moisture levels below 0.1% are implemented in manufacturing operations with a extrusion temperature range of between 180 and 230°C [60].

Trade names of some important commercial PEBAs are PEBAX (Arkema), Vestamid (Evonik), Grilamid (EMS-Chemie), Dynyl (Rhône-Poulenc), and PAE (Ube).

References

[1] C. Vasile, Handbook of Polyolefins, Marcel Dekker, New York, (2000).
[2] T. Kresser, Polyolefin Plastics, Van Nostrand Reinhold Co, New York, (1969).
[3] A. Albertsson, Long-Term Properties of Polyolefins, Springer-Verlag, Berlin, (2004).

[4] J. Soares, T. McKenna, Polyolefin Reaction Engineering, Wiley-VCH, Weinheim, (2012).
[5] A. Peacock, Handbook of Polyethylene, Marcel Dekker, New York, (2000).
[6] K. Whiteley, T. Heggs, H. Koch, R. Mawer, W. Immel, Polyolefins, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co., KGaA, (2000) DOI: 10.1002/14356007.a21_487.
[7] R. Richards, Polyethylene. Nature 179 (4561) (1957) 643–644.
[8] C. Puig, On the co-crystallization phenomenon in blends of high density polyethylene and low density polyethylene, Polym. Bull. 38 (6) (1997) 715–720.
[9] H. Frank, Polypropylene, Gordon and Breach Science Publishers, New York, (1968).
[10] N. Pasquini, A. Addeo, Polypropylene Handbook, Hanser, Munich, (2005).
[11] C. Blass, Polymers in Disposable Medical Devices, Rapra Technology, Shrewsbury, (1999).
[12] V. Sastri, Plastics in medical devices, William Andrew Publishing, (2013).
[13] S. Ebnesajjad, K. Modjarrad, Handbook of Polymer Applications in Medicine and Medical Devices, William Andrew Publishing, (2014).
[14] M. Maitz, Applications of synthetic polymers in clinical medicine, Biosurf. Biotribol. 1 (3) (2015) 161–176.
[15] P. Gunatillake, R. Adhikari, Nondegradable synthetic polymers for medical devices and implants, in: L. Poole-Warren, P. Martens, R. Green (Eds.), Biosynthetic Polymers for Medical Applications, A Volume in Woodhead Publishing Series in Biomaterials, 2016.
[16] S. Fakirov, Handbook of Thermoplastic Polyesters, Wiley-VCH, Weinheim, (2002).
[17] N. Sanches, M. Dias, E. Pacheco, Comparative techniques for molecular weight evaluation of poly (ethylene terephthalate) (PET), Polym. Test. 24 (6) (2005) 688–693.
[18] S. Jabarin, Crystallization kinetics of poly(ethylene terephthalate). III. Effect of moisture on the crystallization behavior of PET from the glassy state, J. Appl. Polym. Sci. 34 (1) (1987) 103–108.
[19] S. Venkatraman, F. Boey, L. Lao, Implanted cardiovascular polymers: natural, synthetic and bio-inspired, Prog. Polym. Sci. 33 (9) (2008) 853–874.
[20] R. Williams, T. Daniels, Polyamides, ISmithers Rapra Pub, Shrewsbury, (1990).
[21] W. Alewelt, G. Becker, L. Bottenbruch, Polyamide, Hanser, München [u.a.], (1998).
[22] R. Gaymans, D. Sikkema, Aliphatic polyamides, in: G. Allen, G.C. Eastmond (Eds.), Comprehensive Polymer Science and Supplements, Pergamon, Oxford, 1989, pp. 357–373.
[23] D. Vroom, Thermal and mechanical analysis of nylon 6 and nylon 6,6 blends, San Jose State University, MS dissertation, (1997)
[24] E. Sorta, G. Dellafortuna, Poly(ester amide)-polyether block copolymers: preparation and some physicochemical properties, Polymer 21 (7) (1980) 728–732.
[25] H. Boublil, E. Okoroafor, M. Belhoucine, J. Rault, M. Atochem, Morphology of polyamide and polyether block amide blends, Polym. Eng. Sci. 29 (10) (1989) 679–684.
[26] Freedoniagroup.com. World Polyethylene—Industry Market Research, Market Share, Market Size, Sales, Demand Forecast, Market Leaders, Company Profiles, Industry Trends and Companies including Dow Chemical, Exxon Mobil and SABIC (2014) Available from: http://www.freedoniagroup.com/World-Polyethylene.html
[27] R. Hoff, R. Mathers, Handbook of Transition Metal Polymerization Catalysts, John Wiley & Sons, (2010).
[28] K. Buschow, Encyclopedia of Materials, Elsevier, Amsterdam, (2001).
[29] K. Ziegler, G. Fink, R. Mülhaupt, H. Brintzinger, Ziegler Catalysts, Springer-Verlag, Berlin, (1995).
[30] D. Malpass, Introduction to Industrial Polyethylene, Scrivener Pub, Salem, MA, (2010).
[31] P. Feucht, B. Tilger, G. Luft, Prediction of molar mass distribution, number and weight average degree of polymerization and branching of low density polyethylene, Chem. Eng. Sci. 40 (10) (1985) 1935–1942.
[32] W. Fan, R. Waymouth, Alternating copolymerization of ethylene and propylene: evidence for selective chain transfer to ethylene, Macromolecules 34 (25) (2001) 8619–8625.
[33] J. Chen, F. Tsai, Y. Nien, P. Yeh, Isothermal crystallization of isotactic polypropylene blended with low molecular weight atactic polypropylene. Part I. Thermal properties and morphology development, Polymer 46 (15) (2005) 5680–5688.
[34] C. Vasile, L. Odochian, I. Agherghinei, Thermoxidative degradation of polypropylene, Additives Polym. 18 (7) (1988) 3.
[35] N. Grassie, Handbook of polymer degradation, Polym. Degrad. Stabil. 40 (1) (1993) 137.

[36] V. Iakovlev, S. Guelcher, R. Bendavid, Degradation of polypropylene in vivo: a microscopic analysis of meshes explanted from patients, J. Biomed. Mater. Res. B 00B (2015) 000–000.
[37] Ethicon.com. (n.d.). PROLENE® Polypropylene Suture | Ethicon. Available from: http://www.ethicon.com/healthcare-professionals/products/wound-closure/non-absorbable-sutures/prolene-polypropylene
[38] Y. Bilsel, I. Abci, The search for ideal hernia repair; mesh materials and types, Int. J. Surg. 10 (6) (2012) 317–321.
[39] Fda.gov. FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence (2008) Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm
[40] H. Köpnick, M. Schmidt, W. Brügging, J. Rüter, W. Kaminsky, Polyesters, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co., KGaA, (2000).
[41] L. Ji, Study on preparation process and properties of polyethylene terephthalate (PET), AMM 312 (2013) 406–410.
[42] Du Pont, Polymeric linear terephthalic esters (1949) 2,465,319.
[43] S. Jabarin, Crystallization kinetics of polyethylene terephthalate. II. Dynamic crystallization of PET, J. Appl. Polym. Sci. 34 (1) (1987) 97–102.
[44] P. Varma, E. Lofgren, S. Jabarin, Properties and kinetics of thermally crystallized oriented poly(ethylene terephthalate) (PET). I: kinetics of crystallization, Polym. Eng. Sci. 38 (2) (1998) 237–244.
[45] G.C. Alfonso, M.P. Verdona, A. Wasiak, Crystallization kinetics of oriented poly(ethylene terephthalate) from the glassy state, Polymer 19 (1978) 711–716.
[46] S. Jabarin, Optical properties of thermally crystallized poly(ethylene terephthalate), Polym. Eng. Sci. 22 (13) (1982) 815–820.
[47] D. Salem, Microstructure development during constant-force drawing of poly(ethylene terephthalate) film1An abbreviated version of this paper was presented at the SPE Annual Technical Conference, 6-10 May 1996, Indianapolis, Indiana, USA. 1, Polymer 39 (26) (1998) 7067–7077.
[48] T. Ferington, The structure of polymers (Miller, M. L.), J. Chem. Educ. 44 (4) (1967) A358.
[49] U. Thiele, Polyester Bottle Resins, Heidelberg Business Media, Heidelberg, (2007).
[50] W. Michaeli, M. Koschmieder, Processing principles for thermoplastic polymers, in: Hashmi Saleem (Ed.), Comprehensive Composite Materials, Reference Module In Materials Science And Materials Engineering, 2000.
[51] W. Carothers, Polymerization, Chem. Rev. 8 (3) (1931) 353–426.
[52] N. Ogata, Synthesis of nylon by carothers, Kobunshi 56 (1) (2007) 14–15.
[53] M. Musser, Adipic acid, Ullmann's Encyclopedia of Industrial Chemistry (2000).
[54] J. Ritz, H. Fuchs, H. Kieczka, W. Moran, Caprolactam, Ullmann's Encyclopedia of Industrial Chemistry (2011).
[55] K. Moskatov, A. Odinokov, Structure and properties of polyamide-6, Polym. Sci. U.S.S.R. 27 (11) (1985) 2738–2742.
[56] R. Palmer, Polyamides, plastics, Encyclopedia of Polymer Science and Technology.
[57] S. Lomakin, G. Zaikov, M. Artsis, Advances in Nylon 6,6 flame retardancy, Int. J. Polym. Mater. 32 (1–4) (1996) 173–202.
[58] M. Kohan, Nylon Plastics Handbook, Hanser Publishers, Munich, (1995).
[59] I. Page, Polyamides as Engineering Thermoplastic Materials, Rapra Technology Ltd, Shawbury, Shrewsbury, Shropshire, UK, (2000).
[60] R. Rulkens, C. Koning, Chemistry and technology of polyamides, in: K. Matyjaszewski, M. Möller (Eds.), Polymer Science: A Comprehensive Reference, Elsevier, Amsterdam, 2012, pp. 431–467.
[61] B. Carlowitz, M. Boysen, Die Kunststoffe, Hanser, München u.a, (1990).
[62] Y. Suzuki, M. Nakamura, A. Aochiama, Asahi Kasei, EP 221188, 1987.
[63] C. Tanaka, A. Chita, S. Nakashima, N. Shimobu, Toray Industries Inc., DE 3145998, 1982.
[64] C. Tanaka, S. Nakashima, M. Kon Dou, Toray Industries Inc., EP 95893, 1983.
[65] G. Deleens, in: G. Legge (Ed.), Thermoplastic Elastomers, Hanser Verlag, München/Vienna/New York, 1990, pp. 215–239.

3 Speciality Plastics in Cardiovascular Applications

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1 Introduction

Many plastics are formulated specifically for use in medical applications. Some of these materials are used within other applications as well and only specific formulations of that material are used for medical devices. The main specialty plastics used for cardiovascular applications are:

- polyurethanes
- polysiloxanes
- polytetrafluoroethylene (PTFE)
- biodegradable plastics

Polyurethanes are a class of widely researched materials and they are found in numerous areas, with their properties ranging from hard plastics to soft gels and applications ranging from furniture foam to shoe soles [1–3]. Among the properties and applications of polyurethanes is the use of these polymers as elastomeric materials [4–6]. It is primarily as elastomeric formulations with certain specific raw materials that have found use in the area of medical applications [7–11]. Polysiloxanes, commonly known as silicones, are also widely researched materials and used in varied applications [12–17]. The use of polysiloxanes as components and adhesives in the field of medical devices is well documented [18–21]. PTFE is a part of the fluorinated polymers group and is well known for its properties of hydrophobicity and low surface friction [22–25], the use of PTFE in the medical devices area is established and documented [26–28]. Materials that degrade in the body after they perform the requisite therapeutic function as medical devices are increasingly being explored as viable options from biomaterials [29–31] with some successful applications being reported [32,33]. Apart from these specialty materials, there are others that have found usage in medical devices, these include polyacetals and polyether ether ketone (PEEK). However, their usage is low in the cardiovascular space and therefore they are not specifically covered in this chapter.

The major material manufacturers for some of these specialty plastics are listed in Table 1, only manufacturers that have grades available for medical use are listed.

2 Polyurethanes

Polyurethanes are a very versatile group of materials with properties allowing them to be used in applications ranging from stretchable fabrics to foams for furniture and insulation to hard plastics parts for electronic devices [1–3]. The polyurethane group of materials is characterized by the presence of the urethane bond; the urethane bond is formed by the reaction of the end groups of isocyanate and hydroxyl on the reacting molecules. Since the existence of the urethane bond describes the polyurethane polymer this implies that the molecules on either side of the end groups could take on many different forms. This flexibility implies that a whole variety of different polyurethanes can be formulated and these polyurethanes can possess a complete range of properties from soft gels to high modulus hard materials [1–3].

2.1 Chemistry of Polyurethanes

The chemistry of the polyurethane reaction was first discovered in 1937 by a team of German chemists working for the chemical company IG Farben, the team was led by Otto Bayer [1]. Polyurethanes are an example of a polymer formed through the step-growth process. The urethane bond is a result of an isocyanate group reacting with a hydroxyl group, as shown in the following,

$$—NCO + —OH \rightarrow —NHCOO—$$

The —NHCOO— linkage is commonly referred to as the urethane linkage, it is also known as the carbamate linkage. The polymerization of polyurethanes is a good example of a step-growth reaction that does not follow the condensation route, that is, there is no production and subsequent release of a small molecule during the formation of the urethane bond.

For the formation of long chain polyurethane, the minimum functionality that the molecules, the bearing the end groups of isocyanates and hydroxyl,

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Table 1 Major Material Manufacturers of Specialty Plastics

Company	Material	Grades
AdvanSource Biomaterials, USA [34]	Thermoplastic polyurethane	Polyether, polycarbonate, and TPUs based on blends of polyether, polycarbonate with polysiloxane • ChronoFlex • ChronoThane • ChronoSilPolyether-based hydrophilic TPUs • HydroMed • HydroThane
BASF, Germany [35]	Thermoplastic polyurethane	Polyether-based TPU 70A–64D • Elastolan 1100
Biomerics, USA [36]	Thermoplastic polyurethane	Polether, polycarbonate, and polysiloxane-based TPUs • Quadrathane • Quadraflex • Quadraplast • Quadrasil
Covestro, Germany [37]	Thermoplastic polyurethane	Polyether-based TPUs 70A–85D • Texin Rx
DSM Biomedical, USA [38]	Thermoplastic polyurethane	Polyether, polycarbonate, and TPUs based on blends of polyether, polycarbonate with polysiloxane • Bionate • Biospan • Carbosil • Pursil • Elasthane
Lubrizol, USA [39]	Thermoplastic polyurethane	Aliphatic and aromatic TPUs based on polyether and polycarbonate soft segments • Pellethane • Tecothane • Tecoflex • Carbothane Polyether-based hydrophilic TPUs • Tecophilic All hard block TPU • Isoplast
Dow Corning, USA [40]	Silicones	HCR LSR PSA Curable adhesives
Momentive, USA [41]	Silicones	HCR LSR PSA Curable adhesives
NuSil, USA [42]	Silicones	HCR LSR PSA Curable adhesives
Wacker Chemie AG, Germany [43]	Silicones	HCR LSR PSA Curable adhesives

HCR, High consistency rubber; LSR, liquid silicone rubber; PSA, pressure sensitive adhesives.

must possess is 2. A stoichiometric ratio with the two molecules then guarantees the formation of high molecular weight polyurethane. As the functionality of either or both of the molecules increases beyond 2.0, the resulting polyurethane tends toward being cross-linked and thermoset in nature.

Most of the polyurethanes used in medical devices, especially in implantable applications tend to be thermoplastic in nature [7–11]. Thermoplastic polyurethanes are referred to as TPUs. TPUs derive their properties through the presence of a microphase structure. In the formulation of TPUs, there is a mixture of hydroxyl containing molecules. The longer chain, higher molecular weight, hydroxyl containing molecule is termed as a polyol whereas the shorter chain, smaller molecular weight, hydroxyl containing molecule is usually referred to as a chain extender. As will be seen later, the isocyanate containing molecule could be either aromatic or aliphatic in nature, however, the hydroxyl containing molecules are almost always aliphatic in nature in the make-up of TPUs [8,9]. When both the hydroxyl containing groups react with the isocyanate containing molecule a urethane linkage is formed. The reaction with the polyol produces chains with urethane bonds spread between the aliphatic chains of the polyol. In other words, the concentration of the urethanes when the isocyanate reacts with the polyol is low. In contrast, the reaction of the isocyanate with the chain extender produces a much higher concentration of the urethane bonds due to the shorter chain length of the chain extender. As a result of the higher concentration of the urethane linkage and shorter, frequently aromatic nature of the isocyanate molecule, the reaction of the isocyanate with the chain extender produces an inflexible structure and this is known as the hard segment. The reaction of isocyanate with the polyol, on the other hand, produces a lower concentration of the urethane linkage that is interspersed with flexible aliphatic chains of the polyol and hence forms what is known as the soft segment. A thermodynamic incompatibility exists between the two phases and as a result there is separation between the two phases. This phase separation gives rise to a segmental structure of TPU and sometimes leads to the material also being referred to as segmented polyurethane (SPU) [4,5]. The separation of the microstructure into distinct hard and soft phases and the resultant biphasic structure plays an important role in the physical properties of TPUs. In simple terms, it can be said the hard phase is responsible for the strength, modulus, and hardness of the material whereas the soft segment decides the elongation properties and the elastomeric nature of the material.

2.2 Raw Materials

2.2.1 Isocyanates

Isocyanates used in the preparation of polyurethanes could be aromatic or aliphatic in nature. The typical examples of aromatic isocyanates include toluene diisocyanates (TDI) and methylene diphenyl isocyanate (MDI), typical aliphatic compounds include hexane diisocyanate (HDI), isophorone diiscocyanate (IPDI), and methylene dicyclohexyl isocyanate (H_{12}MDI). MDI is the most widely used isocyanate to make TPUs, worldwide the production of MDI is of the order of 5 million tons [44]. MDI is available in the pure and polymeric form, pure MDI is used for the manufacture of TPUs. MDI is made from a reaction of aniline and formaldehyde using an acidic catalyst such as hydrochloric acid and subsequently treated with phosgene [45]. The structures of different isocyanates are shown in Fig. 1.

Aromatic isocyanates are stiffer in nature resulting in a stiffer polymer chain with tightly packed hard segment and a higher melting point. The use of an aromatic isocyanate has also been shown to have an enhanced biostability [9] over aliphatic isocyanates.

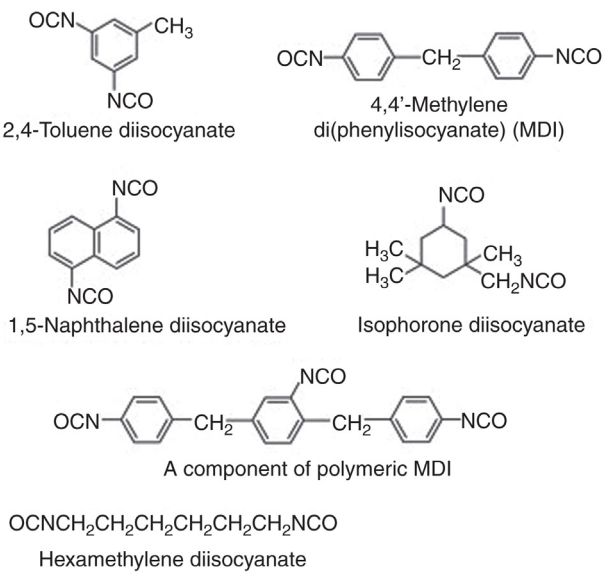

Figure 1 Structures of common isocyanates. *Courtesy: Elsevier Publications; G. Avar, U. Meier-Westhues, H. Casselmann, D. Achten, Polyurethanes, Polym. Sci. 10 (2012) 411–441 [46].*

Aromatic isocyanates tend to interact with light and the presence of chromophores results in increasing yellowness of the polyurethane over time. This instability of polyurethanes made from aromatic isocyanates means that in certain light sensitive applications, aliphatic isocyanates are preferred. However, the use of aliphatic isocyanates is accompanied by a resultant decrease in the material's mechanical properties and biostability.

As indicated earlier, MDI is most commonly used isocyanate for the formulation of TPUs. If aliphatic isocyanate is preferred for the application, a cycloaliphatic version H_{12}MDI is used.

2.2.2 Polyols

Different polyols are used in the formulation of TPUs. Compounds could be polyesters, polyethers, polycarbonates, hydrocarbons, and polysiloxanes, the essential condition, of course, is that they are hydroxyl terminated. The structures of commonly used polyols are depicted in Fig. 2.

The polyol determines to a large extent the nature of the properties of the polyurethane. A polyester backbone contains the ester linkage that is hydrolytically unstable and exposure to water results in material degradation [9]. This property means that polyurethanes made from a polyester polyol are unsuitable for use in a stable, implantable application. Polyether polyols, on the other hand, have very good resistance to hydrolysis but their resistance to oxidation, especially at low hard segment levels, means that they might not be suited for long-term implants where oxidation concerns are important [48]. Polyurethanes based on polycarbonate and polysiloxane diols combine different levels of hydrolytic and oxidative resistance and are used in different implantable applications [8,9,49]. Polyols based on polyisobutylene and polyurethanes made from them have also shown good resistance to hydrolysis and oxidation [50,51].

Chemical Name	Code	Chemical Structure of the Repeating Unit
Poly(ethylene oxide)	PEO	(CH_2CH_2O)
Poly(pro pylene oxide)	PPO	(CH_2CHO) with CH_3
Poly(tetramethylene oxide)	PTMO	$(CH_2CH_2CH_2CH_2O)$
Poly(butylene adipate)	PBA	$(O(CH_2)_4OC(CH_2)_4C)$ with O, O
Polycaprolactone	PCL	$(CH_2CH_2CH_2CH_2CH_2CO)$ with O
Polydimethylsiloxane	PDMS	CH_3, $(Si—O)$, CH_3
Polyisobutylene	PIB	CH_3, $CH_2—C$, CH_3
Poly(ethylene butylene)	PEB	$(CH_2CH)(CH_2CH)$ with CH_2CH_3

Figure 2 Structures of polyols used in polyurethanes. *Courtesy: Elsevier Publications; I. Yilgör, E. Yilgör, G. Wilkes, Critical parameters in designing segmented polyurethanes and their effect on morphology and properties: a comprehensive review, Polymer 58 (2015) A1–A36 [47].*

2.2.3 Chain Extenders

Chain extenders are hydroxyl terminated molecules with a much shorter chain length as compared to polyols. The chain extender compounds may be aromatic or aliphatic and in addition they could also be amine terminated rather than hydroxyl terminated. The reaction of an isocyanate with amine is kinetically very rapid and exothermic [52] and results in the formation of urea groups. These groups can react further and produce biuret cross-links. The tendency of amine terminated chain extenders to produce cross-links and also their speed of reaction with isocyanates limit their usage especially in the formulation of TPUs.

The structure of the chain extenders determines the rigidity of the hard blocks and density of hydrogen bonds. The most common chain extender used in TPUs for medical applications is butane diol (BDO).

2.3 Synthesis of Polyurethanes

Thermoplastic polyurethanes are formed by the step-growth polymerization of isocyanate molecules and hydroxyl terminated molecules. To manufacture thermoplastic polymers each molecule is bifunctional so that only linear chains are formed. This simple picture may be complicated by branching reactions. The final molecular weight that a formulation can achieve is governed by the index of the formulation. If there are equal numbers of hydroxyl and isocyanate groups then, in theory, the molecular weight can become infinite. In practice formulations are often designed to be "off-index."

Thermoplastic polyurethanes are formed by the step-growth polymerization of isocyanate molecules (—NCO) and hydroxyl terminated molecules (—OH). The kinetics of the polyurethane reaction dictates the speed and propensity to form certain end products preferentially over others. The kinetics, similar to other reaction kinetics, is dependent upon the process conditions of reaction and the formulation employed. The kinetics of step-growth polymerization is well understood and documented [52,53].

2.3.1 Kinetics of the Polyurethane Reaction

The basics of the reaction kinetics of the formation of polyurethanes is examining the disappearance of the isocyanate group as a function of time, this leads to the fundamental equation of the kinetics of step-growth polymerization in polyurethane:

$$-\frac{d}{dt}[\mathrm{NCO}] = k[\mathrm{NCO}][\mathrm{OH}] \tag{1}$$

where, [NCO] and [OH] represent the molar concentrations of the isocyanate group and the hydroxyl group.k represents the kinetic constant of the equation.

In a formulation that is perfectly "on-index," the concentration of NCO and OH will remain equal always and the equation may be simplified to:

$$-\frac{d}{dt}[\mathrm{NCO}] = k[\mathrm{NCO}]^2 \tag{2}$$

However, when the system is "off-index" then this simplification may not formally be made. In the off-index case, every NCO that reacts consumes an OH group. This means that the concentration of NCO and OH always differ by a fixed amount:

$$[\mathrm{OH}] = [\mathrm{NCO}] \pm \mathrm{C} \tag{3}$$

C may be determined from the initial formulation:

$$\mathrm{C} = abs([\mathrm{OH}]_0 - [\mathrm{NCO}]_0) \tag{4}$$

Eq. (1) may be rewritten by substituting in Eq. (3) and then rearranging as an integral:

$$-\int \frac{d[\mathrm{NCO}]}{[\mathrm{NCO}]([\mathrm{NCO}]+\mathrm{C})} = \int k\,dt \tag{5}$$

This integral may be solved using the standard integral:

$$\int \frac{dx}{x(x+c)} = -\frac{1}{c}\ln\left(\frac{x+c}{c}\right) \tag{6}$$

This yields the expression:

$$\left[-\frac{1}{c}\ln\left(\frac{x+c}{x}\right)\right]_{[\mathrm{NCO}]_0}^{[\mathrm{NCO}]} = [kt]_0^t \tag{7}$$

This may be rearranged to give:

$$[NCO] = \frac{[NCO]_0 C}{(C+[NCO]_0)e^{Ckt} - [NCO]_0} \tag{8}$$

One can therefore say the rate of decrease of the concentration of the isocyanate groups or in other words, the rate of the polyurethane reaction is dependent on a few factors:

- the initial concentration of the isocyanate groups, $[\mathrm{NCO}]_0$;
- the extent of the "off-index" quantity, C;
- the kinetic constant, k.

The kinetic constant, k, is also dependent on the temperature of the reaction and the type and amount of catalyst used.

The number average molecular weight may be readily determined from the concentration of isocyanate groups remaining in the system. This is possible because the number average molecular weight is simply the ratio of the total mass in grams to the total number of moles. The total number of moles is simply half the number of ends in the system. Hence the M_n is given by:

$$M_n = \frac{\text{Total mass}}{\text{Total number of moles}}$$

$$M_n = \frac{\text{Total mass}}{(\text{Total number of moles end groups})/2} = \frac{2\rho V}{[\text{NCO}]V + [\text{OH}]V} = \frac{2\rho V}{[\text{NCO}]V + [\text{OH}]V} = \frac{2\rho V}{[\text{NCO}]V + ([\text{NCO}] + \text{C})V} \quad (9)$$

This yields the following expression for the number average molecular weight:

$$M_n = \frac{2\rho}{2.[\text{NCO}] + \text{C}} \quad (10)$$

2.3.2 Reactivity of Isocyanates

In the ideal scenario, the —NCO + —OH should be the only reaction taking place in the formation of linear polyurethanes. However, due to the hyperreactivity of the —NCO terminated molecules, a number of side reactions take place. These include the reaction of the —NCO group with a urethane group to give rise to an allophanate linkage, the reaction of the —NCO groups with any residual water molecule to eventually form a biuret linkage, and so on. These side reactions cause the formation of interchain linkages and can lead to cross-linking and gel formation. The side reactions are undesirable from the point of view of polymer consistency and properties. All these side reactions are governed by the kinetics and the reaction conditions.

The multiple reactions in polyurethane formation can be grouped in the form of differential equations and can be solved by various techniques including Monte-Carlo statistical functions. The simulated reaction scheme can allow one to follow each reaction time–temperature step.

The knowledge of the reaction kinetics, thus, allows one to control the reaction conditions to obtain optimum —NCO conversion, reduce side reactions, gel formation, and minimize batch-to-batch variation.

The reaction of the isocyanate group (NCO) during the polyurethane reaction can proceed in the following ways as illustrated in Fig. 3 [54]:

1. *Urethane reaction*

   This is the reaction of the isocyanate group with the hydroxyl group where the NCO group reacts with the hydroxyl (OH) group present at the end of a polyol and this leads to the formation of a urethane bond. The urethane reaction is the primary reaction that leads to the formation of a linear polyurethane chain.

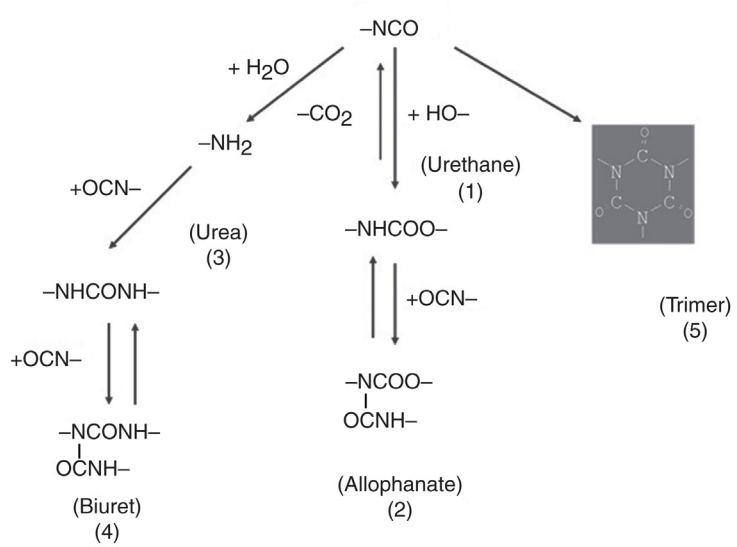

Figure 3 Reactions of the isocyanate (NCO) group.

2. *Allophanate reaction*

   This reaction occurs when an already formed urethane reacts with an isocyanate group leading to a reaction between adjacent molecular chains and branching. This branching, if uncontrolled, could lead to eventual cross-linking. This is a side reaction that is an undesirable route, however, is unavoidable in many urethane systems. The control of the allophanate reaction is effected by controlling the temperature of the reaction and the resulting exotherm. In a two step TPU synthesis, for example, the first step also known as the prepolymer reaction is carried out under a reaction temperature of 100°C to avoid the formation of allophanate groups.

3. *Urea*

   The reaction of the NCO groups with the OH group present on the water molecule leads to the formation of amine (—NH_2) and further reaction forms the urea group. This reaction occurs in all instances as there are traces of moisture present in the poly/diols. This reaction is itself not objectionable as the polymerization with the formation of a difunctional chain continues; however, the presence of the urea group can lead to undesirable branching and side reactions. A control of this reaction is effected by a control of moisture in all the hydroxyl-containing molecules to usually below 200 parts per million.

4. *Biurets*

   Biurets occur as a result of the urea groups, formed in the previous reaction, reacting with an isocyanate group. The reaction leads to the formation of linkages between two chains, branches, and other side reactions.

5. *Trimer*

   Trimerization is the formation of ring structure between three terminal NCO groups. The ring structure is known as the isocyanurate bond and is not thermally reversible unlike the allophanate or biuret structures.

2.3.3 Catalysis of the Polyurethane Reaction

It is seen that the reactions of the NCO group are catalyzed by both basic and acidic compounds. Tertiary amine catalysts are widely used in polyurethane reaction catalysis, these catalysts function by enhancing the nucleophilicity of the diol component. Basic catalysts are known to be far more potent in nature as compared to acidic catalysts. As a result, basic catalysts not only increase the rate of the primary urethane reaction but also increase the rate of reaction of the undesirable side reactions of the NCO [54]. The acid-based catalysts, on the other hand, have been shown to be effective in controlling the side reactions by favoring the progression of the linear urethane reaction [54].

From the illustration of the NCO reactions in Fig. 3, reaction 1 is encouraged more than reactions 2, 3, 4, and 5 in the case of an acid catalyzed system whereas all reactions 1–5 are equally possible with a base catalyzed system. The presence of an acid is not shown to catalyze any branching or cross-linking in the formation of polyurethanes.

In traditional polyether polyols, basic catalysts are used to ring open epoxide-based molecules and initiate an ionic reaction to form longer chain polyether structures. At the end of the manufacturing step, acids are used to neutralize the catalyst to prevent the residual of the basic catalyst being a part of any further reaction of the polyol. Acid number of polyether polyols is a property measured to ensure that the base is properly neutralized [1,3].

Acid number measurement in polyester polyols is more critical than polyether polyols and the reason is that the acid number indicates the presence of carboxylic acid-terminated groups. Carboxylic acid reacts with NCO to effectively chain terminate and also lead to carbon dioxide formation. To avoid these issues an acid value of < 0.5 mg of KOH/g acid is specified for polyester polyols [3].

2.4 Manufacture of Polyurethanes

The step-growth polymerization of polyurethane can proceed either in bulk or in solution. The solvents commonly used for solution polymerization are dimethyl formamide (DMF), dimethylacetamide (DMAc), and tetrahydrofuran (THF). Solution polymerization is suitable for small batches and for reactions that need constant dissolution preventing premature phase separation and the development of molecular weight. Solution polymerization does limit the batch size and one also has to deal with the removal of the solvent in the final application. To keep the viscosity of solution to easy-to-handle levels, the proportion of the solvent used is high and often greater than 70% by weight. Solution polymerized material can further be processed by solvent processing techniques such as film casting or dip molding.

Bulk polymerized polyurethane, on the other hand, is very suited for large-scale production and

does not suffer from any subsequent solvent disposal issues. The formulation, however, has to be amenable for bulk polymerization and not prone to premature phase separation.

Bulk polymerization can proceed through a batch process or a continuous process.

Polyurethane polymerization can either using a one-step process or a two-step process. The difference between the processes is essentially the addition sequence of the raw materials for synthesis. In a one-step process, all the raw materials for the synthesis are added at once, whereas, in a two-step process, the polyol is first reacted with an excess of isocyanate to produce an isocyanate end-capped prepolymer. The prepolymer is then reacted with a stoichiometric quantity of the short chain diol or the chain extender. The prepolymer can also be seen as the soft segment and the reaction of the prepolymer with the chain extender as the formation of the hard segment.

A two-step process is usually employed for the batch polymerization process of thermoplastic polyurethane. In the formation of the prepolymer, the polyol is usually slowly fed to the isocyanate to control the temperature rise of the exothermic urethane reaction. The chain extender is then mixed with prepolymer and dispensed onto trays. These trays are then placed in heated ovens for a fixed period of time. At the end of the curing time, the polymer slabs are removed from the trays, granulated and subsequently melt extruded into pellets. A typical batch process is depicted in Fig. 4.

In a continuous process a twin screw extruder is used as the reactor (Fig. 5) [55,56]. The extruder screws are designed to self-wipe and thus avoid any material hold ups during the reaction. The temperature in the extruder is raised beyond the melting point of the material and therefore the polymerization can be accurately defined as melt polymerization. The high temperature implies that even with a relatively short residence time, of the order of minutes, high conversion and high molecular weights can be obtained at the end of the extruder [53,57]. The high temperature does increase the possibility of the reverse reaction and depolymerization and this has to be kept in mind when designing the process [57].

Apart from being self-wiping, the screws in a twin screw extruder are modular in nature, this modularity allows the configuration of the screw geometry to match the chemistry and kinetics of the polyurethane

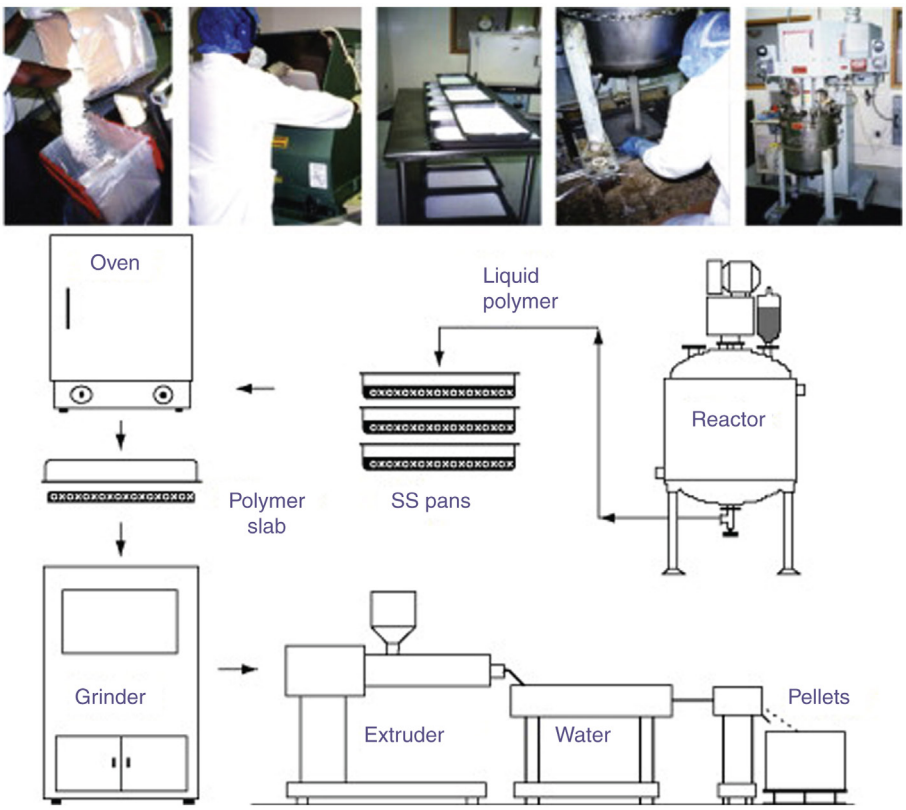

Figure 4 A typical batch production process for polyurethane production. *Courtesy: Elsevier Publications; R. Ward, R. Jones, Polyurethanes and silicone polyurethane copolymers, in: Comprehensive Biomaterials, 2011, pp. 431–477 [55].*

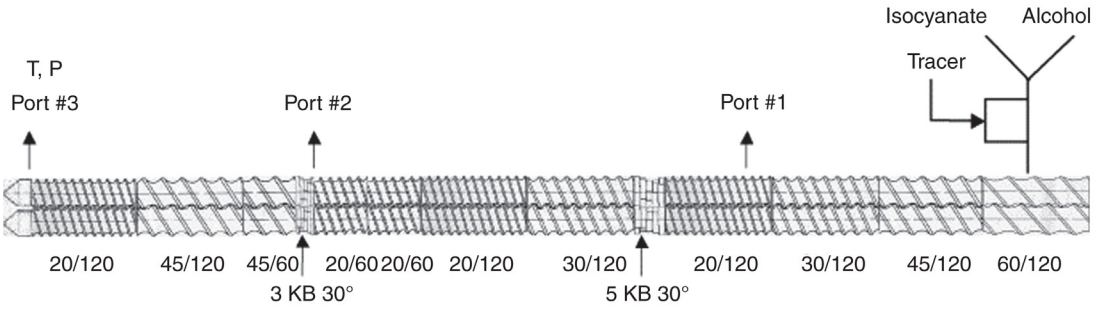

Figure 5 A typical batch production process for polyurethane production. *Courtesy: Elsevier Publications; J. Puaux, P. Cassagnau, G. Bozga, I. Nagy, Modeling of polyurethane synthesis by reactive extrusion, Chem. Eng. Process. 45 (6) (2006) 481–487 [56].*

reaction. In general, the twin screw extruder can be configured for the screws to act as conveying zones by having the screw made of transport elements and as mixing zones by having the screw made of kneading paddle elements. In addition to conveying and mixing zones, the screw can also be configured to act as a reverse pumping element. In that case, melt flow occurs in the opposite direction and to flow in the correct direction, the pressure drop provided by the reverse elements has to be overcome by buildup of pumping pressure in the conveying zone prior to the reverse zone. The reverse elements can increase the residence time within the screw allowing for greater conversion for a formulation. An example of a screw design can be seen in Fig. 5.

To maintain the correct chemistry, the extruder is usually fed with a mass flow controlled liquid feeding system that guarantees the ratio of the mix and thus the stoichiometry of the reaction.

As explained earlier, the synthesis of polyurethanes can proceed in either a one-step process or a two-stage process. In a one-step process, the isocyanate, the polyol, the chain extender and any catalysts or additives are added together in one shot. In a one-shot process, reaction of the isocyanate with the hydroxyls located on the polyol and the chain extender happen simultaneously and so there is considerable importance in the relative reaction rates. If the reaction rates are significantly different, like in the case of a polydimethylsiloxane (PDMS)-based polyol, where the polarities of the isocyanate and the polyol are very far apart, the one-shot process will not work. The difference in polarities slows down the speed of the reaction between the isocyanate and the polyol in relation to reaction of the isocyanate with a more polar chain extender. In such a case the one shot process will produce incomplete reaction of the polyol with the isocyanate and result in high concentration of hard segments with possible cross-links and gels. The one-shot process works well when the polarities of the short chain diol and the long chain polyol are closer, in instances such as using a relatively nonpolar siloxane polyol and a polar BDO chain extender, the one shot process is less effective.

In contrast, a two-step process is more controlled. Here the isocyanate first reacts with the polyol alone in a stoichiometric ratio that allows further reaction with the chain extender. This isocyanate-rich compound is often referred to as the prepolymer. Once the prepolymer is formed it then goes on to further react with an appropriate level of the chain extender to form the final polyurethane. In such a case there is better control over the formation of hard and soft blocks and less randomness is associated with this process.

2.5 Properties of Polyurethanes

Given the variety of polyurethanes that can be constructed from, among other factors, using different raw materials, isocyanates, polyols and chain extenders, stoichiometries, cross-link densities, and different ratios of hard to soft segments one can end up with innumerable of kinds of polyurethane materials and the resultant properties. From a perspective of thermoplastic polyurethanes especially the ones used for biomedical applications the list narrows but is still quite a broad range as seen in the Fig. 6, where the breadth of the elastic modulus achievable with TPUs is compared to other materials.

The dependence of polyurethane properties on the factors stated previously extends to all forms of behavior of polyurethanes with respect to their mechanical, chemical, thermal, rheological, and surface properties. The properties of polyurethanes are decided by many of these factors. Greater hard segment content leads to a harder material with higher

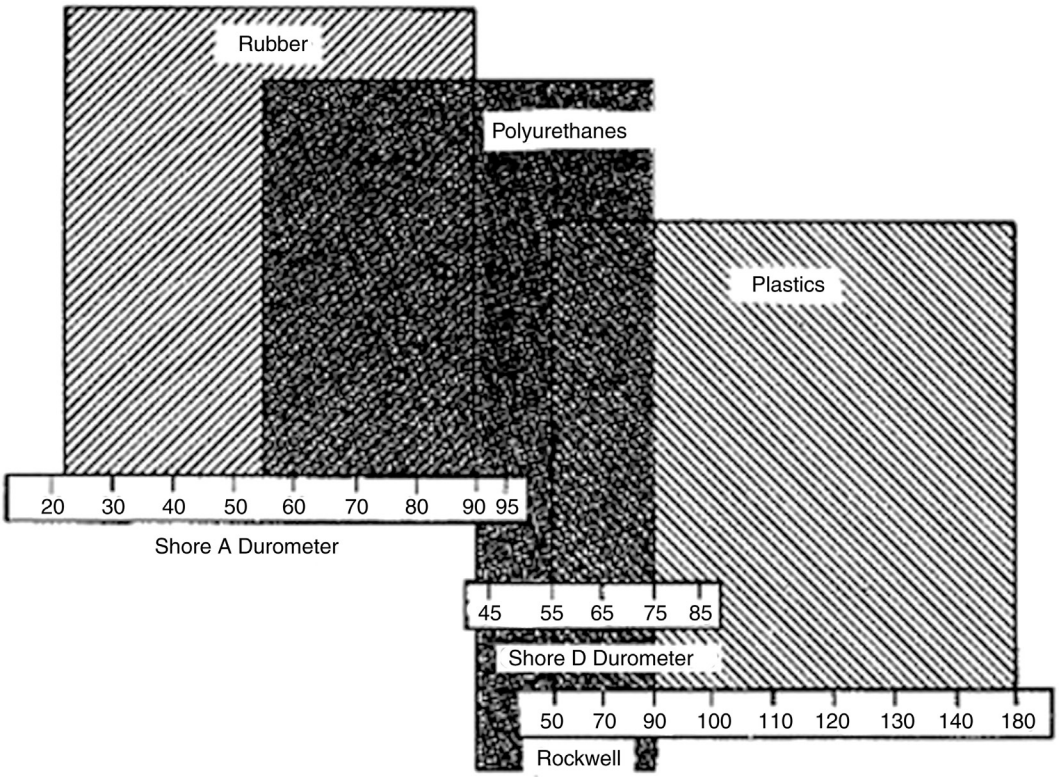

Figure 6 Hardness variation of TPUs. *Courtesy: Elsevier Publications; J. Drobny, Thermoplastic polyurethane elastomers, in: Handbook of Thermoplastic Elastomers, 2014, pp. 233–253 [58].*

modulus, tensile strength values, and lower % elongation. The elastomeric properties are also dependent on factors such as the nature of the raw materials, the stoichiometry used in the formulation and the ratio of the hard blocks to the soft blocks.

- The nature of the raw materials:
  - Aromatic isocyanates tend to give a more integral hard block structure, resulting in greater phase separation and that often leads to higher mechanical properties, greater chemical resistance, and higher melting points in comparison with the nonaromatic isocyanates. Polyurethanes composed of aromatic isocyanates are inherently more biostable than polyurethanes made from a nonaromatic isocyanate [9]. This again is related to the integrity of hard blocks aromatic isocyanates form.
  - The polyols influence polyurethane properties very significantly. The polyol forms the soft segment of the polyurethane and the soft segment is primarily responsible for the elastomeric properties of the polymer. Depending on the molecular weight of the polyol, the extensibility of the material can vary. Smaller chain lengths of the polyol can give a material that is stiffer and less elastomeric than with a longer chain length of the same polyol [8,9]. The nature of the linkage in the main chain of the polyol has a significant impact upon the degree of phase separation between the hard and soft phases. The difference in the polarity of the polyol and the isocyanate essentially determines the amount of phase separation that will occur in the final material [47]. It is seen with greater phase mixing one can obtain greater elastomeric properties [59].
- The nature of the polyol plays a very important role in deciding the chemical properties of polyurethanes. The chemical properties of the main bond in the soft segment decide the interaction of the material with different chemicals. Polyols made with the ester bond as the main linkage are susceptible to hydrolytic cleavage. Hence on exposure to water the material disintegrates. Quite clearly polyurethanes based on polyester polyols cannot be considered for any implantable

devices that rely on the biostability of the polymer. On the other hand, this property of moisture sensitivity can prove to be very useful in designing biodegradable polyurethanes and the molecular weight of the polyester polyol can be used to regulate the kinetics of biodegradation [60]. Polyols made with the ether bond are widely used for polyurethanes in the medical device sector. The ether bond imparts greater moisture resistance to the material but does have a high possibility of oxidation [9,48]. As will be seen later, oxidation and hydrolysis are the main degradative mechanisms the material has to encounter within the body and so a greater susceptibility to either of them limits their use in biostable medical devices. Polyols based on carbonate and siloxane linkages have shown to be superior in their oxidation resistance [48,49] and between them siloxane polyols have shown better resistance to oxidation [48], recent work on using a polyisobutylene polyol has also shown good hydrolytic and oxidation resistance [50,51].

- The chain extenders play a key role in deciding the structure of the hard blocks. A longer chain or a nonlinear chain extender will result in an imperfectly packed hard block structure. Such a hard block structure makes the material more vulnerable to chemical attacks. Lesser resistance to oxidation can be seen with disruption to the hard block structure as evidenced with the use of a mixed chain extender system [61].

- Ratio of hard to soft blocks in polyurethanes
  - The ratio of the hard block to the soft block defines, to a large degree, the elastomeric properties of the polyurethane. As explained earlier, thermodynamic incompatibilities between the isocyanate and the polyol lead to the formation of a phase separated structure. The reaction of the isocyanate with the short chain diol results in the formation of the hard segment whereas the polyol forms the soft segment. The hard segments tend to agglomerate due to steric forces and hydrogen bonding and this agglomeration results in the formation of nanometer-sized domains known as hard blocks. The hard block is defined as the sum of the weight percentage of the isocyanate and the chain extender divided by the weight of the entire polymer. The higher the hard block content of the polyurethane, the harder is the material and correspondingly an increase is observed in the elastic modulus, ultimate tensile strength and a corresponding decrease is seen in the ultimate elongation values. It is interesting to note that similar hard block content will give different mechanical properties depending on the composition of the soft block [8,9]. This difference is due to the polarity of the main linkage in the polyol and the degree of incompatibility between the isocyanate and the polyol. For example, a carbonate-based polyol is more compatible with the isocyanate as compared to a siloxane-based polyol and greater hard segment content is required with carbonate polyol as the soft block to get similar hardness material made using a siloxane polyol as the soft block.

The mechanical properties of a few representative thermoplastic polyurethanes used in the medical industry are given in Table 2.

2.6 Morphology of Polyurethanes

As touched upon earlier, the tendency of polyurethanes to separate into hard and soft phases, due to the thermodynamic incompatibility that exists between the polar isocyanate and relatively nonpolar polyol, is a critical aspect of polyurethane microstructure or morphology. This phase-separated morphology is primarily responsible for the wide range of mechanical properties that polyurethanes possess. Different techniques exist to probe this morphology and these have been documented in various publications [5,7,9], the techniques include thermal characterization methods such as differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA), X-ray scattering techniques such as small-angle X-ray scattering (SAXS) and microscopic techniques such as transmission electron microscopy (TEM) and atomic force microscopy (AFM).

2.6.1 Differential Scanning Calorimetry Studies

DSC is a thermal analysis technique used to characterize the temperatures of glass transition and melting of the material. DSC can also be used to characterize the degree of crystallinity, the degree of phase separation, and the morphological changes that occur in the

Table 2 Mechanical Properties of Some Medical Grade TPUs

Shore A Materials	Specific Gravity	Hardness (Shore A)	Tensile Strength @ Break (MPa)	Tensile Elongation @ Break (%)
Biospan	*	70	41.37	850
Tecophilic	1.1	70	13.79	600
Tecoflex	1.04	72	39.99	660
Carbothane	*	73	36.54	470
Carbothane PC-3575A	1.15	73	36.54	470
ChronoFlex AR-75A	*	75	51.71 (TS@Y)	500
ChronoFlex AL-80A	*	80	37.92 (TS@Y)	590
ChronoFlex C-80A	1.2	80	41.37	450
Elasthane (A)	1.12	80	39.99	800
Estane CP 80AS2	*	82	28	470
Bionate (Corethane) 80A	1.19	83	46.64	531
Pursil	*	83	25.26	492
Carbothane PC-3585A	1.15	84	41.37	410
Pellethane 2102 80A	*	84	39.99	580
Elast-Eon 5-325	*	84	25	680
Estane	1.2	85	42.05	490
Texin 985	1.12	86	37.9	500
Carbosil 90A	*	90	39.98	424
Bionate (Corethane) 90A	1.2	91	55.14	406
Bionate (Corethane) 90A	*	91	55.14	406
Elast-Eon 2A	1.1	92	30	550
Carbothane PC-3595A	1.15	95	48.95	380

Shore D Materials	Specific Gravity	Hardness (Shore D)	Tensile Strength @ Break (MPa)	Tensile Elongation @ Break (%)
Elast-Eon 2D (E2-152)	*	55	25	362
Elasthane (D)	1.12	55	39.99	800
ChronoFlex AL-55D	*	55	57.92 (TS@Y)	330
ChronoFlex C-55D	1.2	55	46.54	400
Bionate (Corethane) 55D	1.21	56	60.55	365
Carbothane PC-3555D	1.15	60	50.33	370
ChronoFlex AL-65D	*	65	62.05 (TS@Y)	300
Carbothane PC-3572D	1.15	71	58.61	360
Bionate (Corethane) 75D	1.22	73	63.23	241
ChronoFlex C-75D	1.2	75	51.71	290
Pellethane 2363	1.13	76	40	380
Tecoplast	1.18	82	69.95	50

*TS@Y is tensile strength at yield, *, no data.*

processing cycle of the material. Transitions in polyurethane thermograms have been attributed to specific phenomena in each of the phases of the material. The glass transition of the soft segment is usually at low temperatures below room temperature. The measure of this temperature is a strong indication of the degree of phase separation present in the material. The closer the glass transition temperature of the material is to the pure polyol, the greater is the phase separation between the hard segment and the soft segment in the material. The farther away the glass transition temperature of the material from the pure polyol glass transition temperature, the greater is the phase mixing between the hard and the soft segments. The higher temperature endothermic transition denotes the melting temperature of the polymer. This transition also denotes the temperature at which the disordering of the ordered hard segment region of the polymer occurs. Many smaller transitions both of the exothermic and endothermic variety have been observed in DSC scans of polyurethanes. These transitions have been attributed to a distribution of hard and soft segments within each other [5,7]. In a series of studies on siloxane-based polyurethanes [48,59,61–65], DSC thermograms were obtained with differing soft segments and variation in the amount of hard segments keeping the soft segment constant. The thermograms are in Fig. 7. In this study [65] the hard segment content was fixed at 40 wt.% whereas the content of the soft segment was varied between 100% polysiloxane (10040) and 100% polyether (0040). The results are a clear indication of increasing immiscibility of the hard and soft segments with increasing nonpolar content in the polyol, in this case the polysiloxane.

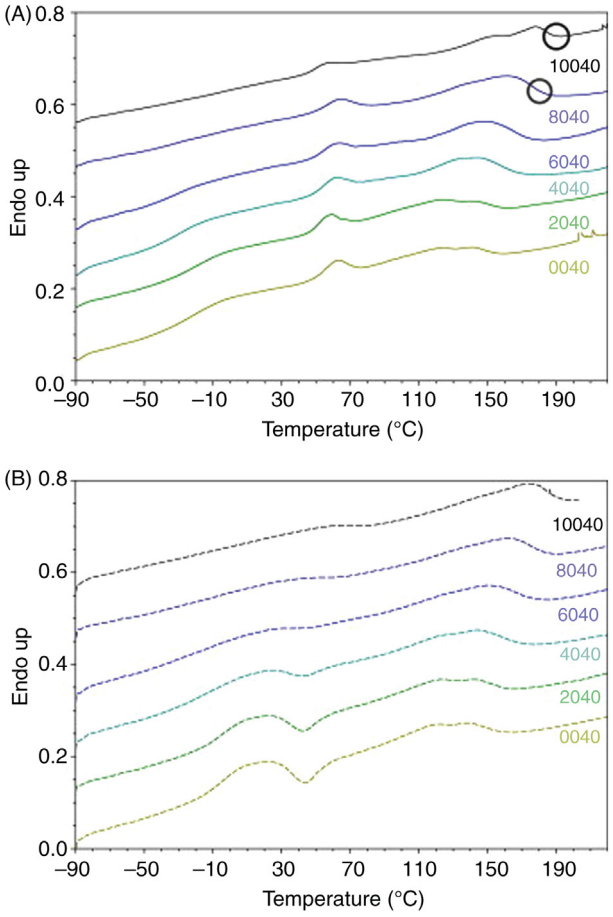

Figure 7 DSC thermograms with varying siloxane contents in the soft segment (A) from first heating, (circles represent the temperatures of disappearance of phases as observed with SAXS) (B) from second heating after fast cooling. *Courtesy: Elsevier Publications; T. Choi, J. Weksler, A. Padsalgikar, J. Runt, Influence of soft segment composition on phase-separated microstructure of polydimethylsiloxane-based segmented polyurethane copolymers, Polymer 50 (10) (2009) 2320–2327 [65].*

2.6.2 Small Angle X-Ray Scattering

Small angle X ray scattering or SAXS is a widely used technique to study the nanoscale structure of materials. The method is very accurate, nondestructive, and can be done with a minimal sample size. In a typical test, a focused beam of X-rays is brought to a sample and the rays that are scattered, by the presence of features within the material, are picked up by a detector placed in the path of the scattering waves. The scattering pattern then is used for the determination of the details of the structural features of the sample.

Several SAXS studies [62,65,66–69] have been conducted with different varieties of polyurethane. Degrees of microphase separation are obtained by using the ratio of the experimental electron density variance to the theoretical electron density variance (i.e., the value calculated for the hypothetical case of complete phase separation) $\left(\frac{\overline{\Delta\eta^2}}{\Delta\eta_c^2}\right)$ [66–68].

The experimental electron density variance $\left(\overline{\Delta\eta^2}\right)$ is determined from the background corrected SAXS data [62]:

$$\overline{\Delta\eta^2}' = cQ = c\int\left\{I(q) - I_b(q)\right\}q^2\,dq \qquad (11)$$

where Q is the invariant (integrated intensity) and the constant c is

$$c = \frac{1}{2\pi^2 i_e N_{av}^2} = 1.76\times10^{-24}\ (\text{mol}^2/\text{cm}^2). \qquad (12)$$

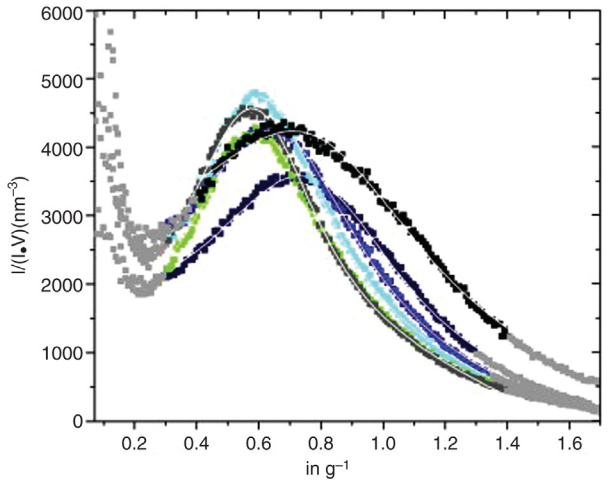

Figure 8 SAXS curves for varying amounts of siloxane in the soft segment (■) 0040; (●) 2040; (▲) 4040; (▼) 6040; (◆) 8040; (◄) 10040. *Courtesy: Elsevier Publications; T. Choi, J. Weksler, A. Padsalgikar, J. Runt, Influence of soft segment composition on phase-separated microstructure of polydimethylsiloxane-based segmented polyurethane copolymers, Polymer 50 (10) (2009) 2320–2327 [65].*

The symbol i_e refers to Thompson's constant for the scattering from one electron (7.94×10^{-26} cm^2) and N_{av} is Avogadro's number.

The theoretical electron density variances $\left(\overline{\Delta\eta_c^2}\right)$ were calculated assuming complete hard and soft segment segregation, and assuming sharp boundaries between hard and soft domains, and is defined as [69]

$$\overline{\Delta\eta_c^2} = \phi_{hs}\phi_{ss}(\eta_{hs} - \eta_{ss})^2 = \phi_{hs}(1-\phi_{hs})(\eta_{hs} - \eta_{ss})^2, \quad (13)$$

where ϕ_{hs} and ϕ_{ss} are the volume fractions of the hard segments and soft segments in hypothetical completely phase-separated copolymers, respectively, and η_{hs} and η_{ss} are the electron densities of completely segregated hard and soft phases, respectively.

A study was done with a mixed polyether–polysiloxane soft segment, the results from the SAXS analysis is shown in Fig. 8.

2.6.3 Atomic Force Microscopy

Atomic Force Microscopy (AFM) has also been used as a tool to measure the microstructure of polyurethanes. The AFM consists of a mechanical arrangement of a cantilever with a sharp tip or probe at one end. That end is used to scan the surface of the sample being tested. The cantilever is usually made from silicon or silicon nitride and the radius of curvature of the tip is extremely small, of the order of nanometers. As the tip is brought near the sample surface, the cantilever mechanism, that is very sensitive to small deflections caused by forces between the tip and the sample surface, maps out the sample morphology. For use in the determination of the morphology of polyurethane specimen, the AFM instrument is used in the tapping mode. In this mode, the cantilever is driven to oscillate up and down at or near its resonance frequency. This oscillation is commonly achieved with a small piezo element in the cantilever holder. The amplitude of this oscillation usually varies from several nm to 200 nm. In tapping mode, the frequency and amplitude of the driving signal are kept constant, leading to constant amplitude of the cantilever oscillation as long as there is no drift or interaction with the surface.

In the same study referred previously [65], AFM was performed on different soft segment variations, the results are shown in Fig. 9 where the sample numbers represent the soft block composition and the hard segment concentration as defined earlier in the text. The bright regions represent hard domains and the darker represent soft phase. The mean size of the hard domains in the phase images is approximately 10 nm and there is no apparent difference in morphology on changing soft phase composition [65].

An important point to note is that this phase separated morphology in polyurethanes is extremely temperature dependent. This temperature dependence means that the morphology of the material is different at different temperatures. This was clearly shown with different measurement techniques in a study by Pongkitwitoon et al. [63], as the circles indicated in Figure 7A, a higher temperature resulted in progressively higher degrees of phase mixing and a good correlation could be made DSC transitions and SAXS data. This temperature dependent morphological data indicates that conducting predictive analyses of aging with techniques such as time–temperature superposition become extremely hard and of limited utility as far as polyurethanes are concerned.

2.7 TPU Rheology and Processing

The thermoplastic nature of TPUs makes them amenable to all thermoplastic processing techniques. Melt and solution processing techniques are widely used in fabricating components out of TPUs for medical applications. A few factors that are to be considered in the melt processing of TPUs are as follows:

Drying of the TPU pellets

It is very important to dry the TPU prior to use in any melt processing operation. A level of less than

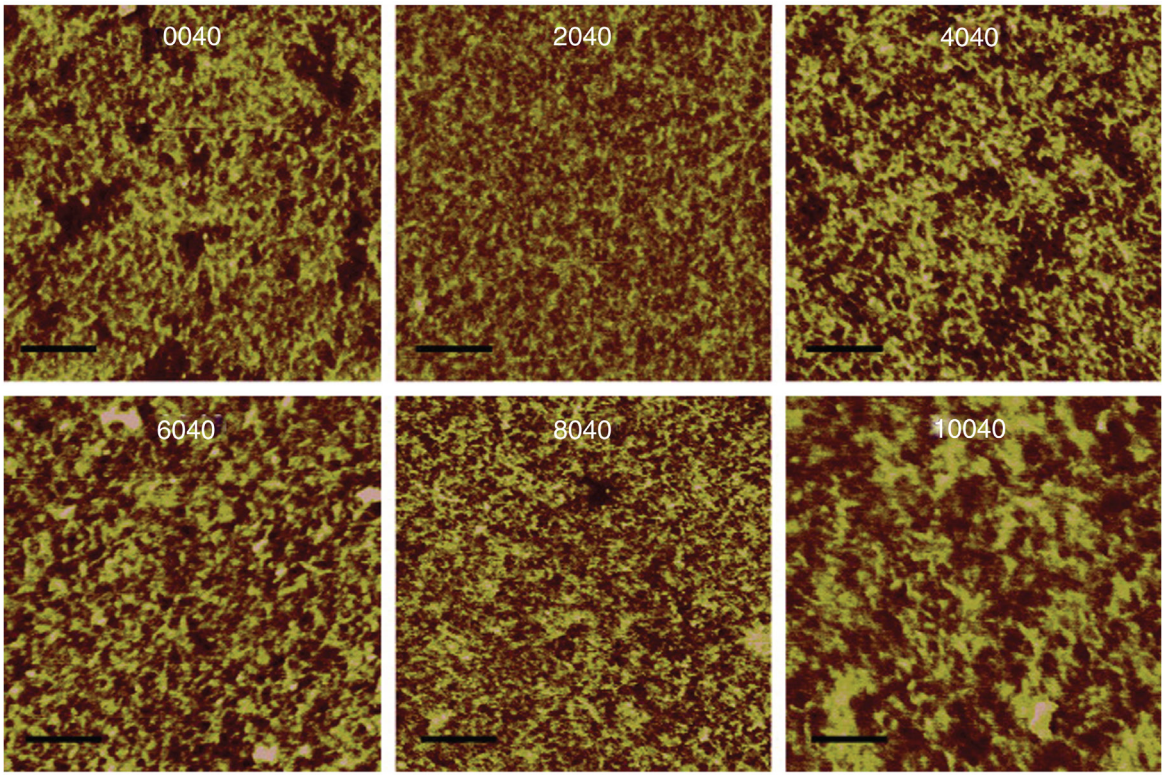

Figure 9 AFM images of varying amounts of siloxane soft segment. *Courtesy: Elsevier Publications; T. Choi, J. Weksler, A. Padsalgikar, J. Runt, Influence of soft segment composition on phase-separated microstructure of polydimethylsiloxane-based segmented polyurethane copolymers, Polymer 50 (10) (2009) 2320–2327 [65].*

200 ppm or 0.02% of moisture is considered acceptable moisture levels for processing [38,39]. This is because the urethane linkage tends to hydrolyze at higher temperatures and will result in chain cleavage leading to a decrease in molecular weight of the material and a loss in the properties of the material.

Depolymerization

The urethane reaction is an equilibrium reaction where the reverse reaction, that is, the formation of isocyanates and hydroxyl containing molecules from the urethane bond, becomes only a factor at high, melt temperatures. In fact, the drying of the TPU is important precisely due to the reversibility of the urethane linkage. As the urethane linkage reverses to form isocyanates, these isocyanate-containing groups will react with any hydroxyl containing groups. Water can be looked upon a monofunctional hydroxyl-containing molecule and the reaction with an isocyanate chain will lead to effective termination of the chain. The phenomenon of TPU depolymerization has been covered by different researchers [47,52,53] and has to be taken into consideration during the melt processing of TPUs.

Effect of allophanates

Another effect seen in the melt rheology of TPUs is the effect of allophanate decomposition. Allophanates, as seen earlier, are linkages formed due to the reaction between an isocyanate group and an already formed urethane bond. The allophanates dissociate at TPU melt temperatures [70] and the dissociation occurs over a period of time, this gives time dependence to the TPU viscosity. The time dependence is a factor of the amount of allophanates present in the system, the kinetics of allophanate dissociation and residence time of the melt in the processing equipment. The time dependence places an additional complexity in the use of simulation software to design the processing equipment. It has been observed that TPU systems with higher incompatibility between the soft and the hard phases show a greater amount of allophanates such as in siloxane-based TPUs [70].

Solvents such as DMAc, DMF, and THF are most often used in the solution processing of TPUs. Different processing techniques such as solvent

casting, dip molding, and solvent-based fiber spinning are widely used to fabricate components for medical usage.

3 Polysiloxanes

All polymers derived from the silicon–oxygen links (Si—O) are referred to as siloxanes or silicones. Siloxane linkages form the backbone of silicone molecules, the main example of which is Polydimethyl Siloxane or PDMS.

3.1 Raw Materials

The siloxane linkage is an inorganic link, silicon itself is tetravalent and when it is attached to carbon a molecule that is both inorganic and organic at the same time is formed. These inorganic siloxanes, called silicates, form approximately 75% of the earth's crust in the form of sand and glass. When joined to another carbon, the molecule is termed as organosilanes. Organosilanes are all manmade siloxanes and have chemical reactions similar to organic compounds.

In a typical process of manufacturing polysiloxanes, silicon is first obtained from sand [14];

$$SiO_2 + 2C \xrightarrow[\text{Heat}]{} Si + 2CO$$

The silicon obtained is further converted, in one process a fluidized bed reactor at 300°C with a copper catalyst is used, to a chlorosilane in reaction with methyl chloride [14];

$$Si + 2CH_3Cl \xrightarrow[\text{Metal Catalyst/Heat}]{} (CH_3)_2SiCl_2 + \text{other}$$

Usually the process yields a mixture of chlorosilanes but the dimethyldichlorosilane is the main product and is obtained and purified by fractional distillation.

Dimethyldichlorosilanes are then hydrolyzed to form either hydroxyl-terminated linear siloxane chains or cyclic siloxane molecules (Fig. 10). The length of the chain or the degree of polymerization and nature of the molecules formed depends among other things on the catalyst used, reaction conditions, and the concentration of the reactants. The length of the linear chain, when formed, is long enough to form an oligomer but is not long enough to be a polymer and not sufficient in that form for most applications [12].

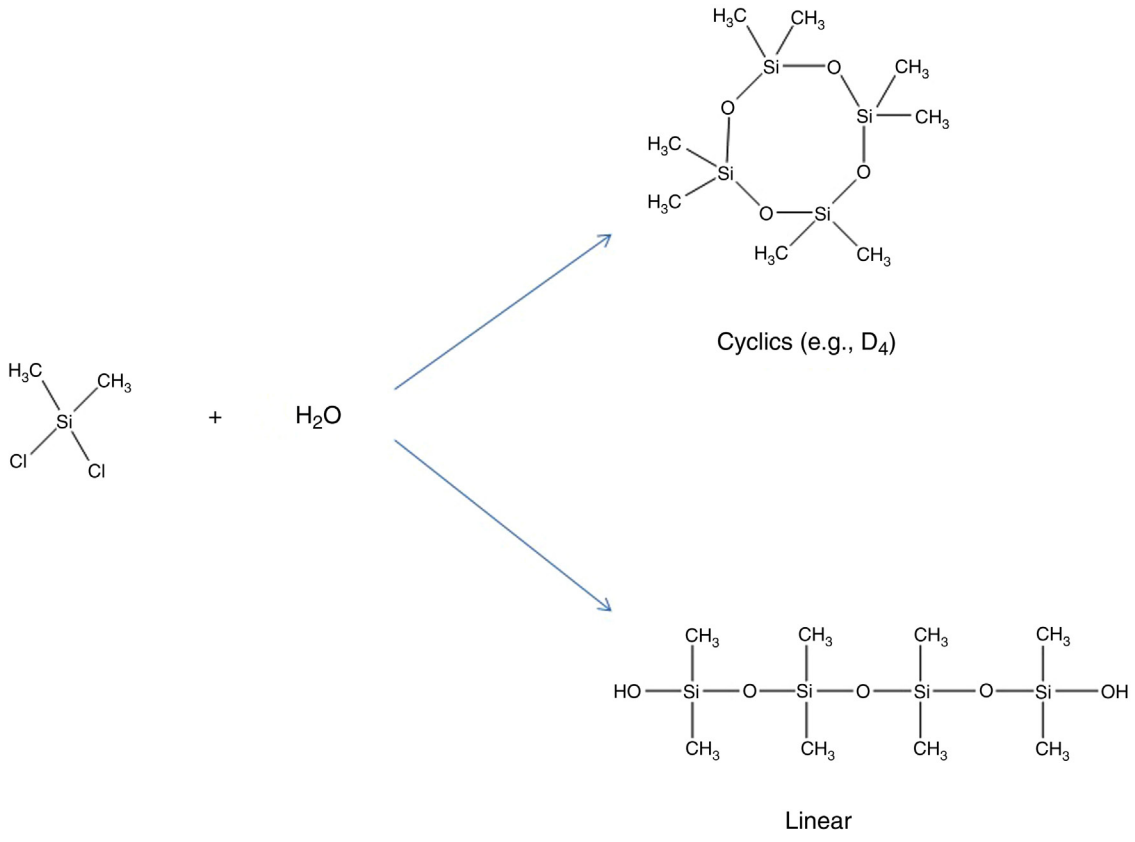

Figure 10 Hydrolysis of dimethyldichlorosilane into cyclics and linear molecules.

3.2 Synthesis of Polysiloxanes

3.2.1 Nomenclature

An important aspect in the industrial chemistry of silicones is its unique nomenclature. This nomenclature is based largely upon the number of oxygen atoms attached to the Si molecule. M is monofunctional in that one oxygen atom is attached to the silicon atom, D is difunctional, T is trifunctional, and Q is quadrafunctional, all according to the number of oxygen atoms attached to the silicon. This nomenclature is explained in Fig. 11 and there are a few corresponding applications in Fig. 12.

In Fig. 13A, a linear silicone polymer is illustrated. In the linear chain (Fig. 13), "*n*" represents the degree of chain length of the siloxane bond units (Si—O), the greater the value of *n*, the higher is the viscosity of the system. Another important aspect of the silicone linear chain is the nature of the "R" units. The R groups present at the end of the chain are termed as end blockers. The reactive nature of the end blockers will decide the further reaction of the linear chain and will play a crucial part in the determination of the kind of cross-link the chain can form.

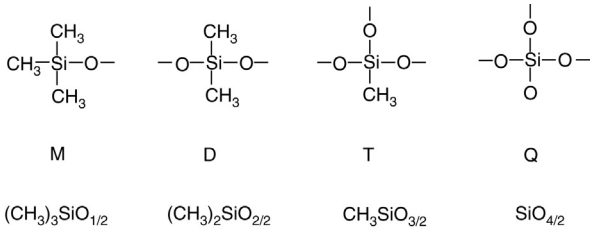

Figure 11 Nomenclature of siloxane compound. *Courtesy: Elsevier Publications; A. Colas, J. Curtis, Silicones, in: Handbook of Polymer Applications in Medicine and Medical Devices, 2013, pp. 131–143 [71].*

3.2.2 End Blockers

The end blocker can be composed of different functional groups and the nature of these functional groups, as mentioned earlier, ultimately decides the further reaction of the linear silicone polymer. Three main function groups that are used in the end

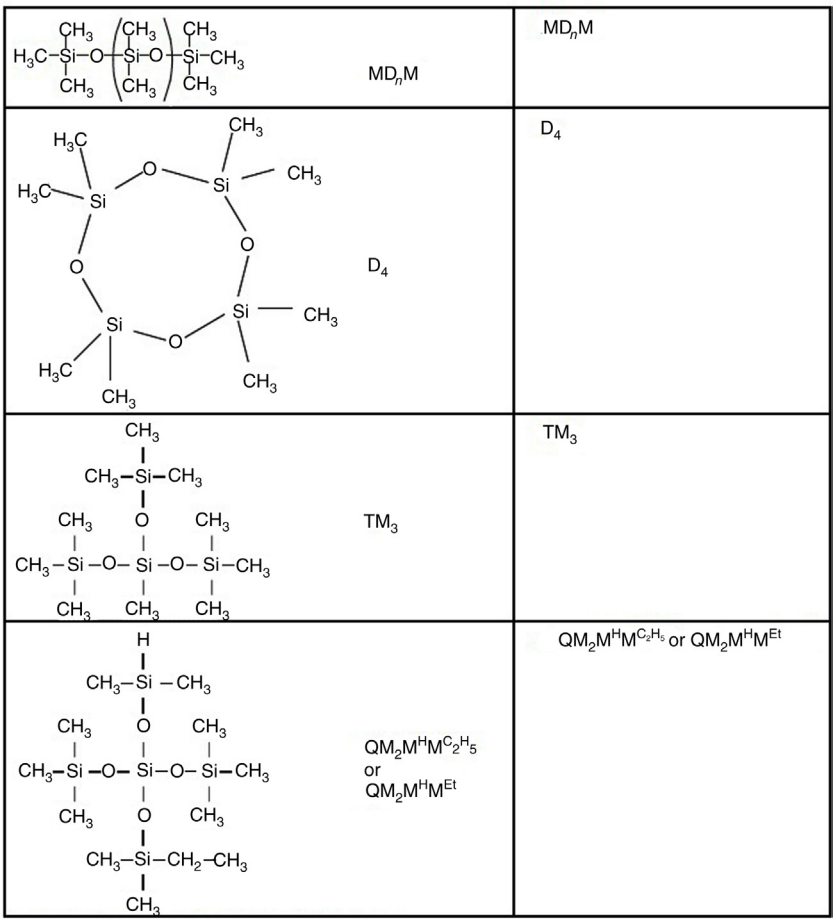

Figure 12 Application of siloxane nomenclature. *Courtesy: Elsevier Publications; A. Colas, J. Curtis, Silicones, in: Handbook of Polymer Applications in Medicine and Medical Devices, 2013, pp. 131–143 [71].*

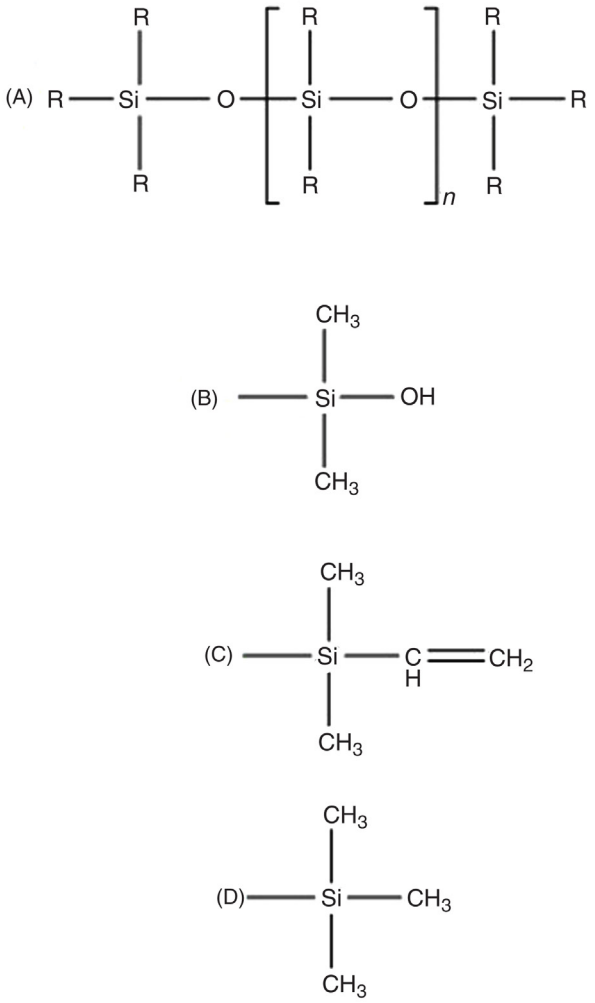

Figure 13 Siloxane linear polymer and end blockers (A) a silicone chain with 'R' terminated end group (B) hydroxyl terminated, termed as silanols, (C) vinyl terminated (D) methyl terminated.

blocking molecules are as depicted in Fig. 13B, hydroxyl, termed as silanols, Fig. 13C, vinyl terminated, and Fig. 13D, methyl terminated.

Based on the end blocker functional groups, the final state of the material is decided. The hydroxyl terminated group lends itself to condensation cure, the vinyl terminated chains can be cross-linked using an addition reaction, whereas methyl termination means no further reaction and the linear polymer formed thus is used as a fluid.

3.2.3 Chain Growth

There are two routes to forming a siloxane long chain molecule:

- polycondensation
- ring opening polymerization (ROP)

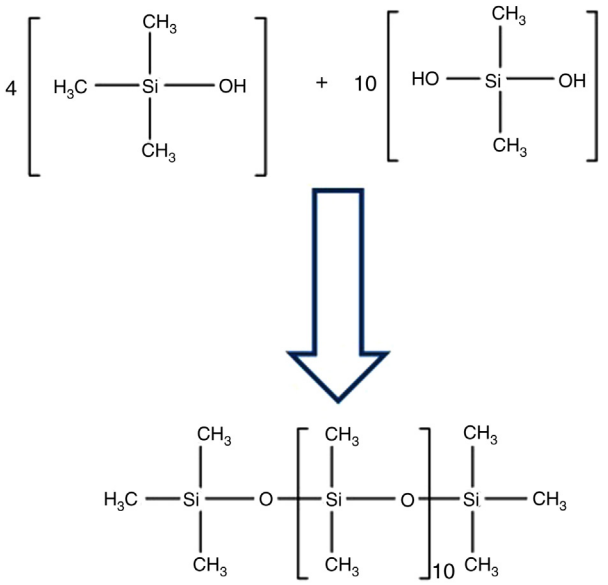

Figure 14 Synthesis of linear siloxane polymer with degree of polymerization = 10.

Polycondensation: In polycondensation, the hydroxyl terminated molecule can be used in a condensation polymerization reaction to further advance the reaction. In the following example (Fig. 14), the formation of a trimethyl-terminated siloxane polymer is illustrated.

Linear silanol compounds can be catalyzed by many acids or bases to combine and form long chains. The long chains are formed by intermolecular condensation involving the formation and elimination of water. A distribution of chain lengths is obtained at the end of condensation reaction. A higher degree of polymerization is favored, as according to the Le Chatelier principle of reaction chemistry, when working under vacuum or at elevated temperatures to reduce the residual water concentration.

Ring opening polymerization (ROP): ROP involves the conversion of a cyclic, ring compound to a linear chain with the aid of an ionic reaction mechanism. The ROP is the preferred route for the manufacture of linear siloxane chains as there are no solvents involved, the yields of the final product are usually high and the raw materials are less expensive in contrast to the ones used in polycondensation. A common cyclic compound used in ROP is octamethylcyclotetrasiloxane, this is a molecule consisting of four siloxane units and is known as D4. For the further advancement of the cyclic compound to linear polymeric siloxane molecule, the ring opening technique is used. The cyclic ring is opened at the Si—CH_3 bond by an ionic mechanism. The ring opening is initiated by a catalyst could either

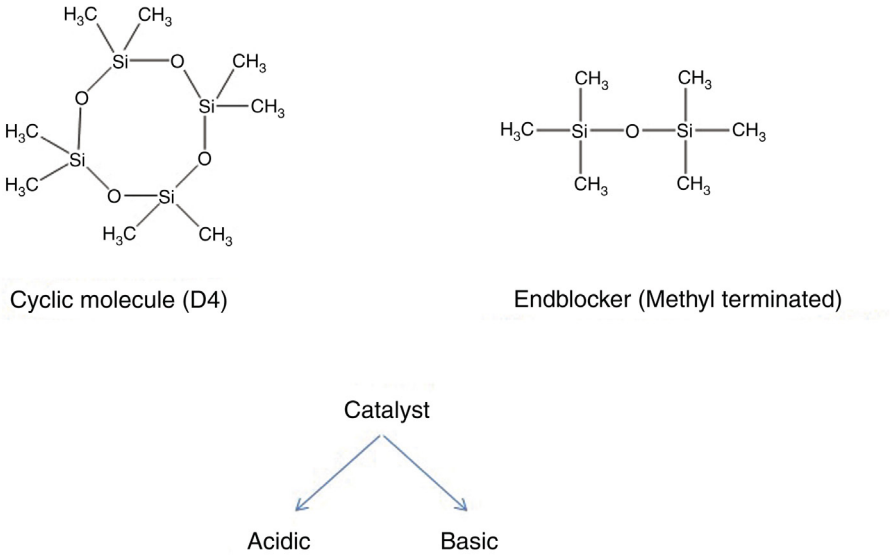

Figure 15 Primary components of the ROP of siloxanes.

be basic or acidic in nature. Some examples of the initiator catalyst are basic molecules such as potassium silanolate, tetramethyl ammonium silanolate and acids such as sulfuric acid and trifluorosolfonic (triflic) acid.

The ROP system consists of the cyclic compound, the catalyst/initiator and a small chain end blocker. The Fig. 15 illustrates the main constituents of an ROP to produce trimethyl terminated linear siloxane.

ROP is an equilibrium reaction and the extent of the reaction depends upon the nature of the substituents attached to the chain. For example, one can obtain 82% conversion with a methyl group on the cyclic and a methyl group on the end blocker, however, with phenyl groups on both the cyclic and the end blocker, the conversion is negligible [72]. ROP always yields a mixture of cyclic and linear molecules. The linear molecule yields are influenced by the steric nature of the substituents on the chain.

3.2.4 Fillers in Polysiloxanes

The linear silicone polymer is frequently compounded with nonreactive filler particles in order to obtain useful properties. The different fillers used can impart a range of properties to the polymer. Thermal and electrical conductivity can be obtained by the use of metallic fillers such as gold, silver, boron nitride, and iron oxide, radio opacity can be obtained by the use of barium sulfate, and mechanical properties can be enhanced by the use of precipitated or fumed silica. By far the most common filler used is silica. Silica interacts with the silicone chains primarily through secondary bonds [71,73] and that interaction significantly alters the mechanical and rheological properties of the polymer. The mechanism of fillers residing in the siloxane network is illustrated in Fig. 16.

Silica can be made using a precipitation technique, using sodium silicate and an acid/metal salt solution:

$$\mathrm{Si(ONa)_4 + 4HCl \rightarrow SiO_2 + 4NaCl + 2H_2O}$$

Silica can also be made by burning silicon tetrachloride in a flame of hydrogen and oxygen.

$$\mathrm{SiCl_4 + 2H_2 + O_2 \xrightarrow[Heat]{} SiO_2 + 4HCl\uparrow}$$

The silica obtained through the flame treatment of silicon tetrachloride is called fumed silica.

Precipitated silica is usually less expensive but less branching and bonding capabilities as compared to the fumed version and as a result the fumed silica gives better reinforcing performance and is preferred as reinforcing filler for mechanical property enhancement.

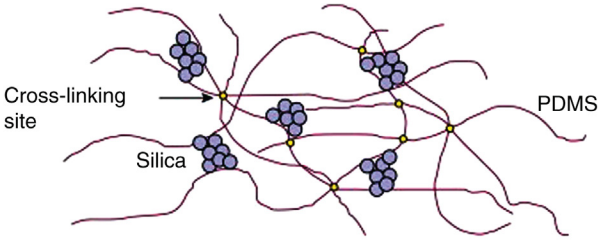

Figure 16 Filler reinforcement of siloxane polymer network. *Courtesy: Elsevier Publications; A. Colas, J. Curtis, Silicones, in: Handbook of Polymer Applications in Medicine and Medical Devices, 2013, pp. 131–143 [71].*

Typically, a loading of 10% up to 60% by weight of the silica is used [73]. A combination of the chain length of the starting silicone material and the amount of loading of the filler can define the final properties and the application of the compounded material. The process of compounding is carried out in powerful mixers. Mixers with high shear called Sigma blade mixers are used by some manufacturers.

3.2.5 Cross-linking

The filled silicone system is reinforced mechanically, however, lacks elastic recovery. To impart any elastic recovery in the system and obtain elastomeric properties, cross-linking the chains in the silicone system is a must to form a three-dimensional network structure. It must be kept in mind that cross-linking has to occur in conjunction with filler incorporation to obtain a high strength elastomer.

The type of cross-linking reaction, as previously explained, is dependent on the terminal functional groups on the end blocker. Three main types of cross-linking reactions are possible, these are [71]:

- condensation cure
- free radical or peroxide cure
- addition cure

In condensation cure, two hydroxyl-containing siloxane groups (silanols) react with each other resulting in the formation of a larger molecule and the elimination of water. Three main types of condensation cure systems are defined by their functional groups:

Acetoxy O—CO—CH_3(AcO)

Alkoxy O—R

Oxime O—N = CR_1R_2

where R (R_1 and R_2) are usually alkyl groups such as methyl, ethyl, propyl, butyl, etc.

The general condensation reaction using the acetoxy group is as shown in Fig. 17. The condensation reaction is generally preceded by a hydrolysis reaction (Fig. 17) to create the hydroxyl groups at the end of the silicone molecule for further reaction. The hydrolysis reaction is usually initiated by atmospheric moisture. In the case of silicone adhesives, for example, hydrolysis is initiated by exposure to room humidity from a sealed container. The cross-linking reaction then proceeds as shown in Fig. 18.

Condensation cure reactions occur at room temperatures and so are also known as RTV or room temperature vulcanization systems. These cures are usually catalyzed by organometallic catalysts. As these cures are initiated by atmospheric moisture, the cures start at the surface of the product and then proceed into the system this also makes the depth of the cure limited. With an active compound leaving the sample as the cure proceeds there is an associated shrinkage during the cure and this has to be taken into account during the design of the system and its cure. The active leaving group is also a consideration for system design. Acetoxy end groups on siloxane molecules lead to the liberation of acetic acid during condensation cure, acetic acid can be too corrosive for certain applications especially involving electronic components, in such cases, alkoxy end group systems are used. Alkoxy systems during condensation cure liberate alcohols such as ethanol and can be less corrosive than acetic acid [74].

Peroxide cure occurs with a free radical mechanism. The cure with a peroxide system is activated by heat. This curing mechanism is most effective with the presence of a vinyl group in the siloxane molecule. The peroxide used is typically dicumyl

Figure 17 Condensation cure mechanism—hydrolysis of acetoxy end blocked polymer.

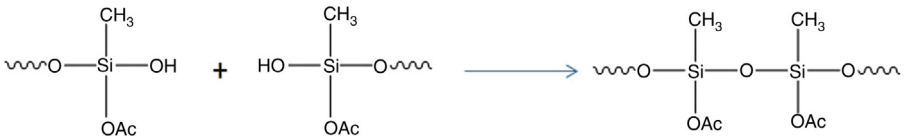

Figure 18 Condensation cure mechanism: reaction between hydroxyl end groups on the siloxane polymer chain.

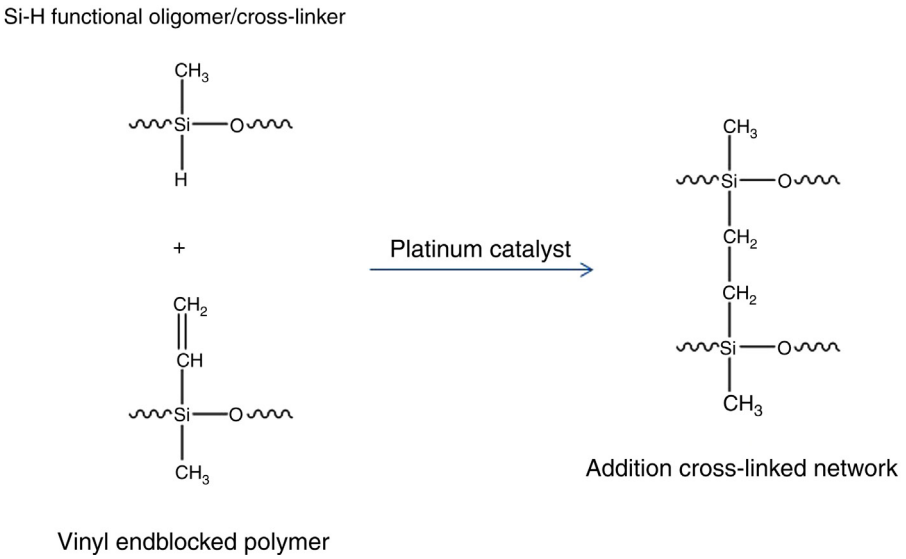

Figure 19 Addition cure mechanism of polysiloxanes with hydrosilylation.

peroxide. There are no corrosive by-products in this curing system, it is good for thick section curing, however, postcuring is typically required, there are by-products due to temperature cure and oxygen has been seen to inhibit cure [74].

The problems of shrinkage, by-products, and postcuring are eliminated by the use of platinum-based catalysts in the mechanism of addition cure. In addition cure, cross-linking is achieved by reacting vinyl end blocked polymers with Si—H groups carried by functional oligomer or cross-linker. The reaction result in low volatile evolution and it is also seen that very low levels of catalysts are effective in completing the addition cure reaction. The reaction mechanism is as shown in Fig. 19.

As indicated, the Si—H group on the oligomer is reacted with the vinyl group on the polymer and this reaction is called hydrosilylation. The catalyst used, the Pt derivative, is susceptible to certain compounds such as sulfur that act as poisons and inhibitors.

3.3 Properties of Polysiloxanes

Organic polymers are mainly composed of carbon chains as the backbone whereas silicones contain the siloxane linkage or alternating silicon and oxygen atoms. The comparative sizes and electronegativity of the atoms are given in Table 3 [72].

The bond lengths and the bond angles are larger with Si—O as compared to C—C. This bond arrangement gives rise to many of the unique properties of siloxanes as listed in Table 4 [71,72].

The mechanical properties of silicone elastomers are dependent on three different factors. These factors are [16,17,71].

- nature of the polymer
- filler type and treatment
- cross-link density

The polymer can vary in terms of the chain architecture; the chains can differ in their chain length or molecular weight, the branching of the chains and the functional groups that are attached to the end of the chain. These differences can result in significant effects on the mechanical properties of the resultant elastomer. A higher base molecular weight results in greater ultimate elongation of the elastomer. A greater degree of cross-linking and branching will result in higher modulus and durometer of the material; it will also result in lower ultimate elongation. The type of filler affects the interaction that it has with the base polymer. For example, certain types of silica fillers can promote hydrogen bonding between the filler and the polymer. Excessive hydrogen bonding can

Table 3 Comparative Atomic Sizes of Carbon and Silicon Linkages and Their Electronegativity

	Atomic Radius (*A*)	**Electronegativity**
Carbon	0.914	2.5
Silicon	1.32	1.8

Table 4 Effect of Molecular Structure on Silicone Properties

Molecular Structure	Material Properties	Material Performance
Strong Si—O bonds	Thermooxidative stability	Physiological inertness Biological stability Thermal stability
Low bond angle and lack of steric hindrance	Flexibility Low glass transition temperature Liquid materials with high molecular weights	Soft, low modulus materials Gel materials
High atomic size	Permeability to water vapor and oxygen Solubility of gases	Gas permeability
Nonpolar	Hydrophobic Low surface tension	Physiological inertness Biocompatibility

Table 5 Mechanical Property Ranges of Silicones with different cure systems

Property	Peroxide Cure	Addition Cure	Condensation Cure
Hardness	25–80 Shore A	5–80 Shore A	10–60 Shore A
Ultimate tensile strength	≤12 MPa	≤12 MPa	<5 MPa
Elongation at break	≤600%	≤1350%	≤1200%
Tear strength (pounds per inch/ppi)	50–200 ppi	50–250 ppi	30–150 ppi

result in a phenomenon known as creep hardening. Creep hardening occurs when the elastic modulus of silicone base increases over time due to the hydrogen bonding effects. The creep hardening is, however, reversible through shear actions of mixing or milling. The creep hardening is also significantly reduced when silica is subjected to a different treatment. The type of the curing/cross-linking system used also determines the mechanical properties of the material to a large degree. Condensation cure systems have generally a lower tensile strength compared to addition or peroxide cure systems. A general illustration of the range of mechanical properties in silicone elastomers is presented in Table 5.

3.4 Processing Silicone Elastomers

Silicone elastomers have to be cross-linked to serve as components with useful physical properties. The cross-linking is many times in addition to filler incorporation [73]. The cross-linking implies that silicones are thermosets and as such cannot be used in normal thermoplastic processing equipment. Processing of thermosets involves the formation of the desired product shape before final cross-linking or cure.

To avoid premature curing of the elastomer during storage, shipping of the materials and prior to the formation of the desired product shape, silicone systems are frequently available as two-part systems. In a two-part system, for example, one part contains the polymer and the catalyst, the other part contains polymer and the cross-linker. These parts are mixed at a fixed ratio prior to subjecting the material to the processing operation. There are several processing methods that are used for thermosetting materials, in general and for silicone elastomers in particular these include casting, extrusion, and molding. The actual processing operation selected depends upon the viscosity of material to be used and the shape and configuration of the final product [75].

If high molecular weight silicone polymers are used the resultant product is high consistency rubbers (HCRs). HCRs are useful for their high tear strength and high ultimate tensile elongations. HCRs are usually supplied as two-part materials, if the materials are based on peroxide cure, then one part contains the peroxide initiator. If the two-part system uses addition cure then one part contains the platinum catalyst [76]. As a result of the high molecule of weight of the HCR, the two parts are mixed using a high shear system such as a two roll mill. The mixed material is then shaped into preforms before being subjected to processing operations

such as compression molding, transfer molding, and injection molding. The cure or the cross-linking of the system occurs at elevated temperatures encountered in the processing operations. HCR systems are also suitable for extrusion operations; here the extruder is fed with the premixed HCR in the form of strips and ribbons. The high molecular weight HCR has enough integrity to form the shape of the article or tubing when leaving the extruder. The article then enters a curing oven to complete the cross-linking [71,75].

When low molecular weight silicone polymers are used the resultant product is liquid silicone rubber (LSR). LSRs are also provided as two-part systems; however, the two parts can be mixed much more easily as compared to HCR systems. In contrast with using a two roll mill in the case of an HCR, the components for LSR can be mixed using much simpler devices such as a static mixer prior to processing. The processing of LSR is usually done with a specialized injection molding machine for silicone systems. In the process of liquid injection molding, LSR is injected into a hot mold where the system is cross-linked [77]. The liquid injection molding system allows for greater control over the processing of silicone systems with precise control over ratios, injection pressures, injection volumes, and mold temperatures. The injection molding system is, however, specialized and cannot be used for processing other plastics; it can, therefore, be an additional investment.

3.5 Silicone Adhesive Systems

The basics of polymer adhesion were covered in Chapter 1, these fundamentals apply to silicone adhesives. Adhesion could be chemical or physical. Chemical adhesion is usually the strongest and involves the formation of chemical bonds between the substrate and the adhesive. Physical bonding may depend on weak adsorption forces such as van der Waals forces or mechanical interlocking. For good adhesion it is important to get good surface wettability with the adhesive, the surface wettability is frequently measured using contact angles. The nature of the substrate's surface is also critical with factors such as the cleanliness of the surface and the roughness of the surface playing a major role.

Silicone bonding adhesives are commonly formulated as one part room temperature cure elastomer systems that use a condensation cross-linking reaction as described earlier. In many situations, surfaces of the substrate are primed before the application of the adhesive. Priming is done with the aid of coupling agents [71]. Typically two reactive groups are present on the coupling agent; one group reactive to the substrate and the other to the adhesive.

Silicone systems are provided as pressure sensitive adhesives (PSA) as well. PSA systems are supplied as dispersions in a solvent. The solvent is volatile and on application of the PSA system, the volatile carrier solvent evaporates quickly leaving a tacky silicone layer that can be adhered to another object through the application of pressure [71].

4 Polytetrafluoroethylene

Polytetrafluoroethylene (PTFE) is a fluorocarbon compound that is made of high molecular weight chains consisting entirely of carbon and fluorine. PTFE was accidentally discovered in the 1930s by DuPont chemist Roy Plunkett [25]. Plunkett was experimenting with tetrafluoroethylene gas for refrigerant use when the high pressure in the gas bottle combined with the presence of iron inside the container led to the polymerization of the TFE gas giving rise to PTFE. In this case, the iron inside of the container acted as a catalyst at the high pressures required for polymerization. It is observed that the properties of the polymer formed were unique, the material was extremely hydrophobic, and neither water nor water-containing substances wetted the polymer. Additionally, PTFE had one of the lowest coefficients of friction of any solid [22]. PTFE also showed very stable properties at high temperatures. This combination of properties meant that PTFE was used in varied applications such as coatings on nonstick cookware to heat shields on space crafts. The best known brand-name for PTFE is Teflon [78].

4.1 Raw Materials

The manufacturing of PTFE polymer is based on the polymerization of the monomer TFE. TFE was first prepared in 1933. The current commercial synthesis routes are based on calcium fluoride, sulfuric acid, and chloroform. The TFE monomer is typically made in multiple stages, first calcium fluoride reacts with sulfuric acid in a double substitution reaction to form hydrogen fluoride [25].

$$CaF_2 + H_2SO_4 \rightarrow CaSO_4 + 2HF$$

The hydrofluoric acid is then reacted with chloroform ($CHCl_3$) yielding monochlorodifluoromethane and hydrochloric acid:

$$CHCl_3 + 2HF \rightarrow CHClF_2 + 2HCl$$

The boiling point of monochlorodifluoromethane is −40.8°C, this low temperature boiling point means that it is used as an effective refrigerant [25].

Further monochlorodifluoromethane is reacted at high temperatures in the pressure of a metal catalyst to yield TFE. In one process, this reaction is carried out by passing monochlorodifluoromethane through a platinum tube at 700°C.

$$2CHClF_2 \rightarrow CF_2 = CF_2 + 2HCl$$

The TFE made by this pyrolysis process includes many ring structures that can be toxic and hence the TFE needs to be purified before any further reactions. Purity of the monomer is an important requirement for polymerization in general and chain-growth polymerizations in particular. The presence of impurities will not only affect chain growth but the toxic nature of the impurities will also affect the final product. In the purification process, TFE gas is first scrubbed to remove any hydrochloric acid and then distilled to separate other impurities [24,25].

4.2 Synthesis of PTFE

TFE is polymerized into PTFE by the free radical, chain-growth polymerization process [79].

$$n\ F_2C = CF_2 \rightarrow —(F_2C — CF_2)_n—$$

The polymerization reaction is very exothermic and as TFE can explosively decompose to tetrafluoromethane and carbon, special arrangements in the equipment are required for the polymerization to prevent hot spots that might initiate this explosive side reaction. Pure TFE can polymerize exothermically even at low temperatures, that is, at temperatures initially below that of room temperature.

The polymerization of TFE is a batch process; the initiator for the polymerization is usually a water-soluble peroxide such as ammonium persulfate or disuccinic peroxide. A redox catalyst is used for low temperature polymerization. Polymerization temperature and pressure usually range from 0 to 100°C and 0.7 to 3.5 MPa.

PTFE is made by two major processes commercially: one process is termed the granular process as the process leads to the production of solid, stringy, irregular particles, or granules [24,79]. The other process leads to a manufacture of a dispersion of polymer particles. The particles are of much finer particle size and lower molecular weight than the granules. In the granular process, PTFE is usually polymerized by the use of TFE alone without any comonomers. A peroxide initiator may be used and the reaction carried out in an aqueous medium with vigorous stirring. Most of the granular polymer is formed in the gas phase. One method of producing the latter involves the use of a 0.1% aqueous disuccinic acid peroxide solution. The reactions are carried out at temperature up to 90°C [24].

Other methods include decomposition of TFE under the influence of an electric arc and polymerization carried out by emulsion method using peroxide initiators, for example, H_2O_2 (hydrogen peroxide) and ferrous sulfate. In some cases oxygen is used as initiator. It must be kept in mind that no matter what the method employed in the polymerization of TFE, all reactions are highly exothermic and have to be carefully controlled to avoid any explosive situations [25].

4.3 Structure and Properties of PTFE

The chemical structure of PTFE is composed of essentially a linear chain of —C—F_2—C—F_2— without any appreciable branching. The unique properties of PTFE are associated with carbon—fluorine bond which is extremely strong and stable. Due to the presence of C—F bonds, PTFE molecule possesses outstanding chemical inertness, high heat resistance, and remarkable electrical insulation characteristics this is in addition to excellent frictional properties it possesses [24,25]. Further, where two fluorine atoms are attached to a single carbon atom there is a reduction in the C—F bond distance from 1.42 to 1.35 Å. As a result of this increased attraction, bond strength between the carbon and fluorine atoms is very high and values up to 504 kJ/mole have been reported [22,25]. Since the only other bond present in the chain is the stable C—C bond, PTFE has very high heat stability, even when heated above its crystalline melting point. Due to high crystallinity and high bond strengths of its primary bonds, there are no solvents for the polymer at room temperature.

As PTFE is a linear polymer free from any significant amount of branching, the resultant molecular structure is highly dependent on the ordering of the linear chains. As compared to the molecule of polyethylene that is in the form of a planar zigzag leading to its crystalline structure, this planar zigzag form is sterically impossible with that of PTFE due to the size difference in the atoms. The fluorine atoms are significantly larger than those of hydrogen and as a result the PTFE molecule takes up a twisted zigzag pattern. The twisted zigzag pattern is formed with the

fluorine atoms packing tightly in a spiral around the carbon—carbon skeleton. The compact interlocking of the fluorine atoms leads to a molecule of great stiffness and it is this feature which leads to the high crystalline melting point and thermal form stability of the polymer [24].

The structural arrangement also leads to observable transitions of the PTFE molecule; first-order and second-order transitions have been reported for PTFE [24,25]. Below 19°C the crystalline system of PTFE is a nearly perfect triclinic, above this temperature the unit cell changes to hexagonal. Between the temperatures of 19 and 30°C, the chain segments become increasing disorderly and the preferred crystallographic direction disappears. A change in the arrangement causes a large change in the specific volume of PTFE and it increases almost 2% [80], this must be considered in the measurement of the dimensions of articles from PTFE and the temperature that it is subjected to. The crystallinity of PTFE polymer as fabricated and that has not been melted is greater than 94%, once melted the degree of crystallinity goes down and hence fabricated PTFE parts are less crystalline. The degree of crystallinity of the finished product will depend on the rate of cooling from the processing temperatures. On first melting the melting point of the materials is ~342°C, on remelting; this decreases by around 15°C as the material cannot recrystallize to the same degree as before melting [24].

The attraction between the molecules of the PTFE polymer chains is small; this results in the computed solubility parameter being 12.6 $(MJ/m^3)^{1/2}$ [25]. With this value of solubility parameter, PTFE is very difficult to dissolve. As a result traditional solvent-based characterization or processing is not common with PTFE. Molecular weight of the polymer is not measured by chromatographic methods but an indirect method known as standard specific gravity (SSG). In the SSG method, a polymer sample is prepared in a standardized way and the principle is that the SSG of a low molecular weight material is higher as it has a tendency to crystallize more [24]. At temperatures approaching the melting point certain fluorinated liquids such as perfluorinated kerosene are able to dissolve the polymer.

The polymer in bulk does not thus have the high rigidity and tensile strength which is often associated with polymers with a high softening point. Mechanical properties of PTFE are generally inferior to other engineering plastics. Usually compounding with fillers allows for greater mechanical properties to be achieved [24]. Some of the representative properties of the material are shown in Table 6 [81].

Table 6 Representative Properties of PTFE Material

Property	Value
Ultimate tensile strength	20–30 MPa
Elongation at break	200–400%
Flexural modulus	275–620 MPa
Durometer hardness	50–65 Shore D
Specific gravity	2.1–2.3 g/cm^3

PTFE melts possess a high viscosity and the polymer is also prone to chemical degradation above melting temperatures. This obviates the processing of PTFE on traditional thermoplastic melt processing equipment. PTFE can be processed using techniques similar to metal powder processing, where the PTFE powder is molded into a preform and then sintered [24]. PTFE tubes are extruded using a dispersion of PTFE into a paraffinic carrier, extrusion of this paste is carried out at low temperatures [82] and the carrier is evaporated in step prior to the final sintering. The properties of PTFE part are dependent on the type of polymer and the method of processing. The polymer itself may differ in the particle size of the powder or the molecular weight of the polymer chains. The particle size influences the ease of processing and the ultimate amount of voids in the final part, whereas the molecular weight influences the degree of crystallinity and hence the resultant physical properties of the part. Extrusion of PTFE pastes also lead to the formation of shear induced fiber-like structures or fibrils, these fibrils can act as reinforcement for the polymer structure and can enhance the physical properties of the polymer.

PTFE parts have to be frequently etched after processing and before being used in a part. The etching process is necessary where bonding with another material is required.

Etching is typically done with a chemical solution, such as a sodium solution, that removes fluorine molecules from the exterior of the PTFE part. This removal of the fluorine molecules creates a part surface layer with a deficiency of electrons [83]. This surface then becomes more chemically responsive to bonding to a different material. Etching does impact the part with a slight discoloration on the surface and a loss of a degree of surface lubricity, however, this effect is only restricted to the surface and only a few angstroms are affected. The effectiveness of etching can be measured by the change in the surface properties of the part using techniques such as contact angle.

5 Biodegradable Polymers

The materials developed for the cardiovascular applications so far have been focused on biological stability. This has implied that the materials were biologically inert and stable in all in vivo environments. As we have seen, all the commercial polymers be it commodity polymers such as polyolefins, polyamides, and polyethylene terephthalate or specialty polymers such as polyurethanes, polysiloxanes, and fluorinated polymers that are used in cardiovascular applications tend to be biologically stable. In the recent years, there has been a shift in approach to implantable devices. Instead of implanting permanent devices, a temporary device that can help the body to regenerate the damaged tissues and organs is considered more beneficial to the patient. This approach involves the use of biodegradable polymers [29,30]. One of the major challenges in the design of the biodegradable polymer is the way it has to function in the body. The biodegradable polymer must support the tissue regeneration process while providing mechanical support and then disintegrate into nontoxic products with no harm to the system [31].

There have been different materials investigated for their application as biodegradable medical device materials [31]. These have included:

- polyesters
- polyanhydrides
- polycarbonates
- polyphosphazenes
- polyurethanes

A number of families of polyester-based polymers are utilized as biodegradable materials. The primary chemical property that polyester materials depend on is the hydrolysis of the ester group in the polymer chain. The hydrolysis of the ester group is eliminated to a large degree in polyethylene terephthalate to the presence of long chains and the associated order and crystallinity of the chains. In biodegradable polyesters, the crystallinity of the long chains is avoided. The degradation of polyanhydrides is dependent on the hydrolytic instability of aliphatic anhydride groups. Polyanhydrides are also hydrophobic in nature and degrade by surface erosion and this makes them attractive for controlled release applications [29,31]. In contrast, the hydrophilic nature of the polycarbonates is used to initiate degradation with the susceptible group in polycarbonates. Polyphosphazenes are high molecular weight, linear polymers with an inorganic backbone consisting of alternating phosphorus and nitrogen atoms attached to two-side groups. With appropriate side groups polyphosphazenes can become biodegradable [30,31]. Amino acid ester substituted polyphosphazenes have been widely investigated as biodegradable polymers. The hydrolysis of ester groups is also used in the formulation of biodegradable polyurethanes [31]. The ester groups are used in the soft segment or in different parts of the hard segment. Even though there are different options in the development of biodegradable implantable polymers, polyesters such as polyglycolide, polylactides, and their copolymers are the most accepted for use in the clinic [32,33].

Polylactic acid or polylactide (PLA) is one of the most widely used biodegradable materials [32,33,84]. PLA is derived from renewable and natural resources such as cornstarch, tapioca roots, or sugarcane. There are several industrial routes to manufacturing PLA where the two main monomers that are used are lactic acid and lactide. The most common route to making PLA is the ring opening polymerization (ROP) of the lactide with metal catalysts such as tin octoate. The reaction can occur in solution, in the melt or as a suspension. PLA is present in three main isomeric forms and these isomeric forms are important in the determination of material's crystallinity. ROP tends to give the racemic form of the polymer. The racemic form is one that has equal amounts of left and right handed chains of a chiral molecule. The chiral form of the molecule and the resulting configuration decides the degree of crystallinity of the final polymer. The degrees of crystallinity along with the molecular weight of the material, to a large degree, decide the mechanical properties of the PLA. Semicrystalline PLA has an approximate tensile strength of 50–70 MPa, tensile modulus of 3 GPa, flexural modulus of 5 GPa and an elongation at break of 4% [85–87]. The same characteristics of the polymer that decide it's mechanical properties also play a role in deciding it's solubility. Chlorinated or fluorinated solvents such as hexafluoro isopropanol or HFIP is most suited for complete dissolution of PLA. Other solvents such as acetone, pyridine, dimethyl sulfoxide, and DMF have also been observed to work with certain polymer states of crystallinity, molar mass, and isomerism. PLA has a melting point between 150 and 160°C, it is a thermoplastic and therefore can be processed like most thermoplastics on standard thermoplastic processing equipment. 3D printing of PLA has also been reported [88].

Glycolic acid is the monomer that can be polymerized by means of polycondensation or ROP to polyglycolic acid (PGA). In many processes

glycolide, the cyclic dimer or cyclic diester of glycolic acid, can be used for solution or melt polymerization methods. The most common synthesis method used to produce a high molecular weight form of the polymer is ROP of glycolide. In the ring opening process the common catalysts used include organo tin, antimony, or zinc-based systems. PGA is a rigid thermoplastic material with high crystallinity (46–50%). The glass transition and melting temperatures of PGA are 36 and 225°C, respectively [31]. Due to the high crystallinity of the polymer, PGA is not soluble in most organic solvents; the exceptions are highly fluorinated organic solvents such as hexafluoroisopropanol [89].

The attractiveness of PLA and PGA polymers for use in the medical device sector as biodegradable materials is characterized by the hydrolytic instability due to the presence of the ester linkage in its backbone. The breakup of the molecule due to water results in the formation of compounds that are easily digestible within the body [32,33]. The degradation process is erosive and appears to take place in two steps during which the polymer is converted back to his monomeric form. In the first step, water diffuses into the amorphous regions of the polymer matrix and in the process reacts with ester bonds. The second step starts off to the amorphous regions have been eroded leaving the crystalline portion of the polymer susceptible to hydrolytic attack. Upon the collapse of the crystalline regions the entire polymer dissolves. Enzymes in the body, especially enzymes with esterase activity, act as catalysts in the hydrolysis process. The monomeric degradation product whether it may be lactic acid or glycolic acid is nontoxic and is either digested or excreted by the body. The kinetics of the degradation mechanism are dependent on many factors including the level of crystallinity, molecular weight of the polymer, the application etc., many times to control the degradation blends of PGA and PLA are used.

References

[1] G. Oertel, L. Abele, Polyurethane Handbook, Hanser Publishers, Munich, (1985).

[2] G. Woods, The ICI Polyurethanes Book, Published jointly by ICI Polyurethanes and Wiley, Chichester, West Sussex, (1987).

[3] W. Gum, W. Riese, H. Ulrich, Reaction Polymers, Hanser Publishers, Munich, (1992).

[4] C. Hepburn, Polyurethane Elastomers, Springer, Dordrecht, the Netherlands, (1992).

[5] C. Prisacariu, Polyurethane Elastomers, Springer, Wien, (2011).

[6] I. Clemitson, Castable Polyurethane Elastomers, second ed., CRC Press, Hoboken, NJ, (2015).

[7] S. Cooper, J. Guan, Advances in polyurethane biomaterials, Elsevier Ltd.

[8] P. Vermette, Biomedical Applications of Polyurethanes, Landes Bioscience, Georgetown, TX, (2001).

[9] N. Lamba, K. Woodhouse, S. Cooper, M. Lelah, Polyurethanes in Biomedical Applications, CRC Press, Boca Raton, FL, (1998).

[10] S. Dumitriu, Polymeric Biomaterials, Marcel Dekker, New York, NY, (1994).

[11] M. Szycher, Szycher's Handbook of Polyurethanes, CRC Press, Boca Raton, FL, (2013).

[12] P. Bruins, Silicone Technology, Interscience Publishers, Easton, PA, (1970).

[13] P. Jerschow, Silicone Elastomers, Rapra Technology Ltd, Shawbury, UK, (2001).

[14] L. Rösch, P. John, R. Reitmeier, Silicon compounds, organic, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co., KGaA, (2000).

[15] G. Chandra, R. Allen, Organosilicon Materials, Springer, Berlin, (1997).

[16] G. Koerner, Silicones, Chemistry and Technology, CRC Press, Boca Raton, FL, (1991).

[17] S. Clarson, J. Semlyen, Siloxane Polymers, Prentice Hall, Englewood Cliffs, NJ, (1993).

[18] M. Stratmeyer, Silicone in Medical Devices, U.S. Dept. of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Devices and Radiological Health, Rockville, MD, (1991).

[19] J. Fink, High Performance Polymers, William Andrew, Oxford, UK, (2014).

[20] S. Spear, P. Hedén, Allergan's silicone gel breast implants, Expert Rev. Med. Dev. 4 (5) (2007) 699–708.

[21] R. Winn, P. Redinger, K. Williams, RTV silicone adhesives for medical devices, J. Biomater. Applic. 3 (4) (1988) 635–648.

[22] F. Bouquet, Engineering Properties of Teflon, Systems Co., Graham, WA, (1989).

[23] S. Ebnesajjad, Expanded PTFE Applications Handbook, William Andrew Publishing, S.l., (2012).

[24] S. Ebnesajjad, Introduction to Fluoropolymers, Elsevier Science & Technology, Amsterdam, (2013).

[25] J. Drobny, Technology of Fluoropolymers, Taylor & Francis Ltd, Hoboken, NJ, (2008).

[26] P. Polterauer, Use of polytetrafluoroethylene aortic bifurcation grafts, Surgery 118 (5) (1995) 916.
[27] E. Richter, Die Akzeptanz von PTFE im subkutanen Bindegewebe (Acceptance of PTFE in subcutaneous connective tissue), Biomedizinische Technik (Biomed. Eng.) 34 (10) (1989) 243–247.
[28] E. Saikaly, Surgical reconstruction of non malignant superior vena cava syndrome by PTFE graft, J. Case Rep. 4 (1) (2014) 120–122.
[29] C. Agrawal, J. Parr, S. Lin, Synthetic Bioabsorbable Polymers for Implants, American Society for Testing and Materials, West Conshohocken, PA, (2000).
[30] K. Khemani, C. Scholz, Degradable Polymers and Materials, American Chemical Society, Washington, DC, (2006).
[31] P. Gunatillake, R. Mayadunne, R. Adhikari, Recent developments in biodegradable synthetic polymers, Biotechnol. Annu. Rev. 12 (2006) 301–347.
[32] S. Wayangankar, S. Ellis, Bioresorbable stents: is this where we are headed?, Prog. Cardiovasc. Dis. 58 (3) (2015) 342–355.
[33] P. Serruys, J. Ormiston, Y. Onuma, E. Regar, N. Gonzalo, H. Garcia-Garcia, K. Nieman, N. Bruining, C. Dorange, K. Miquel-Hébert, S. Veldhof, M. Webster, L. Thuesen, D. Dudek, A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods, The Lancet 373 (9667) (2009) 897–910.
[34] Advbiomaterials.com., Products (2016). Available from: http://www.advbiomaterials.com/products/index.html
[35] Elastollan.basf.us., Elastollan—the high performance TPU (2016). Available from: http://www.elastollan.basf.us/industries/health
[36] Biomerics, Medical Polymers—Biomerics (2016). Available from: http://biomerics.com/products/medical-polymers/
[37] C. Communications, Texin® thermoplastic polyurethane (TPU) resin (2016). Available from: http://www.tpu.covestro.com/Products/Texin.aspx
[38] Dsm.com., Biomedical polyurethanes (2016). Available from: http://www.dsm.com/markets/medical/en_US/products-page/products-biostable-polyurethanes.html
[39] http://www.lubrizol.com, TPU Medical Supplies—LifeScience Polymers—The Lubrizol Corporation (2016). Available from: https://www.lubrizol.com/LifeScience/Medical-Polymer-Solutions/Medical-Supplies.html
[40] Dowcorning.com., Healthcare Solutions—Rubber and Elastomers—Dow Corning (2016). Available from: http://www.dowcorning.com/content/healthcare/healthrubber/?e=Healthcare+Products
[41] Momentive.com., Momentive.com—Health Care and Life Sciences (2016). Available from: http://www.momentive.com/industries/health-care/
[42] Transforming the science of silicone into the Chemistry of Care, Nusil.com. (2016). Available from: https://nusil.com/LifeSciences
[43] W. AG, Medical devices—Wacker Chemie AG (2016). Available from: http://www.wacker.com/cms/en/industries/healthcare/med_tec/med_tec.jsp
[44] Marketsandmarkets.com., Isocyanate Market worth $38,729 Million by 2019 (2016). Available from: http://www.marketsandmarkets.com/PressReleases/isocyanate.asp
[45] C. Six, F. Richter, Isocyanates. Organic, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co., KGaA, (2003).
[46] G. Avar, U. Meier-Westhues, H. Casselmann, D. Achten, Polyurethanes, Polym. Sci. 10 (2012) 411–441.
[47] I. Yilgör, E. Yilgör, G. Wilkes, Critical parameters in designing segmented polyurethanes and their effect on morphology and properties: a comprehensive review, Polymer 58 (2015) A1–A36.
[48] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, In vitro oxidation of high polydimethylsiloxane content biomedical polyurethanes: correlation with the microstructure, J. Biomed. Mater. Res. A 87A (2) (2008) 546–556.
[49] E. Christenson, J. Anderson, A. Hiltner, Biodegradation mechanisms of polyurethane elastomers, Corros. Eng. Sci. Technol. 42 (4) (2007) 312–323.
[50] J. Kang, G. Erdodi, J. Kennedy, Polyisobutylene-based polyurethanes with unprecedented properties and how they came about, J. Polym. Sci. A 49 (18) (2011) 3891–3904.
[51] S. Jewrajka, J. Kang, G. Erdodi, J. Kennedy, E. Yilgor, I. Yilgor, Polyisobutylene-based polyurethanes. II. Polyureas containing mixed PIB/PTMO soft segments, J. Polym. Sci. A 47 (11) (2009) 2787–2797.
[52] C. Macosko, RIM, Hanser, Munich; Vienna; New York, (1989).

[53] V. Verhoeven, A. Padsalgikar, K. Ganzeveld, L. Janssen, A kinetic investigation of polyurethane polymerization for reactive extrusion purposes, J. Appl. Polym. Sci. 101 (1) (2006) 370–382.
[54] H.L. Hess, et al. , Ind. Eng. Chem. 51 (8) (1959) 929–934.
[55] R. Ward, R. Jones, Polyurethanes and silicone polyurethane copolymers, Comprehensive Biomaterials, Elsevier Ltd, (2011) pp. 431–477.
[56] J. Puaux, P. Cassagnau, G. Bozga, I. Nagy, Modeling of polyurethane synthesis by reactive extrusion, Chem. Eng. Process. 45 (6) (2006) 481–487.
[57] V. Verhoeven, A. Padsalgikar, K. Ganzeveld, L. Janssen, The reactive extrusion of thermoplastic polyurethane and the effect of the depolymerization reaction, Int. Polym. Process. 21 (3) (2006) 295–308.
[58] J. Drobny, J. George, Handbook Of Thermoplastic Elastomers, PDL(Plastics Design Library)/William Andrew Publishing, Norwich, NY, 2007, pp. 233–253.
[59] T. Choi, K. Masser, E. Moore, J. Weksler, A. Padsalgikar, J. Runt, Segmented polyurethanes derived from novel siloxane-carbonate soft segments for biomedical applications, J. Polym. Sci. B 49 (12) (2011) 865–872.
[60] L. Tatai, T. Moore, R. Adhikari, F. Malherbe, R. Jayasekara, I. Griffiths, P. Gunatillake, Thermoplastic biodegradable polyurethanes: the effect of chain extender structure on properties and in-vitro degradation, Biomaterials 28 (36) (2007) 5407–5417.
[61] T. Choi, J. Weksler, A. Padsalgikar, R. Hernéndez, J. Runt, Polydimethylsiloxane-based polyurethanes: phase-separated morphology and in vitro oxidative biostability, Aust. J. Chem. 62 (8) (2009) 794.
[62] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, Microstructural organization of three-phase polydimethylsiloxane-based segmented polyurethanes, Macromolecules 40 (15) (2007) 5441–5449.
[63] S. Pongkitwitoon, R. Hernández, J. Weksler, A. Padsalgikar, T. Choi, J. Runt, Temperature dependent microphase mixing of model polyurethanes with different intersegment compatibilities, Polymer 50 (26) (2009) 6305–6311.
[64] R. Hernandez, J. Weksler, A. Padsalgikar, T. Choi, E. Angelo, J. Lin, L. Xu, C. Siedlecki, J. Runt, A comparison of phase organization of model segmented polyurethanes with different intersegment compatibilities, Macromolecules 41 (24) (2008) 9767–9776.
[65] T. Choi, J. Weksler, A. Padsalgikar, J. Runt, Influence of soft segment composition on phase-separated microstructure of polydimethylsiloxane-based segmented polyurethane copolymers, Polymer 50 (10) (2009) 2320–2327.
[66] R. Bonart, E. Müller, Phase separation in urethane elastomers as Judged by low-angle X-Ray scattering. II. Experimental results, J. Macromol. Sci. B 10 (2) (1974) 345–357.
[67] R. Bonart, E. Müller, Phase separation in urethane elastomers as judged by low-angle X-ray scattering. I. Fundamentals, J. Macromol. Sci. B 10 (1) (1974) 177–189.
[68] L. Leung, J. Koberstein, Small-angle scattering analysis of hard-microdomain structure and microphase mixing in polyurethane elastomers, J. Polym. Sci. 23 (9) (1985) 1883–1913.
[69] D. Tyagi, J. McGrath, G. Wilkes, Small angle X-ray studies of siloxane-urea segmented copolymers, Polym. Eng. Sci. 26 (20) (1986) 1371–1398.
[70] E. Cosgriff-Hernandez, E. Tkatchouk, T. Touchet, N. Sears, A. Kishan, C. Jenney, A. Padsalgikar, E. Chen, Comparison of clinical explants and accelerated hydrolytic aging to improve biostability assessment of silicone-based polyurethanes, J. Biomed. Mater. Res. A 104 (7) (2016) 1805–1816.
[71] A. Colas, J. Curtis, Silicones, In: K. Modjarrad, S. Ebnesajjad (Eds.), Handbook of Polymer Applications in Medicine and Medical Devices, 2013, pp. 131–143.
[72] S. Clarson, J. Semlyen, Siloxane Polymers, Prentice Hall, Englewood Cliffs, NJ, (1993).
[73] D. Paul, J. Mark, Fillers for polysiloxane ("silicone") elastomers, Prog. Polym. Sci. 35 (7) (2010) 893–901.
[74] A. Smith, The Analytical Chemistry of Silicones, Wiley, New York, NY, (1991).
[75] W. Lynch, Handbook of Silicone Rubber Fabrication, Van Nostrand Reinhold, New York, NY, (1978).
[76] W. Noll, Chemistry and Technology of Silicones, Academic Press, New York, NY, (1968).
[77] J. Sommer, Elastomer Molding Technology, Elastech, Hudson, OH, (2003).
[78] Chemours.com., Teflon ™| Chemours Teflon™ Nonstick Coatings and Additives (2016). Available from: https://www.chemours.com/Teflon/en_US/

[79] S. Ebnesajjad, Non-Melt Processible Fluoroplastics, Plastics Design Library, Norwich, NY, (2000).
[80] N. McCrum, An internal friction study of polytetrafluoroethylene, J. Polym. Sci. 34 (127) (1959) 355–369.
[81] Zeusinc.com., PTFE Tubing, Heat Shrink, Multi-lumens & Profiles | Zeus (n.d.). Available from: http://www.zeusinc.com/materials/ptfe
[82] I. Ochoa, S. Hatzikiriakos, Paste extrusion of polytetrafluoroethylene (PTFE): surface tension and viscosity effects, Powder Technol. 153 (2) (2005) 108–118.
[83] S. Khatipov, N. Sadovskaya, A. Obvintsev, A. Kasatkin, Investigation of the supramolecular structure of PTFE via two-stage chemical etching, J. Synch. Investig. 9 (6) (2015) 1184–1194.
[84] K. Uhrich, D. Abdelhamid, Biodegradable and bioerodible polymers for medical applications, in: L. Poole-Warren, P. Martens, R. Green (Eds.), Biosynthetic Polymers for Medical Applications, A Volume in Woodhead Publishing Series in Biomaterials, 2016.
[85] D.W. Grijpma, A.J. Nijehuis, P.G.T. van Wijk, A.J. Pennings, High impact strength aspolymerized PLLA, Polym. Bull. 29 (1992) 571–578.
[86] L. Fambri, A. Pegoretti, R. Fenner, S.D. Incardona, C. Migliaresi, Biodegradable fibres of poly(L-lactic acid) produced by melt spinning, Polymer 38 (1) (1997) 79–85.
[87] P. Tomala, Biodegradable self-reinforced composite materials; manufacturing structure and mechanical properties, Clin. Mater. 10 (1992) 29–34.
[88] J. Shim, M. Kim, J. Park, R. Pati, Y. Yun, S. Kim, H. Song, D. Cho, Three-dimensional printing of antibiotics-loaded poly-ε-caprolactone/poly(lactic-*co*-glycolic acid) scaffolds for treatment of chronic osteomyelitis, Tissue Eng. Regen. Med. 12 (5) (2015) 283–293.
[89] W. Amass, A. Amass, B. Tighe, A review of biodegradable polymers: uses, current developments in the synthesis and characterization of biodegradable polyesters, blends of biodegradable polymers and recent advances in biodegradation studies, Polym. Int. 47 (2) (1998) 89–144.

4 Biological Properties of Plastics

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1 Introduction

The performance of a medical device in in vivo conditions is dependent on the behavior of the material it is composed of. The biological properties of a plastic are crucial in its use in medical applications. Two main aspects of the biological properties of a plastic are evaluated; these aspects are the biocompatibility and the biostability. In some ways one can term biocompatibility as the reaction of the body to an implanted device whereas biostability can be said to be the reaction of the implanted device to the environment in the body. Biocompatibility is of relevance to all medical devices whether these come in short-term contact with the body or if these are permanently implanted. Biostability, on the other hand, is of greater importance as the device implantation duration increases.

There are a number of tests designed to evaluate the biocompatibility of a device. These tests depend on the nature of the device and its contact with bodily fluids. These tests can be short term in vitro such as cytotoxicity or long term in vivo such as implantation studies. The tests detailed out in the standard ISO 10993 are often used as the starting point to define the tests required for any device.

ISO stands for International Organization for Standardization, an international standards development organization [1]. ISO 10993 defines the various tests that regulate the evaluation of a device for biological compatibility [2]. ISO 10993, as of November 2007, is divided into a number of parts detailing the testing, these parts are as follows:

- Part 1: Evaluation and testing
- Part 2: Animal welfare requirements
- Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity
- Part 4: Selection of tests for interaction with blood
- Part 5: Tests for cytotoxicity: in vitro methods
- Part 6: Tests for local effect after implantation
- Part 7: Ethylene oxide sterilization residuals
- Part 8: (withdrawn)
- Part 9: Framework for the identification of potential degradation products
- Part 10: Tests for irritation and sensitization
- Part 11: Tests for systemic toxicity
- Part 12: Sample preparation and reference materials
- Part 13: Identification and quantification of degradation products from polymers
- Part 14: Identification and quantification of degradation products from ceramics
- Part 15: Identification and quantification of degradation products from metals and alloys
- Part 16: Toxico-kinetic study design for degradation products and leachables
- Part 17: Establishment of allowable limits for leachable substances
- Part 18: Chemical characterization of materials
- Part 19: Physico-chemical, mechanical, and morphological characterization
- Part 20: Principles and methods for immune toxicology testing of medical devices

The tests for biostability are often based on the application of the device and the particular environment the device encounters in service. The wide variety of in vitro and animal tests used for biostability leave the results open to interpretation and the relevance of the results is debated as often the results do not reflect results obtained from actual human clinical data [3,4]. Nevertheless the biostability tests can act as an important screening exercise and pointers to material performance in vivo.

Before use as a medical device, the material and the device have to undergo sterilization to render it effectively aseptic for the sterile environment of the body [5,6]. Even though sterilization is not strictly a biological property of the material, the behavior of the material in the sterilization process is an important pointer to the suitability of the plastic in its application within the medical sector.

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2 Biocompatibility

Biocompatibility is generally defined as the ability of a material or device to perform its function in the body, at the same time, eliciting an appropriate host response. The goal of biocompatibility evaluation is to predict whether a material or device presents any potential harm to the patient. The response of the body tissue systems to any introduced material or device can be measured by various means of in vitro and in vivo evaluation.

2.1 In Vitro Tests

In vitro tests refer to culturing of cells outside the body; the Latin term literally means "in glass." Various in vitro tests and assays are included in the testing procedure series of ISO 10993. In vitro assays often act as useful tools to indicate any potential issues and hazards associated with any material. Both solid materials and their extracts can be used for in vitro biocompatibility evaluation. A limited number of in vitro tests have been validated for final material risk assessment purposes as one of the limitations of an in vitro test is that the output data cannot be directly extrapolated to dosage levels to humans. Very often the outputs from any in vitro test have to be confirmed with an in vivo test. There exists, however, a need for more accurate in vitro tests as the development of more accurate tests can result in faster data without the need for animal testing.

2.1.1 Cytotoxicity

The tests for in vitro cytotoxicity are described in ISO 10993-5. Three different approaches are described in the standard: an extract test, a direct contact test, and an indirect contact test. Cellular cytotoxicity is measured by the evaluation of the cell morphology, cell damage, and cell growth or by measurement of cellular activity.

Direct contact cell culture is very commonly used in studies of biocompatibility involving new biomaterials [7]; one of the advantages of this test is that the specific type of cell that the device will come in contact with can be used. For example, biomaterials intended for cardiovascular applications use human or animal endothelial cells whereas materials intended for hard tissue or orthopedic applications are studied with osteoblasts [7]. The direct contact test commonly involves the development of a monolayer of L-929 mammalian fibroblast cells on a culture plate. Biomaterial specimens under investigation are placed on these cell layers with fresh culture medium and incubated for 24 h at 37°C. After exposure, the cells are stained with appropriate histological stains. Light microscopic evaluation is then used to identify cells adherent to the culture plate. The use of established cell lines such as the L-929 mammalian fibroblast cell line offers the advantage of less assay repeatability, reproducibility, and efficiency. Cells are observed for visible signs of toxicity, such as a change in the size or appearance of cellular components or a disruption in their configuration, in response to the test and control materials [2,7,8].

When low molecular weight extractables are of concern, the extract test is used to evaluate the biocompatibility. The extraction method, detailed in ISO 10993, is usually carried out in different solvents and at various dilutions. The solvents are chosen to be hydrophobic and hydrophilic in nature. The extract test permits the examination of the potential toxicity of the extracts and the identification of materials within a biomaterial that may be cytotoxic [7].

The elution test method constitutes the indirect cytotoxicity test evaluation, in this method solvent extraction is first done; extracts are obtained by placing the test and control materials in separate cell culture media under standardized conditions such as, 3 cm^2 of device surface area or 0.2 g/mL concentration of culture medium for 24 h at 37°C. Each fluid extract obtained is then applied to a cultured-cell monolayer, replacing the medium that had nourished the cells to that point. In this way, test cells are supplied with a fresh nutrient medium containing extractables derived from the test article or control. The cultures are then returned to the 37°C incubator and periodically removed for microscopic examination at designated times for as long as 3 days.

2.1.2 Genotoxicity

Genotoxicity is the measure of the ability of the biomaterial to cause any permanent alteration to the genetic structure of the cells within the host. This permanent alteration to the genetic structure is known as genetic mutation. This mutation is inheritable and the agent that causes it is known as a genotoxin [9]. Genetic mutations are many times associated with cancerous growths. Genotoxicity is indicated for materials where the composition reveals possible interaction with cellular genetic material, testing is also required when the material composition is unknown. Genotoxic tests are especially required for biomaterials that are used in implantable medical devices with prolonged exposure [9,10].

The in vitro tests include three critical genotoxicity endpoints: genetic mutations, structural chromosomal aberrations, and numerical chromosomal aberrations. No single test is capable of identifying all end points so a battery of tests is usually recommended. One popular method of determining genetic mutations is the Ames test which is a bacterial reverse mutation test. A positive result in the Ames test indicates that the material is mutagenic and a potential carcinogen [11,12].

The procedure was described in a series of papers in the early 1970s by Bruce Ames and his group at the University of California, Berkeley [13,14]. In the Ames test, bacterial strains of *Salmonella typhimurium* and *Escherichia coli* are used to detect point mutations. These strains carry mutations in genes involved in the synthesis of a specific protein, histidine. These strains require histidine for growth, but cannot produce it. The method tests the capability of the tested substance in creating mutations that result in a state where the cells can grow on a histidine-free medium. [13]

A micronucleus (MN)-based test can also be used for in vitro genotoxicity. The MN assay is used for the detection of MN in the cytoplasm of interphase cells and this can be performed using either rodent or human cells [10].

The in vitro genotoxicity tests are a good indication as to proceed with further in vivo testing. If the results from the in vitro tests for mutagenicity or DNA damage come back negative, additional in vivo testing is not required. Acceptable results from a battery of genotoxicity tests can go a long way toward ensuring the safety of a proposed biomaterial or device; in many cases good data from genotoxic testing can justify not pursuing other in vivo tests such as device carcinogenicity, particularly if there is existing information about the chemical composition of the material and its history of usage indicating a lack of genotoxicity of the material in question [9].

2.1.3 Hemocompatibility

Medical devices that come in contact with blood and/or blood components need to be tested for hemocompatibility. Blood is a highly complex biochemical system and its various components play various roles including oxygen transport, tissue repair, and immunologic response. To preserve the critical nature of blood function, the implanted device contacting blood must be hemocompatible. The types of cardiovascular devices with blood contact are implanted devices such as pacemakers, grafts, stents, vascular grafts, etc., external communicating devices such as cannula, catheters, guidewires, etc., and external diagnostic devices.

Hemocompatibility testing needs to evaluate the following issues [15]:

- Thrombosis
- Coagulation
- Platelets
- Hematology
- Complement system

ISO 10993-4 addresses the various in vitro and in vivo tests for hemocompatibility. The in vitro tests may not answer all the questions surrounding these issues but further in vivo testing is based on the outcomes of the in vitro tests. The in vitro tests include complement activation (immunology), hemolysis (hematology), and partial thromboplastin time (coagulation) tests. Such in vitro test methods are usually quick and inexpensive and do not require the use of animals that in vivo methods do. Complement activation is the most relevant immunology test for devices exposed to circulating blood. An increase in a downstream complement component over baseline levels indicates activation of the complement cascade. Acceptable complement activation limits are usually ones that compare well with favorable materials and devices. A standardized ASTM hemolysis test method [14] is available for determining the hemolytic potential of a device or material. The hemolysis in vitro tests involve a quantitative measurement of plasma hemoglobin. An increase in plasma hemoglobin correlates with the disintegration (lysis) of the red blood cells, thereby indicating hemolytic activity of the material exposed to the cells. A device's effects on blood coagulation may be measured in vitro by determining the rate of clot formation or the partial thromboplastin time of plasma exposed to the biomaterial or device during an incubation period. The reaction of white blood cells to materials can also be used as an effective hematology test.

2.1.4 Irritation and Sensitization

Components in biomaterials, especially the ones that are prone to being extracted, can cause allergic or sensitization reactions in the host. The sensitization reaction is a local tissue response characterized by the signs of inflammation such as redness and swelling and sometimes this inflammation is accompanied by an increase in local temperature and associated pain. Different chemicals are capable of causing this

sensitization reaction. These chemicals may cause either immediate or delayed reaction. These chemicals may be present in device materials as additives, processing or manufacturing aids, or inadvertent contaminants. For example, the organo-metallic catalysts and stabilizers used in different plastic material formulations are chemicals capable of causing irritation and necrosis when applied to mucosal surfaces; residual concentrations of ethylene oxide present in gas-sterilized devices can produce an irritant response if they are not reduced to acceptable levels before the device is used; and residues of such contaminants as chemical detergents in a particular batch of materials or devices can cause unexpected irritation responses in users or patients [8]. The potential for the material for these allergic reactions can be assessed by the in vitro skin model irritation assay. The in vitro skin irritation assays use a reconstructed human-skin model that consists of a supporting collagen and a functional outer skin layer, the outermost layer of the skin is known as the stratum corneum [10,16]. The principle of the in vitro skin model is based on the premise that the leachables from the material are able to penetrate through the stratum corneum by diffusion and are cytotoxic to the underlying cells.

The outcome of the test is measured by the viability of the underlying tissue concurrently using a positive and negative reference control. The viability is determined with metabolically converted vital dyes. The most frequently used assay is MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) [10,16]. As with other in vitro tests, a negative outcome would need confirmation with an in vivo test.

2.2 *In Vivo Testing*

In vivo testing follows the initial in vitro screening tests and becomes necessary under certain conditions. In general, materials that show nontoxic results in in vitro tests will be nontoxic in in vivo assays. Materials displaying toxic results in in vitro tests need to be tested with further in vivo tests and the results of these tests are necessary to determine its acceptability for clinical use. It should be noted that low levels of toxicity may not necessarily preclude the use of a material or device in clinical applications. One example of where the risk of low levels of toxicity is outweighed by the clinical advantage is in glutaraldehyde-fixed porcine valves. Glutaraldehyde has shown to display low levels of toxicity and the treatment of the porcine tissue for preservation with glutaraldehyde leaves glutaraldehyde residues on the valve that produce adverse effects in vitro. Despite the negative in vitro findings, this material is still used in the development of prosthetic heart valves for clinical use [7,17].

2.2.1 In Vivo Genotoxicity

In vivo genotoxicity tests are typically indicated when a genotoxic response is observed in the in vitro tests. However, testing requirements vary from country to country and certain regulatory bodies [2,9] require in vivo results as a part of the overall genotoxic assessment regardless of the in vitro testing results. In vivo genotoxic testing is usually carried out in rodent hematopoietic cells and observation of chromosomal damage is done in them. The two most common assays used are as follows:

- In vivo mouse micronucleus assays
- In vivo chromosomal aberration assay

In subjecting the animals to these assays, extraction of the material or device is used as the means. ISO 10993-3 is generally used as the standard to direct sample preparation and extraction conditions but depending on the regulatory body, exhaustive extraction techniques may be used.

The in vivo micro nucleus test is the more popular of the two genotoxicity tests [10]. Samples are delivered as extracts through mainly the intravenous or intraperitoneal route. Blood samples are collected at regular intervals and analyzed for the presence of micronucleus. The numbers of micronucleus in the animals are compared to the controls to determine whether the materials in the device had any effect on the micronucleus numbers [10].

The in vivo chromosomal aberration assay is conducted on similar animal numbers and groups as with the micro nucleus test. Animals are dosed based on volume per body weight calculations, the animals are then sacrificed and their bone marrow cells harvested. The metaphase cells are scored for chromosomal aberrations and compared with positive and negative controls to determine whether the materials in the device led to any genotoxic effects.

2.2.2 Carcinogenicity

Testing for carcinogenicity is only indicated in the following situations [7,10]:

- A positive response in genotoxicity testing
- Known presence of a carcinogenic species within the material to be implanted

- Any longer term implanted material without a safe clinical usage history

Traditional testing for carcinogenicity involved chronic or lifelong studies in rodents. This meant using a number greater than 50 animals and implanting them with device/material samples for a duration greater than 18 months. At the end of the study, both the survival among the rodents and the incidence of tumor formation helped determine the carcinogenicity of the device. Apart from this test being a very expensive and long study, several instances of false positives were reported [18]. The false positive was a result of the rodents developing sarcoma around implanted foreign materials within 8–9 months of implantation [18].

A genetically modified mouse model is currently being used as an alternative to the traditional carcinogenicity testing model. The rasH2 mouse model is most commonly used. The rasH2 mouse contains multiple copies of the human c-Ha-ras proto-oncogene as well as its native murine Ha-ras gene. This genetic modification causes these mice to be very susceptible to tumor development following exposure to carcinogens [10]. The transgenic mouse test is of a much shorter duration, 6 months rather than the minimum of 18 months in the traditional test, it needs lesser number of animals for the outcome (<25) [19] and is prone much less of the false positive results as the mice are implanted for a duration lower than sarcoma development. Therefore the transgenic mouse test is less expensive and more attractive for testing the carcinogenicity of a material. Further details of this test can be found in references [18,19].

2.2.3 Hemocompatibility

The effect of any blood contacting material and device combination on blood thrombosis, coagulation, platelets, hematology and the complement system can be addressed effectively through the previously discussed in vitro test methods. In vivo tests for hemocompatibility mainly focus on the thrombosis aspect of blood interaction. Local tissue response and the efficacy of the device can also be tested using in vivo hemocompatibility testing.

One of the primary reasons for performing in vivo hemocompatibility is to mimic conditions of blood flow and geometry in the vasculature during implantation. These conditions are not necessarily captured during in vitro tests. These tests are best done on the finished device so as to reflect the exact conditions of blood flow the device will encounter during service. For true reflection of device performance, larger animals are chosen for the test. Typically animal models include canines, swine, and sheep [7,10]. These animals have blood vessels of a size large enough to accommodate medical devices designed for humans. However, the fact that the sizes of blood vessels are smaller than in humans and that the blood properties are different than human blood, interpretation of results can be sometimes complicated [20].

Although a standardized test for the in vivo thrombosis doesn't exist, a 4 h, nonheparinized, venous implant is considered by some as the standard model [10,20]. This model is utilized for many cardiovascular devices. The device to be evaluated is inserted mainly through the jugular vein of the test animal. The device is then threaded down the vessel and toward the heart for a distance of approximately 15 cm [10,20]. A comparative control is inserted in the opposite vein. The control used in this study has a clear history of use and thus is useful for comparison. The results of the 4 h test are evaluated as in Table 1.

2.2.4 Systemic Toxicity

Part 11 of the ISO 10993 standard deals with the systemic toxicity effects of the implantation of a medical device in the body. Systemic toxicity implies the toxicity of the extractable or leachable chemicals emanating from the implanted device and having an effect on tissues and organs remote from the location of implantation. The leachable chemicals are transported to the remote location via the lymphatic or the circulatory system of the body. Systemic toxicity testing has been divided into acute, subacute,

Table 1 Subjective Thrombosis Scoring Scheme (ISO 10993-4) [10]

Score	Description
0	No thrombosis
1	Minimal thrombosis, for example, at one location or a very thin layer
2	Slight thrombosis, for example, minimal clotting at multiple locations
3	Moderate thrombosis, for example, less than ½ length of implant covered with clot
4	Severe thrombosis, for example, greater than ½ length of implant covered with clot
5	Vessel occluded

Table 2 Recommended Minimum Group Sizes (ISO 10993-11)

Study Type	Rodent	Nonrodent
Acute	5	3
Subacute	10 (5/sex)	6
Subchronic	20 (10/sex)	8
Chronic	(20/sex)[a]	[a]

[a]*Expert statistical consultation for chronic study group size is recommended.*

subchronic, and chronic situations. Acute toxicity is usually a test done to determine gross signs of toxicity and [10] as a result, the test is performed on limited number of animals for a short time. As studies are done to evaluate other forms of systemic toxicity, the duration of the study and animal group sizes involved tend to increase [10]. Guidance on the group sizes is as in Table 2

Nonrodent tests are usually not required for medical devices as opposed to drugs and pharmaceuticals.

Acute systemic toxicity is tested through extracts administered through both the intravenous route and the intraperitoneal route. Acute systemic toxicity is defined as the adverse effects occurring at any time after single, multiple, or continuous exposures of a test sample within a 24-h period [2,10]. The mice are observed for symptoms of toxicity and their functions such as lethargy, hyperactivity, convulsions, weight loss, and death are recorded. The observations are typically for a minimum of 3 days and the dosage is frequently exaggerated to improve the sensitivity of the tests.

Longer duration toxicity tests are used to evaluate subacute and subchronic toxicity. Subacute toxicity is defined as adverse effects occurring after multiple or continuous exposure between 24 h and 28 days; subchronic toxicity is defined as the adverse toxicity effects occurring for up to 90 days of multiple or continuous exposure, whereas chronic toxicity is defined as the adverse effects occurring with repeated administration of a sample for a major part of the life span which for rodents is typically 6 months in duration. The rationale for choosing a test and the length of exposure is dictated by the nature of clinical use of the device. The route of exposure can be through either injection of extracts or device/material implantation. Subcutaneous implants are often chosen as a route of exposure for long-term implanted devices [20]. The size of the implant is dependent on that of the device used in the application. A large safety factor, up to 100 times device weight/body weight, is used for increased sensitivity. Many times, especially for larger devices, such a safety factor may not be possible to achieve, in those cases multiple implant sites can be used. An advantage of the implantation study for toxicity is that the study can be successfully combined with the implantation study. The animals are monitored daily for signs and symptoms of toxicity and at the end of the test period the animals are euthanized and autopsies are conducted.

Systemic toxicity tests may also be used for the evaluation of pyrogenicity of a device. Some compounds when present in the body at sufficiently high doses are capable of causing an increase of body temperature or a fever. These fever causing compounds are called pyrogens. To test for the pyrogenicity of a device, extracts are typically used and the temperature of the animal is measured over time. A significant increase in body temperature indicates the presence of pyrogens in the device.

2.2.5 Implantation

For most of the devices that are implanted in vivo and come in contact with living tissues, it is important to assess the impact of the effects of that device on the contacted tissues. The implantation study as described in ISO 10993-1 plays an important role in forming that assessment. In the implantation study, the medical device or the material is surgically implanted into an appropriate site within an animal. The tissue and the site of implantation are decided by the clinical use of the device. The most common implantation tissues are muscular and subcutaneous. Specialized tissues and sites may be chosen as appropriate for the site of device implantation in a clinical setting [7].

The assessment of the material impact is done carefully by both macroscopic and microscopic or histological examination of the surrounding tissues at different time points. Multiple time point analysis is required to ensure accurate determination of the impact of the biomaterial on the surrounding tissues. This assessment should take into account the changing response of tissue over time and also the variable rate of release of any degradable species from the material or device. The final assessment should be done at a time when the surrounding tissues reach an equilibrium state or homeostasis. It is estimated that homeostasis is achieved in biostable materials in a time between 12 and 26 weeks [10]. That duration can vary considerably in degradable materials and depends on the rate of material

degradation and homeostasis is said to occur at the point of complete material degradation. Short-term intervals generally range from 1 to 4 weeks in duration whereas long-term intervals typically range from 12 to 56 weeks.

For short-term evaluation of biomaterials for up to 12 weeks, smaller animals such as rodents, guinea pigs, or rabbits are utilized. Animals of a larger size and greater life expectancy are preferred for implantation tests of a longer duration [21]. Sometimes the entire device instead of a material is tested, heart valves are tested in sheep, calves are used for the testing of ventricular assist devices or a total artificial heart (TAH) and cardiac rhythm management (CRM) devices such as pacemakers and defibrillators are tested in dogs.

The use of relevant controls is an important aspect of the implantation assessment. It is important to compare the response of the material under test to the response of a well-known and accepted material. The macroscopic assessment is determined on the zone of tissue response and the encapsulation of the implanted material. The microscopic assessment is based on tissue inflammation, cell death or necrosis, cell thickening or fibrosis, vascularization, fatty infiltration, and any other tissue alteration [20]. The control used in the study must have similar shape and size to the material or device being assessed, for example, in the evaluation of a porous, mesh device, if a solid, smooth material is used as a control, wrong conclusions could be reached as the surface area of the mesh exposed to tissues is much larger as compared to a smooth, solid material.

2.2.6 Sensitization, Irritation, and Intradermal Reactivity

As described earlier, in vitro tests exist for the determination of the sensitization and irritation nature of a medical device. Many regulatory agencies, however, require an in vivo for confirmation of the in vitro results especially in the case of a negative in vitro result.

The tests for irritation and sensitization focus on leachables from the materials and hence focus on the extracts of the materials in appropriate solvents. There are different varieties of irritation tests where the device is exposed to different types of tissues such as skin, ocular, mucous membrane, and intracutaneous. The exposure choice is based on the type of tissue contact the device has in the body.

For cardiovascular implanted devices, the intracutaneous assay is typically used as the most relevant test. As with other biocompatibility tests, the results of the irritation assay are compared with controls and the final assessment is based on this comparison. In a standard intracutaneous irritation assay, two extracts are examined [7,10]. The extraction is done in saline and pure vegetable oil. A known volume of the test and control extracts, ~ 0.2 mL, are then injected intradermally into albino, New Zealand White (NZW), rabbits. The injections occur in rows at multiple points and the blisters that occur at the injection sites are examined periodically over 72 h for erythema and edema. This examination uses a scoring scheme as outlined in Table 3.

ISO 10993-10 describes in detail the procedures for in vivo sensitization testing. The guinea pig maximization test (GPMT) is typically used for cardiovascular devices. Device or material extracts in polar (saline) and nonpolar solvents (vegetable oil) are intradermally injected along with controls into multiple animals. Usually, a week after the initial injection, the sites are scored for erythema and edema using a scoring method as in Table 4. Scores of 1 or greater are usually considered evidence of sensitization [10].

Table 3 Irritation Scoring Scheme (ISO 10993-10:2010)

Reaction	Irritation Score
Erythema and eschar formation	
No erythema	0
Very slight erythema	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema	4
Edema formation	
No edema	0
Very slight edema	1
Well-defined edema	2
Moderate edema—raised approximately 1 mm	3
Sever edema—raised more than 1 mm and extending beyond exposure area	4
Maximum possible score for irritation	8

Table 4 Scoring Chart for GPMT, Magnussen and Klingman (ISO 10993-10)

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and/or swelling	3

3 Foreign Body Reaction

After implantation of a device into the host, all medical devices initiate several blood–material and tissue–material interfacial responses [22,23]. These responses are a combination of normal adaptive responses to tissue injury and the reaction to foreign devices. These reaction processes begin instantaneously upon device implantation and length of the responses are dependent on the particular properties of the material that make up the device particularly the material's surface and bulk chemical of the biomaterial. The implantation of biomaterials leads to a variety of responses and body reactions that include blood–material interactions, protein adsorption, provisional matrix formation, acute inflammation, chronic inflammation, granulation tissue development, foreign body reaction, and fibrosis or fibrous capsule development. From a perspective of the body, any insertion or implantation of a device injures the tissues and organs involved. This, therefore, initiates an injury response which activates several mechanisms with the ultimate aim to bring back the situation to one of homeostasis [22]. The nature of the response depends upon the degree of intervention that is required for the device implantation procedure. Implantation first initiates blood to material interactions and these occur with protein adsorption on the device surface. The nature of the protein adsorption determines the development of a transient provisional matrix that forms on and around the device. The provisional matrix is the initial thrombus development at the interface of the tissue and device.

3.1 Protein Adsorption

One of the first interactions with the body of an implanted device occurs within the first few seconds of implantation in the form of protein adsorption. This is the first response of the body's immune system in

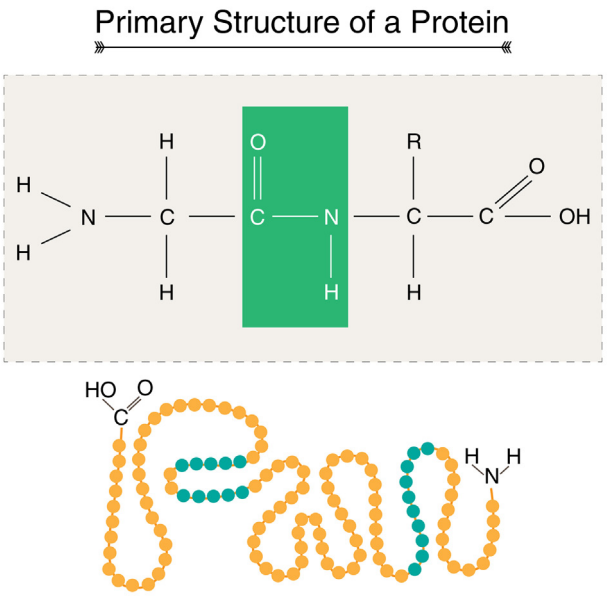

Figure 1 A typical protein molecule.

trying to coat the material with proteins to contain, neutralize, or isolate the foreign body. Proteins are biomolecules that are composed of amino acid subunits. They are high molecular weight, heterogeneous; contain regions of varying polarity, charge, and hydrophilicity. A typical protein molecule is illustrated in Fig. 1. Protein molecules can exhibit both amphoteric and amphiphilic properties. A typical configuration of a protein molecule has the hydrophobic side groups toward the inside and the amino acids with the hydrophilic side groups toward the molecular periphery. As the protein molecules contact the implanted device surface, a number of interactions are possible involving electrostatic and polar forces. These interactions are mainly dependent upon the surface of the device and the nature of the protein molecule. Once the protein layer is deposited on the device surface, other events such as interaction of blood cells and platelets follow. It is widely recognized that the nature of protein layer adsorption influences the subsequent events, that is, correct protein adsorption could reduce the risk of thrombosis [22,23].

Protein adsorption occurs spontaneously when the process of adsorption leads to greater release of energy than is required for the process. In other words, Gibbs free energy during the adsorption process is negative. The Gibbs free energy can be expressed as

$$\Delta_{ads} G = \Delta_{ads} H - T\Delta_{ads} S \quad (1)$$

where Δ_{ads} is the change in value during adsorption, G is the Gibbs free energy, H is the enthalpy, S is the entropy, and T is the temperature.

For adsorption to occur spontaneously, Gibbs free energy of adsorption ($\Delta_{ads}G$) has to be less than zero.

Once the protein adsorption process is underway, the rate of adsorption becomes important. This rate is dependent on the transport mechanism involved, diffusion, thermal convection, or bulk flow [24,25]. The combined adsorption process can be modeled using partial differentials of protein concentrations with time and distance as in the following equation:

$$\frac{\partial c}{\partial t} + v(y)\frac{\partial c}{\partial x} = D\frac{\partial^2 c}{\partial y^2} \tag{2}$$

where c is the concentration, t is the time, $v(y)$ is the velocity distribution across the flow path, D is the protein diffusivity, x is the axial direction of flow, and y is the perpendicular direction to the flow.

Using a boundary condition stating that the flux at the surface is equal to the intrinsic rate of adsorption and for a transport limited case in a nonflowing system, the adsorption rate is given by [24,25]

$$\frac{dn}{dt} = C_o\left(\frac{D}{\pi t}\right)^{\frac{1}{2}} \tag{3}$$

where D is the diffusion coefficient, n is the surface concentration of protein, C_o is the bulk concentration of proteins, and t is the time.

The blood plasma contains more than 100 types of proteins. Three main proteins, collectively known as the "big three" constitute more than 3/4th of the entire protein population, these are albumin, gammaglobulin (γ − globulin, IgG), and fibrinogen. Studies of biomaterial interactions have focused on the identification of factors that decide the composition of the protein layer on the surface of the implanted device and mainly on the "big three" types of proteins. Studies have found that preferential adsorption of albumin on the surface of the device leads to an improvement in the short-term thromboresistance of the device [25,26]. Conversely, the adsorption of either gamma globulin or fibrinogen on the device surface can lead to increased platelet adhesion.

It is observed that the process of protein adsorption on biomaterial surfaces is a dynamic phenomenon. There is constant competition of protein molecules with one another over-binding sites on the surface of an implanted device. This competition is referred to as the Vroman effect, named after Leo Vroman, a Dutch-American scientist, who observed this process and postulated this effect [25,26]. According to the Vroman effect, small and abundant molecules will be the first to coat a surface. However, over time, molecules with higher affinity for that particular surface will replace them.

The deposition of protein layers on the surface of the device with proteins such as albumin, fibrinogen, and gamma globulin is linked to the subsequent reaction of the cells and tissues in the body to the implanted device. The protein layers modulate any inflammatory or wound healing responses of the body. The Vroman effect will mean that these responses are also time dependent. Protein adsorption thus leads to the formation of a provisional thrombus at the blood-device interface [26].

3.2 Tissue Inflammation

Following the formation of the provisional matrix, the processes of acute inflammation, chronic inflammation and foreign body reaction occur. The events following protein adsorption and the provisional matrix formation may not occur in sequence. In some cases, it is very likely for these events to overlap or occur simultaneously [22].

Inflammation is considered to be a tissue-device response; however, many of the mechanisms involved are similar to a blood-device response hence can be said to be part of the same process of host response. It must be noted that the response of the tissue to the implantation is also dependent on the site or the organ involved and the extent of the injury. Inflammation is generally defined as the reaction of tissue to local injury. Inflammation serves to contain, neutralize, dilute, or wall off the injurious agent or process [22,24]. Inflammation also sets into motion a series of events that help to heal the injury through repair of the injured tissue by regeneration of native cells, formation of a scar tissue, or a combination of these two processes. Acute inflammation is a relatively short-term process. Acute inflammation may last for as little as a few minutes but might last for longer, up to a few days, depending on the type of injury. One of the primary roles of acute inflammation is the transport of white blood cells or leukocytes to the site of the injury. Initially, the leukocytes consist mainly of neutrophils. The neutrophils are replaced by macrophages over a period of time and this is mainly due to the transient lifespan of neutrophils. The main role of the leukocytes in acute inflammation is to phagocytose foreign materials. Phagocytosis is the process by which a foreign material is absorbed and internalized into the body by the leukocytes. The phagocytosis process proceeds by completely engulfing the foreign material. In the case

of a device, complete engulfment is not possible due to the size difference between the device and the leukocytes. This therefore leads to incomplete phagocytosis or frustrated phagocytosis. However, certain events in phagocytosis do happen in acute inflammation despite the size disparity. As acute inflammation subsides, the neutrophils are replaced by monocytes and with frustrated phagocytosis the monocytes differentiate into macrophages [22]. The appearance of monocytes and macrophages is a sign of chronic inflammation.

The monocytes and the macro phages initiate the healing response of the body. With the progress of this healing response several new blood vessels are formed as a result. The new blood vessels are formed by budding or sprouting of preexisting blood vessels in a process known as neovascularization or angiogenesis. The new blood vessels give the appearance of a pink, soft granular structure upon the healing tissue and this tissue is known as the granulation tissue. Depending on the extent of injury, granulation tissue may be seen as early as 3–5 days following implantation of a biomaterial [22,24].

In an attempt to phagocytose the device, monocytes and macrophages combine to form larger sized cells known as foreign body giant cells (FBGC). The foreign body response of the body to the implanted device is composed of a combination of granulation tissue and FBGCs. The composition of the combination is dependent on the form and surface of the device. The relationship between the surface area and the volume of the device plays an important role in determining the foreign body response. For example, high-surface-to-volume implants such as fabrics, porous materials, particulate, or microspheres will have higher ratios of macrophages and FBGCs in the implant site than smooth-surface implants [22,23]. Smoother surface implants tend to have greater degree of fibrosis as compared to porous implants. Fibrosis or fibrous encapsulation is generally considered the end stage of the healing response of the body to an implanted device.

4 Biological Degradation

With the variety of processes and mechanisms occurring after the implantation of a device inside the body, degradation of a polymer inside the body can occur if any these processes affects the stability of the main chain in the polymer. For polymeric degradation to occur there has to be presence of a chemically sensitive bond in the structure of the polymer. This bond has to react with one of the numerous species present or generated in the body during and after the process of implantation. The general progress of reaction of that particular bond to the chemically active media begins with the process of adsorption of the media onto the polymer surface; this is followed by the diffusion and absorption of the medium into the bulk of the polymer. The species can react with the suspect bond and begin the process of degradation. The degraded products have to then diffuse out of the polymer and wash away from the polymer surface to complete the degradation process.

4.1 Hydrolysis

Polymer degradation can generally be classified into two mechanisms: hydrolysis and oxidation. Hydrolysis is derived from the Greek word combination of hydro and lysis, where lysis means to unbind. Hydrolysis is thus defined as the reaction with water where the water molecules lead to cleavage of chemical bonds within a material. In many ways hydrolysis is often seen as the opposite of condensation. In condensation the formation of water is usually accompanied by the growth in the chain of the polymer; in hydrolysis the reaction goes the opposite way where the reaction with a water molecule results in the breakage of already formed polymer bonds.

Hydrolysis is accelerated with the presence of a small amount of catalysts within water [27]. The catalysts could be the presence of any ions within the water. The rate of hydrolysis not only depends upon the susceptible chemical bonds within the polymer but also on the concentration of water inside the material. Both hydrolysis by pure water and catalysis by the presence of salts require water in the polymer. Hydrophilic polymers are more susceptible to hydrolysis and subsequent hydrolytic degradation as compared to hydrophobic polymers. Following surface moisture absorption, the rate of diffusion of water within the polymer is also quite critical. It is observed that the highest biodegradation of certain polymers occurs most rapidly when the rate of diffusion and permeability are highest [28]. Many other properties of polymers can also affect the hydrolytic nature of a polymer, if a chemically susceptible bond is shielded by either a hydrophobic structure or crystalline regions, the effective rate of hydrolysis can slow down. In a cross-linked polymer, high levels of cross-link can suppress hydrolysis. The ratio of surface area to volume of a device affects the rate of hydrolysis, a high ratio of exposed surface area to

volume as in a porous structure can greatly increase the rate of hydrolysis. The presence of mechanical stress is also seen to increase the rate of hydrolysis. The molecular weight of polymer does not directly seem to have a direct effect on the hydrolysis rate; however, a relatively high molecular weight polymer might show a slower decrease in the loss of properties due to hydrolysis.

Carbonyl bonds, that is, a carbon atom double bonded to oxygen (C = O) is most hydrolytically susceptible among commonly used medical plastics [28]. The carbonyl bond could be attached to other atoms in the polymer such as oxygen and nitrogen and these bonds could be esters, amides, carbonates, and urethanes. Among carbonyl polymers, anhydrides display the highest hydrolysis rates followed, in order, by esters and carbonates. Other carbonyl groups such as urethane, imide, amide, and urea can normally demonstrate good long-term stability in vivo especially if the group is contained within a hydrophobic backbone or highly ordered morphological structure. The rate of hydrolysis and the associated drop in the physical properties of the polymer determine if the polymer can be used for implantation and if it can be what the duration of the implant would be. Different medical polymers have the carbonyl group in them. Poly (ethylene terephthalate) (PET) has been used commonly as a long-term implant for many years is particularly favored in the manufacture of vascular grafts and heart valve sewing rings. The susceptible ester group in PET is protected by the highly crystalline structure found in the molecular structure. Thermoplastic polyurethane (TPU) synthesized using a polyester polyol; also contain the ester group that is prone to hydrolysis. Reaction with water leads to a breakdown of the urethane molecule as has been noted in several studies [28,29]. Their tendency to hydrolyze has meant that the use of these materials in biologically stable medical device is not recommended. Identification of the hydrolytic behavior of the polyester polyol–based TPUs led to the widespread use of polyether polyol–based TPUs for implantable applications. Poly (tetramethylene oxide) (PTMO) was the most common macrodiol in medical applications and several formulations were developed based on PTMO [30]. The ether group as such was considered to be hydrolytically stable. TPUs made from a polycarbonate-based polyol were extensively investigated and used for implantable applications; however, the material's hydrolytic performance is unclear. The hydrolysis of the carbonate linkages has been hypothesized to be the main mechanism of biodegradation of polycarbonate polyurethanes [31]. Studies have also shown that the degradation of poly (carbonate) urethanes in the biological environment may involve monocyte-derived macrophages and enzymes such as cholesterol esterase. These enzymes have been shown to accelerate the process of hydrolytic degradation of polycarbonate-based TPUs [32]. Other TPUs containing a siloxane-based polyol have been shown to be hydrolytically stable, commercially available siloxane-based TPUs (Elast-Eon and Pursil) have a combination of polyether and polysiloxane in their soft segments. The ether groups, as previously noted, as well as the siloxane groups are considered as hydrolytically stable. Nylon 6 (polycaproamide) and nylon 6,6 [poly(hexamethylene adipamide)] contain a hydrolyzable amide connecting group. These polyamide polymers can degrade by ion-catalyzed surface and bulk hydrolysis. In addition, hydrolysis due to enzymatic catalysis leads to surface erosion [33]. Quantitatively, nylon 6,6 lost 25% of its tensile strength after 89 days, and 83% after 726 days in dogs [34]. As hydrolysis results in chain cleavage of polymers the physical properties of polymers can be significantly affected once hydrolysis begins. Hydrolysis can be followed effectively by measuring the molecular weight of the material during its lifetime.

4.2 Oxidative Pathway

The oxidation degradation pathway is similar in many aspects to degradation following the hydrolytic pathway. The primary difference between the two mechanisms is, of course, the presence of susceptible chemical groups. Groups susceptible to oxidation allow the abstraction of an atom or an ion and subsequent resonance stabilization of the oxidized product which is either a radical or an ion. Similar to the principles of hydrolysis, oxidation degradation can be accelerated by an increase in concentration of the oxidizing species and also by the presence of a catalyst. The rate of diffusion of the oxidizing species in the material is therefore quite significant. The rate of oxidizing degradation can be slowed down when the susceptible chemical group is shielded by the presence of either cross-links or crystallinity. In a similar manner to hydrolysis, the rate of oxidation can dramatically increase based on the surface area to volume ratio of the device. Porous structures containing a susceptible group have been known to oxidize significantly faster.

As seen earlier, a series of events is set in motion as a device is implanted in the body; these events

begin with protein adsorption on the device's surface followed by acute inflammation, chronic inflammation, granulation, and ultimate foreign body reaction. Right after the protein adsorption phase, the inflammation cycle starts in which the immune system responds and tries to attack, destroy, or isolate the foreign body. Inflammation begins with the neutrophils but these are quickly replaced with monocytes. Monocytes are known to migrate to the site of the subsequent inflammation and rapidly differentiate into macrophages [35]. For large devices these macrophages fuse into FBGCs. A direct correlation between these FBGCs and damage to the devices, pacemaker leads, has been observed [36]. This established the role of FBGCs in the production of the degradative mechanisms. This phenomenon is well documented by Christenson et al. [35]. Adherent leukocytes release a variety of different species that are known to promote or catalyze polymer degradation. These include acids, enzymes, and the reactive oxygen intermediates (ROI). It has been observed that ROI cause maximum degradation; of these ROIs the hydroxyl radical ($\cdot OH$) is considered the most potent [37–39]. Hydrogen peroxide (H_2O_2) is also released by the macrophages and is an effective oxidant.

In combination with metal ion, hydrogen peroxide can degrade to release hydroxyl radicals. The metal ion here acts as a catalyst in the process of oxidation and this reaction is known as the Haber Weiss reaction. The catalysis of hydrogen peroxide with a transition metal ion, cobalt, in the Haber Weiss reaction is shown as follows:

$$Co^{++} + H_2O_2 \rightarrow Co^{+++} + OH^- + OH^{\cdot}$$

This phenomenon is known as metal ion oxidation (MIO) and has been frequently observed in implanted cardiac leads [40]. Cardiac leads in pacemakers and defibrillators contain a cobalt-based metallic coil for the sensing and conduction controlling heart rhythm signals. The hydrogen peroxide H_2O_2 released by the macrophages can react with cobalt (Co) on the metal coils to release hydroxyl radicals. The insulation on cardiac leads is either silicone or polyurethane based and to address the mechanical weakness of silicones there has been a considerable effort in moving to polyurethane systems for lead insulation. Another oxidation-based degradation process that has received attention in the examination of explanted cardiac leads is termed as environmental stress cracking (ESC). It differs from classic ESC, which involves a susceptible material at a critical level of stress in a medium. Classic ESC is not accompanied by significant chemical degradation [41]. ESC as observed in TPUs on explanted leads is characterized by surface attack of the polymer and by chemical changes induced by oxidation. Both MIO and ESC are oxidation based and can ultimately lead to device failures; however, the appearance of these is visually different. MIO is characterized by pitting and cracking of the insulation appearing close to the metal coil, whereas ESC appears as micro-cracks on the surface of the insulation. The cracks caused by ESC display a regular pattern and show the presence of "tie fibers" bridging the gaps indicative of ductile failure rather than brittle fracture [40]. FTIR studies have also indicated that ESC is a surface phenomenon where the oxidation of the material is seen predominantly on the surface. This is in contrast to metal ion oxidation where the cracks display a brittle failure and oxidation is noticed throughout the material [40,41].

The oxidation resistance of polyurethane materials is clearly critical to the success of the application of these polymers as insulation for cardiac leads. As a result, polyurethane oxidation resistance has been extensively studied and reported in the literature [35–38]. Thermoplastic polyurethane (TPU) materials based on polyether polyols were first used for lead insulation primarily because the polyether materials had a greater hydrolytic resistance compared to polyester-based polyurethanes. Polyether-based TPUs are, however, prone to oxidation primarily due to the presence of the ether group in the formulation. The generally accepted oxidative mechanism is the removal of the alpha-methylene hydrogen atom from the soft segment of the polyether. This ultimately results in chain scission and the formation of low molecular weight species [42,43]. After relatively short periods of time in both in vivo and in vitro trials, Fourier transform infra-red (FTIR) data have shown a sharp reduction in the ether peak (1110 cm^{-1}) and the presence of a new peak at 1174 cm^{-1} that indicates cross-linking due to the combination of lower molecular weight chains formed as a result of chain scission [35]. It is seen that the degree of ether peak reduction depends to an extent on the level of hard block content in polyether-based TPUs; the greater the hardness, the lower the presence of the ether linkage and the lower the degradation. This, as we have seen earlier, is a result of the susceptible ether bond being shielded by greater amount of order in the hard segment. As a result, polyether-based materials of greater than 50% by weight content of the hard blocks are preferred for implantable applications [44]. The greatest drawback of these high hard block materials is the high elastic modulus, relative

stiffness, and the fact that they remain oxidatively susceptible to degradation [35]. The oxidation susceptibility of polyether TPUs led to the exploration of polycarbonate-based TPUs as an alternative [45,46]. The carbonate linkage in the polyol was considered to be more oxidatively stable than the ether linkage. Although literature suggested improvements, further experience with the use of these materials both in vitro and in vivo has led to clear observations of failures similar to polyether-based TPUs [47,48]. FTIR-based studies have confirmed a decrease in the carbonate oxygen linkage (1253 cm^{-1}) and the appearance of a new peak at 1174 cm^{-1} after explant. The presence of this new peak confirms the existence of a new cross-linked molecule. The next evolution, polydimethylsiloxane (PDMS)-based materials offered a step change in improving resistance against oxidation. One example of PDMS-based polyether urethane, Elast-Eon 2A (E2A), synthesized utilizing 20% poly (hexamethylene oxide) PHMO/80% PDMS for the soft segments and MDI/butanediol (BDO) for the hard segments has been shown to be significantly more biostable through improved resistance to oxidation and hydrolysis over polyether- and polycarbonate-based PUs through a number of in vitro and in vivo studies [49–51]. PDMS-based materials, such as E2A, have been studied extensively in terms of their morphology. Characterization by different means including small angle X ray scattering (SAXS) reveals a very distinctive structure with PDMS forming an almost complete phase separated structure. This high degree of phase separation leads to the formation of highly agglomerated hard blocks and this in turn leads to a high degree of biostability as both PDMS and well-formed hard blocks are resistant to biological degradative mechanisms [49,52] and effectively shield any susceptible chemical groups from oxidation or hydrolysis.

The level of the siloxane molecule present in the TPU has often been a good indication of the degree of oxidation resistance of the TPU. It is established that a certain minimum level of siloxane is required to offer substantial oxidation resistance [53]. The effect of the high siloxane content on oxidation resistance is because the rest of the soft block is populated by oxidatively unstable functional groups. As such, there are significant differences in the oxidation resistance between a “high” siloxane containing TPU such as Elast-Eon and relatively “low” siloxane TPU such as Pursil20 or PurSil35. The Pursil materials contain up to a maximum of 35% of siloxane in the polymer of the polyurethane as opposed to more than 48% of siloxane content in the polymer in Elast-Eon. The greater concentration of ether bonds in Pursil both as a result of lower siloxane content and the use of PTMO versus PHMO (in Elast-Eon) will result in lower oxidation resistance.

5 Testing Techniques to Evaluate Biostability

With the known susceptibility of different materials one can predict the performance based on the chemical structure of the material. However, the confirmation of this predicted behavior has to be done by testing the material in a hydrolytic or oxidative environment. There are many techniques to look at the performance of materials from a degradation perspective. These include tests done in a laboratory or in vitro environment, in vitro tests done under accelerated conditions, tests done in animals or in vivo tests, and finally testing the performance of the material or device in a clinical setting.

5.1 In Vitro Tests

Given the long durations of testing to confirm the stability of polymer in the body and the associated risks, there have been numerous attempts to arrive at a shorter duration study allowing one to predict the long-term performance of such materials. However, as can be seen in the following discussion all accelerated techniques have associated limitations.

5.1.1 Hydrolysis—High Temperature Water Aging

A common technique to look for stability of polymers in hydrolysis is to look at placing polymers test pieces or fully formed devices in water and following them over a period of time. The evolution of the properties of the polymer during the aging process can be assessed by looking at the changes in molecular weight, tensile strength, and other properties over time. The variables in this in vitro hydrolytic test are the actual solution used for the hydrolysis, the pH of the hydrolytic solution, and the temperature of the test. To get polymer behavior representative of an in vivo environment, it is important to maintain conditions similar to what the material would experience inside the body. In many tests [3,4] either saline or phosphate buffer solution (PBS) is chosen as the hydrolytic medium, the pH is maintained at 7.4, the pH of blood inside the body and the temperature is kept

at body temperatures or 37°C. These conditions work well for materials that are hydrolytically unstable. One can then see a discernible change occurring in the properties of the polymer with these given conditions in a short time. In fact these types of tests are very commonly used for biodegradable materials to test for the degradation behavior. With a material that is more stable it is difficult to see any changes in the polymers properties for a short period of time. It is known that a basic pH and a higher temperature will result in faster hydrolytic degradation. Many tests have therefore been done at different values of basicity and temperatures to accelerate the degradation conditions.

High temperature water aging of thermoplastic polyurethanes (TPUs) has been attempted in different studies. The decrease in the properties of polyester-based TPU as compared to a polyether TPU is quite apparent [54]. In many other studies, efforts were made to see whether the other types of TPUs contribute to hydrolytic stability. All studies reported a decrease in the ultimate tensile strength of the samples soaked in water. The studies themselves have used different times and temperatures of soaking [54–56]. It is surprising that all TPUs regardless of the soft block macrodiol used have shown a similar decrease in tensile strength, indicating clearly that the decrease is independent of any degradation in the specific macrodiol structure. Many publications target the urethane bond as being the most susceptible to hydrolysis at high temperatures [57,58]. Urethane bonds are present in the hard phase as well as the soft phases, due to incomplete segregation of hard and soft segments, which is typical of TPUs. It is worth noting that different phase transition (trigger) temperatures exist depending on the formulation of the TPU. A TPU with higher hard block content might start showing a decrease in the tensile strength at a higher temperature than one with a lower hard block content. This is merely due to the greater transition temperatures of the higher hard block material; higher transition temperatures protect the hydrolytically susceptible urethane bond to a higher temperature. It is also seen that PDMS-based TPUs show slightly greater resistance of hydrolytic property degradation at higher temperatures compared to even higher hard block TPU. This could be due to the higher degree of hydrophobicity imparted by the presence of the extremely hydrophobic PDMS in the soft block. It is mentioned in a number of studies that with increasing temperatures, the microstructure of TPUs changes as evidenced by the change in the density levels of electrons in the hydrogen bonding area [24]. It is important to note that the degradation of mechanical properties observed in TPU samples at high temperature cannot be observed at body temperatures, as the morphology at high temperatures is distinct from the morphology at body temperatures [44]. Hence, it is advisable to treat the data obtained from high temperature tests cautiously.

Some tests use the time temperature superposition principle to predict the long-term behavior of the polymer with respect to hydrolytic stability. The time-temperature superposition principle (TTS) is used frequently to estimate the performance of polymers over longer periods of time. TTS uses the principle that application of stress at one temperature over a specific period of time is equivalent to the application of the same stress over a shorter period of time at a higher temperature. Collecting data over a range of temperatures leads to the establishment of a shift factor and subsequently to a master curve which allows the estimation of performance of a material over a much long period of time than is practically possible at lower temperatures. TTS is utilized due to the viscoelastic nature of polymers, where their stress–strain behavior changes with time. TTS has been widely used to predict lifetimes of plastics in high strain environments. TTS does well to estimate stresses and longevity for homopolymers. However, when TTS is applied either to immiscible polymer blends or to multiphase polymer systems it is compromised. The primary reason for this is that all the components within the system react differently to temperature. The predictions made with TTS with morphologically complex TPUs tend to be inaccurate [59,60]

The principle of TTS requires temperature to be the only variable that changes during the experiment and there are no differences in the morphologies of the component materials. To apply TTS accurately then, all component materials must therefore have similar responses to changing temperature [61]. Polymer blends may be characterized with TTS as long as they are miscible which is characterized by a single glass transition temperature or T_g. Immiscible blends of polymers are; block copolymers or a multicomponent system like some polyurethanes where more than one T_g exists.

An established method to test for the applicability of TTS is to plot the loss and storage modulus at different temperatures, obtained from the DMTA, against each other. A perfectly linear relationship between the loss modulus (E'') and the storage modulus (E') indicates that there are no microstructures present in the polymer that are activated by temperature. Deviation from linearity, on the other hand, clearly points to the presence of microstructure changes and TTS cannot be applied for any prediction [61,62]. Polyurethanes

are often referred to as rheologically complex materials and therefore predicting the rheological performance at a different time–temperature positions based on previous time–temperature data is not feasible.

5.1.2 In Vitro Oxidation

In vitro oxidation studies have often been used as an indication of the oxidative resistance of a material. Quite a few of these tests have focused on cardiac lead insulation materials. The use of hydrogen peroxide frequently with cobalt chloride has been tried in many of these studies in trying to simulate the environment experienced by cardiac lead insulation situations. The studies have traditionally looked at polyether- and polycarbonate-based TPUs [37,57,63]. Several studies led by Runt et al. [49,51,52] have relied on the results from in vitro testing methods using hydrogen peroxide to test the oxidative properties of PDMS-based polyurethanes. Their results demonstrate superiority of the PDMS-based TPUs in in vitro oxidation. While some studies have attempted to correlate in vitro studies with in vivo behavior [35,64], this has been a challenge, primarily due to the inability to predict the level and variation of the oxidative radicals present in the macrophages. As such in vitro studies have often employed higher oxidative concentrations to provide a relative indication of the TPU's resistance to oxidation.

5.2 In Vivo Studies

Studies with implantation into animals form a significant part of development and understanding of biostability in existing and new polymers for medical devices. Different animal models are suitable for different types of studies. Small animals such as rats and rabbits can be used when polymer is tested as materials. In such cases, the polymers are implanted into the animals as subcutaneous coupons. These coupons are then extracted and tested at different time points to evaluate the stability of the polymer. For device testing, larger animals are required. Pacemakers and defibrillators are tested in canine models, and heart valves and cardiac grafts are tested in sheep models.

Many in vivo studies were performed for assessing different materials for cardiac lead insulation. In a study by Simmons et al. [50], different TPUs were tested as dumbbells subcutaneously implanted into the back of rabbits. Polyether (Pellethane 2363-80A and Pellethane 2363-55D), polycarbonate (Bionate 55D) and siloxane-based TPUs (Elast-Eon 2A), with differing hard block contents, were tested for biostability in vivo for periods ranging from 3 to 24 months. All samples were explanted and examined using scanning electron microscopy (SEM), attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), and X-ray photoelectron spectroscopy (XPS) to investigate surface morphological changes. Gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and tensile testing provided bulk characteristics. These results revealed the flexible silicone polyurethane E2A provided significantly better biostability than the control material having similar durometer (softness), Pellethane 80A, and equal or superior biostability to both of the higher durometer negative control polyurethanes, Pellethane 55D and Bionate 55D.

5.3 Clinical Studies

A comprehensive assessment of cardiac lead insulation for over 5 years of human implantation was recently reported [65]. This study employed microscopy imaging, molecular weight determination, FTIR spectroscopic analysis, and tubing tensile properties to evaluate the performance of polyether-based polyurethanes of varying hardness and E2A. The conclusion shows that the robustness of the siloxane-based E2A is on par, if not superior, to the performance in vivo of the harder formulation (55D) polyether-based TPU. This is in contrast to the in vitro experiments performed at high water temperatures providing contradictory conclusions [32]. Several in vitro and high temperature aging techniques have been attempted to evaluate the eventual failure mechanisms and biostability of different plastics including polyurethane formulations. Temperature-based aging tests have had the least success in predicting service life for implantable applications. This is primarily due to the nature of the testing and utilization of high temperatures. Increases in temperature have shown to change the morphology of plastics, in general, and copolymers such as polyurethanes in particular. As such the polymer properties measured at high temperature have no relevance to implantable conditions.

In vitro tests utilizing hydrogen peroxide have been useful in demonstrating the oxidation resistance of particular formulations. Direct correlation of these tests to in vivo conditions requires further investigation. Long term in vivo data, despite all their limitations, are still the most significant and relevant in assessing an implantable material's biostability.

6 Sterilization

The inside of the human body is aseptic, that is, there is absence of harmful microorganisms in the living tissue. Whenever there is a break in that sterility or asepsis, the break is referred to as contamination and any contamination allows microorganisms to enter a surgical site and gain access to the inside of the body. It is therefore critical that all items used in surgery are capable of maintenance of the asepsis. Sterilization of all surgical instruments and medical devices is the method used to maintain the aseptic nature of the body [5,6]. Sterilization is the process of elimination or deactivation of all microorganisms within a part for use in any aseptic application. Sterilization is accomplished with the use of either physical or chemical agents to act against any present microorganisms. The microorganisms can include living and other biological agents such as bacteria, viruses, fungi, spore forms, and prions [5,6].

It is known that any surgery will never be completely sterile. There will always be some level of bacteria present. However, it is important that the level of bacteria present is below a critical number of bacteria that are required to cause an infection. This critical number is around 10^5 microorganisms per gram (~100,000 microorganisms/g) of tissue or milliliter of fluid [6,70]. As long as bacterial or microorganism levels do not exceed this number, the normal immune defenses of the body can prevent infection. The goal of sterilization is, therefore, to prevent the addition of any bacteria to the surgical site. The degree of sterilization can be quantified thus [5]:

$$\frac{N}{N_0} = 10^{\left(\frac{-t}{D}\right)}$$

where N is the number of microorganisms present in object after sterilization, N_0 is the number of microorganisms present in object before sterilization, and t is the sterilization time.

The value of D is a function of the sterilization conditions and is also a function of the type of microorganism. D-value refers to decimal reduction time and is the time or sterilization dosage required at a given conditions, such as temperature to eliminate at least 90% of the exposed microorganisms [5,6]. The D variable in the equation is often used as a comparative value to evaluate the effectiveness of a given set of conditions or technique.

The different techniques of sterilization that are used with medical devices are as under [5,69]:

- Heat
  - Dry heat
  - Steam
- Gaseous chemical sterilization
  - Ethylene oxide
  - Nitrogen dioxide
  - Ozone
- Liquid chemical sterilization
  - Gluteraldehyde
  - Formaldehyde
  - Hydrogen peroxide
  - Peracetic acid
- Radiation sterilization
  - Gamma sterilization
  - Electron beam sterilization

Table 5 gives a description of the effect of the sterilization technique on the plastic [65–67].

Table 5 Effect of Sterilization Techniques on Different Cardiovascular Plastics

Plastic	Steam	Dry Heat	Ethylene Oxide	Gamma Radiation	E-beam Radiation
High density polyethylene	Poor	Poor	Good	Good	Good
Low density polyethylene	Poor	Poor	Good	Good	Good
Polypropylene	Good	Fair	Good	Good	Good
Nylon 6, Nylon 66	Fair	Fair	Good	Fair	Fair
Polyethylene terephthalate (PET)	Poor	Poor	Good	Good	Good
Thermoplastic polyurethane (TPU)	Poor	Poor	Good	Fair	Fair
Silicone	Good	Good	Good	Good	Good
Polytetrafluoroethylene (PTFE)	Fair	Fair	Good	Poor	Poor
Polylactic acid (PLA)	Poor	Fair	Good	Good	Good

6.1 Steam Sterilization

The use of steam under pressure is most commonly used by hospitals to sterilize surgical items. The device used for steam sterilization is called an autoclave and the process is commonly referred to as autoclaving. Autoclaving is generally carried out in a pressurized oven; with the aid of pressure the temperature of steam is increased to between 121 and 130°C [67,68]. Increasing pressure of steam in a closed container causes the temperature of the steam to rise. The three factors that dictate the success of steam sterilization are temperature, pressure, and exposure time. When microorganisms are exposed to the correct temperature and pressure for the right amount of time, they are destroyed and the items they were on become sterile. In a typical cycle, the article is exposed to a pressure of 15 pounds per square inch (100 kPa) for a period of 3–15 min at a temperature range of 121–134°C [68]. The success of autoclaving plastics is dependent on the thermal properties of the material. Materials such as thermoplastic polyurethanes and polyethylenes have transition temperatures at or below the steam sterilization temperature and are not suitable for the process. Plastics that are hydrolytically unstable are also not recommended for the process. In general, autoclaving is not widely used for medical device sterilization.

6.2 Dry Heat Sterilization

The destruction of microorganisms through the use of dry heat is a gradual process and takes longer to reach the level of sterility as compared to steam sterilization. A standard dry heat sterilization cycle takes 2 h at 160°C [67]. Most plastics cannot withstand these high sterilization temperatures; this combined with low heat transmission properties of plastics make them unsuitable for the dry heat sterilization process.

6.3 Ethylene Oxide Sterilization

Ethylene oxide (EO, ETO) sterilization is one of the most common methods of sterilization used for most medical devices. ETO is highly effective alkylating agent as it is compatible with most materials, capable of penetrating most plastics and can kill all known microorganisms. ETO sterilization is especially suitable for parts that are sensitive to temperatures and pressures required for steam- and heat-based sterilization methods. A typical cycle of ETO sterilization is carried out between a temperature of 30°C and 60°C, a relative humidity of greater than 30%, and a gas concentration between 200 and 800 mg/L [67,69]. Most plastics, especially the ones used in the cardiovascular sector, are compatible with ETO sterilization and thus ETO is the preferred sterilization technique in the cardiovascular industry.

Great care has to be taken in the use of ETO sterilization as the ethylene oxide gas is highly flammable, toxic, and potentially carcinogenic. ETO can cause numerous health problems and is also environmentally harmful; its use is, therefore, strictly regulated.

6.4 Radiation Sterilization

The use of radiation for sterilization relies on the elimination of microorganisms through ionizing radiation. The ionizing radiation uses short wavelength and high energy radiation to destroy microbes. The strength of radiation is measured in units of kilogray (kGy) or Megarad (Mrad), 1 Gy is described as 1 joule of energy on 1 kg of material or 1 Gy = 1 J/kg [67]. 1 kGy = 0.1 Mrads, as a general rule, 2.5 Mrad (25 kGy) radiation is adequate to sterilize articles in air [67,70]. The required dosage is approximately twice as high under anerobic conditions. Gamma radiation is emitted by a radioisotope, such as Cobalt-60(^{60}Co) or cesium-137 (^{137}Cs). Gamma radiation is highly penetrative and is capable of penetrating thick walled objects as effectively as thin objects; it is equally effective for the dense objects. The high penetration allows material to be sterilized in the bulk state. The e-beam sterilization method uses an electron beam generator of between 1 and 12 mega electron volt (MeV) to produce a high energy beam for sterilization. The e-beam radiation has a much lower depth of penetration as compared to gamma radiation. Gamma radiation can penetrate up to a thickness of 50 cm or 20 inches while e-beam radiation can penetrate up to 5 cm thick objects [67]. Radiation, of either variety, can affect the plastic due the excitation or ionization of the atoms in the polymer chain. The excitation can either result in chain scission or in cross-linking of the chains. Chain scission can lead to lower molecular weight material and a loss in tensile strength whereas cross-linking can lead to increasing brittleness of the polymer with a loss in impact strength. It has been observed that polymers containing aromatic groups have much greater resistance to radiation damage than those with aliphatic structures [70].

References

[1] ISO. ISO—International Organization for Standardization. Available from: http://www.iso.org/iso/home.html

[2] S. Gad, Standards and methods for assessing the safety and biocompatibility of biomaterials. In: U. Braun, E. Lorenz, M. Maskos (Eds.), Characterization of Biomaterials, 2013, pp. 285–306. Investigation M. Jaffe, W. Hammond, P. Tolias, T. Arinzeh, 2011.

[3] U. Braun, E. Lorenz, M. Maskos, Investigation of the durability of poly(ether urethane) in water and air, IJAO 34 (2) (2011) 129–133.

[4] A. Coury, P. Slaikeu, P. Cahalan, K. Stokes, C. Hobot, Factors and interactions affecting the performance of polyurethane elastomers in medical devices, J. Biomater. Appl. 3 (2) (1988) 130–179.

[5] S. Lerouge, A. Simmons, Sterilisation of Biomaterials and Medical Devices, Woodhead Publishing, Cambridge, (2012).

[6] A. Booth, Sterilization of Medical Devices, Interpharm Press, Buffalo Grove, IL, (1999).

[7] J. Anderson, Biocompatibility. In: K. Matyjaszewski, M. Möller (Eds.), Polymer Science: A Comprehensive Reference, Elsevier, Amsterdam, 2012, pp. 363–383.

[8] Mddionline.com. A Practical Guide to ISO 10993-5: Cytotoxicity | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (1998). Available from: http://www.mddionline.com/article/practical-guide-iso-10993-5-cytotoxicity

[9] G. Johnson, P. Upman, R. Wallin, A Practical Guide to ISO 10993-3: Genotoxicity | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (1998). Mddionline.com. Available from: http://www.mddionline.com/article/practical-guide-iso-10993-3-genotoxicity

[10] W. De Jong, J. Carraway, R. Geertsma, In vivo and in vitro testing for the biological safety evaluation of biomaterials and medical devices. In: J-P Boutrand (Ed.), Biocompatibility and Performance of Medical Devices, Philadelphia, PA, Woodhead Publishing, 2012, pp. 120–158.

[11] K. Mortelmans, E. Zeiger, The Ames Salmonella/microsome mutagenicity assay, Mutat. Res. 455 (1–2) (2000) 29–60.

[12] B. Ames, W. Durston, E. Yamasaki, F. Lee, Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection, Proc. Natl. Acad. Sci. 70 (8) (1973) 2281–2285.

[13] J. McCann, N. Spingarn, J. Kobori, B. Ames, Detection of carcinogens as mutagens: bacterial tester strains with R factor plasmids, Proc. Natl. Acad. Sci. 72 (3) (1975) 979–983.

[14] ASTM F756-13, Standard Practice for Assessment of Hemolytic Properties of Materials, ASTM International, West Conshohocken, PA, 2013.

[15] J. Buchanan, P. Upman, R. Wallin, A Practical Guide to ISO 10993-4: Hemocompatibility | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (1998). Mddionline.com. Available from: http://www.mddionline.com/article/practical-guide-iso-10993-4-hemocompatibility

[16] R. Wallin, P. Upman, A Practical Guide to ISO 10993-10: Irritation | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (1998). Mddionline.com. Available from: http://www.mddionline.com/article/practical-guide-iso-10993-10-irritation

[17] T. Takigawa, Y. Endo, Effects of glutaraldehyde exposure on human health, J. Occup. Health 48 (2) (2006) 75–87.

[18] H. Rubin, Carcinogenicity tests, Science (2003) 241–245. doi:10.1126/science.241-b.

[19] M. Morse, Transgenic mouse models as alternatives to the 2-year mouse bioassay (2012). Criver.com. Available from: http://www.criver.com/about-us/eureka/blog/october-2012/transgenic-mouse-models

[20] S. Gad, M. McCord, S. Gad, Safety Evaluation in the Development of Medical Devices and Combination Products, Informa Healthcare, New York, (2008).

[21] A. Ucuzian, H. Greisler, Biocompatibility of cardiovascular devices, In: Gourlay, Terence, R.A. Black (Eds.), Biomaterials and Devices for the Circulatory System, Cambridge, Woodhead Publishing, 2010, pp. 54–85.

[22] J. Anderson, A. Rodriguez, D. Chang, Foreign body reaction to biomaterials, Semin. Immunol. 20 (2) (2008) 86–100.

[23] D. Williams, On the mechanisms of biocompatibility, Biomaterials 29 (20) (2008) 2941–2953.

[24] N. Lamba, K. Woodhouse, S. Cooper, M. Lelah, Polyurethanes in Biomedical Applications, CRC Press, Boca Raton, (1998).

[25] Y. Missirlis, W. Lemm, Modern Aspects of Protein Adsorption on Biomaterials, Kluwer Academic Publishers, Dordrecht, (1991).
[26] N. Peppas, Surface and interfacial aspects of biomedical polymers. Vol. 2, protein adsorption, Biomaterials 7 (4) (1986) 310.
[27] C. Baes, R. Mesmer, The Hydrolysis of Cations, Wiley, New York, (1976).
[28] D.M. Crawford, A.R. Teets, D. Flanagan, Differential scanning calorimetry as a method for indicating hydrolysis of urethane elastomers. Technical Report, US Army, Belvoir Research, Fort Belvoir, Virginia 2463 (June 1988).
[29] L.F. Wang, Q. Ji, T.E. Glass, T.C. Ward, Synthesis and characterization of organosiloxane modified segmented polyether polyurethanes, Polymer 4 (2000) 5083–5093.
[30] M. Szycher, Biostability of polyurethane elastomers: a critical review, J. Biomater. Appl. 3 (2) (1988) 297–402.
[31] J. Santerre, K. Woodhouse, G. Laroche, R. Labow, Understanding the biodegradation of polyurethanes: from classical implants to tissue engineering materials, Biomaterials 26 (35) (2005) 7457–7470.
[32] J.P. Santerre, R.S. Labow, G.A. Adams, Mast enzyme-biomaterial interactions: effect of biosystems on degradation of polyurethanes, J. Biomed. Mater. Res. 27 (1993) 97–109.
[33] L. Razumovskii, V. Markin, G. Zaikov, Laws governing three-component sorption in the system water-hydrogen chloride-polyamide, Polym. Sci. U.S.S.R. 27 (2) (1985) 334–341.
[34] V. Chytrý, J. Kopecˇek, Die Makromolekulare Chemie 184 (7) (1983) 1345–1353.
[35] E. Christenson, J. Anderson, A. Hiltner, Biodegradation mechanisms of polyurethane elastomers, Corros. Eng. Sci. Technol. 42 (4) (2007) 312–323.
[36] Q. Zhao, N. Topham, J. Anderson, A. Hiltner, G. Lodoen, C. Payet, Foreign-body giant cells and polyurethane biostability: In vivo correlation of cell adhesion and surface cracking, J. Biomed. Mater. Res. 25 (2) (1991) 177–183.
[37] K. Stokes, A. Coury, P. Urbanski, Autooxidative degradation of implanted polyether polyurethane devices, J. Biomater. Appl. 1 (3) (1986) 411–448.
[38] M. Tanzi, D. Mantovani, P. Petrini, R. Guidoin, G. Laroche, Chemical stability of polyether urethanes versus polycarbonate urethanes, J. Biomed. Mater. Res. 36 (4) (1997) 550–559.
[39] J. Santerre, K. Woodhouse, G. Laroche, R. Labow, Understanding the biodegradation of polyurethanes: from classical implants to tissue engineering materials, Biomaterials 26 (35) (2005) 7457–7470.
[40] B. Ratner, Biomaterials Science, Elsevier Academic Press, Amsterdam, (2004).
[41] M. Ebert, B. Ward, J. Anderson, R. McVenes, K. Stokes, In vivo biostability of polyether polyurethanes with polyethylene oxide surface-modifying end groups; resistance to biologic oxidation and stress cracking, J. Biomed. Mater. Res. A 75A (1) (2005) 175–184.
[42] M.A. Schubert, M.J. Wiggins, J.M. Anderson, A. Hiltner, Role of oxygen in biodegradation of poly(etherurethane urea) elastomers, J. Biomed. Mater. Res. 34 (4) (1997) 519–530.
[43] S.J. McCarthy, G.F. Meijs, N. Mitchell, P.A. Gunatillake, G. Heath, A. Brandwood, K. Schindhelm, In-vivo degradation of polyurethanes: transmission-FTIR microscopic characterization of polyurethanes sectioned by cryomicrotomy, Biomaterials 18 (21) (1997) 1387–1409.
[44] K. Stokes, The biocompatability and biostability of new cardiovascular materials and devices, in: D. Zhou, E. Greenbaum (Eds.), Implantable Neural Prostheses 2: Techniques and Engineering Approaches, Springer, New York, 2010, pp. 1–24.
[45] I. Khan, Analysis and evaluation of a biomedical polycarbonate urethane tested in an in vitro study and an ovine arthroplasty model. Part I: materials selection and evaluation, Biomaterials 26 (6) (2005) 621–631.
[46] E.M. Christenson, M. Dadestan, M. Wiggins, J.M. Anderson, Poly (carbonate urethane) and poly ether urethane) biodegradation: in vivo studies, J. Biomed. Mater. Res. 69A (2004) 407–416.
[47] E.M. Christenson, J.M. Anderson, A. Hiltner, Oxidative mechanisms of poly (carbonate urethane) and poly (ether urethane) biodegradation: in vivo and in vitro correlations, J. Biomed. Mater. Res. 70A (2004) 245–255 Print.
[48] Y.W. Tang, R.S. Labow, J.P. Santerre, Enzyme-induced biodegradation of polycarbonate polyurethanes: dependence on hard segment concentration, J. Biomed. Mater. Res. 56 (2001) 516–528.
[49] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, In vitro oxidation of high polydimeth-

ylsiloxane content biomedical polyurethanes: correlation with the microstructure, J. Biomed. Mater. Res. A 87 (2) (2008) 546–556.
[50] A. Simmons, J. Hyvarinen, R.A. Odell, D.J. Martin, et al. Long-term in vivo biostability of poly(dimethylsiloxane)/poly(hexamethylene oxide) mixed macrodiol-based polyurethane elastomers, Biomaterials 25 (20) (2004) 4887–4900.
[51] T. Choi, J. Weksler, A. Padsalgikar, R. Hernéndez, J. Runt, Polydimethylsiloxane-based polyurethanes: phase-separated morphology and in vitro oxidative biostability, Austral. J. Chem. 62 (8) (2009) 794.
[52] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, Microstructural organization of three-phase polydimethylsiloxane-based segmented polyurethanes, Macromolecules 40 (15) (2007) 5441–5449.
[53] R. Ward, Y. Tian, K. White, E. Christenson, J. Anderson, M. Ebert, K. Stokes, Optimizing silicone content in thermoplastic silicone-urethanes used in chronicallly implanted medical devices, Soc. Biomater. Meeting Transac. 162 (2005) 160.
[54] A. Boubakri, K. Elleuch, N. Guermazi, H.F. Ayedi, Investigations on hygrothermal aging of thermoplastic polyurethane material, Mater. Des. 30 (10) (2009) 3958–3965 Print.
[55] U. Braun, E. Lorenz, M. Maskos, Investigation of the durability of poly(ether urethane) in water and air, Int. J. Artif Organs 34 (2) (2011) 129–133.
[56] BASF. N.p.: BASF, n.d. Properties of BASF Polyurethanes. BASF. Web. Available from: http://www.polyurethanes.basf.com/pu/KUInternet/KU/en_GB/function/conversions:/publish/KU/content/product/Elastollan_Material_PropertiesR1.pdf
[57] M. Szycher, Biostability of polyurethane elastomers: a critical review, J. Biomater. Appl. 3 (2) (1988) 297–402.
[58] R.N. Jana, H. Bhunia, Accelerated hygrothermal and UV aging of thermoplastic polyurethanes, High Perform. Polym. 22 (2010) 3–15.
[59] K.A. Chaffin, A.J. Buckalew, J.L. Schley, X. Chen, et al. Influence of water on the structure and properties of PDMS-containing multiblock polyurethanes, Macromolecules 45 (22) (2012) 9110–9120.
[60] A. Padsalgikar, E. Cosgriff-Hernandez, G. Gallagher, T. Touchet, C. Iacob, L. Mellin, A. Norlin-Weissenrieder, J. Runt, Limitations of predicting in vivo biostability of multiphase polyurethane elastomers using temperature-accelerated degradation testing, J. Biomed. Mater. Res. B 103 (1) (2014) 159–168.
[61] C.D. Han, Rheology and Processing of Polymeric Materials, Oxford University Press, Oxford, (2007).
[62] C.D. Han, J.K. Kim, On the use of time-temperature superposition in multicomponent/multiphase polymer systems, Polymer 34 (12) (1993) 2533–2539.
[63] M.J. Wiggins, B. Wilkoff, J.M. Anderson, A. Hiltner, Biodegradation of polyether polyurethane inner insulation in bipolar pacemaker leads, J. Biomed. Mater. Res. 58 (3) (2001) 302–307.
[64] E.M. Christenson, M. Dadestan, M. Wiggins, J.M. Anderson, Poly (carbonate urethane) and poly ether urethane) biodegradation: in vivo studies, J. Biomed. Mater. Res. 69A (2004) 407–416.
[65] L. McKeen, The Effect of Sterilization on Plastics and Elastomers, William Andrew, Norwich, N.Y, (2012).
[66] L. Massey, The Effects of Sterilization Methods on Plastics and Elastomers, William Andrew Pub, Norwich, NY, (2005).
[67] V. Sastri, Material requirements for plastics used in medical devices, Plast. Med. Devices (2014) 33–54.
[68] N. Bhana, A. Zanwar, V. Trivedi, D. Jain, A review: steam sterilization a method of sterilization, J. Biol. Sci. Opin. 1 (2) (2013) 138–141.
[69] H. Shintani, Performance of qualification of ethylene oxide gas sterilization process, Pharmaceutical Regulatory Affairs: Open Access, 04 (02) (2015) 3–5.
[70] Mddionline.com. Polymer Materials Selection for Radiation-Sterilized Products | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2000). Available from: http://www.mddionline.com/article/polymer-materials-selection-radiation-sterilized-products

PART II

Cardiovascular System: Structure, Assessment, and Diseases

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1 Introduction

The cardiovascular system in the human body is the primary system that is responsible for the circulation of blood and nutrients to and from the cells and tissues in the body [1]. The complex cardiovascular network is illustrated in Fig. 1. In the cardiovascular system, blood carries with it the nutrients and oxygen to the cells and carries from it metabolic waste products and carbon dioxide (Fig. 2). Blood is composed of cells suspended in plasma [2]. Plasma constitutes about 55% of the blood fluid and is composed of more than 90% by water and also contains dissolved proteins, ions, hormones, and blood cells. Blood cells are composed of red blood cells or erythrocytes (RBC), white blood cells or leukocytes (WBC), and platelets [2]. RBCs are the most abundant cells present in the human blood. The RBC contain hemoglobin, the hemoglobin is an iron-containing protein that shows a great affinity for oxygen and it is this affinity that is responsible for the efficient transport of oxygen along with the blood to various parts of body. The hemoglobin is what gives blood its characteristic red color, when the hemoglobin contains oxygen, the blood is bright red and when it is deoxygenated it turns dark red. WBCs comprise the main constituents of the body's immune system and help in fighting all infectious diseases and foreign invaders inside the body. The main function of platelets, also known as thrombocytes, is to stop any bleeding associated with injury to the blood vessels by clotting blood flow [2].

With the aid of blood circulation, the cardiovascular system can be said to perform four main functions [1]:

- transport of nourishment to the cells and waste products from the cells,
- maintenance of body's immune system,
- stabilize body temperature and pH, and
- maintain bodily stability or homeostasis.

The following sections look at the aspects of the cardiovascular system in terms of its structure, its evaluation or assessment and the effects of its malfunctioning or cardiovascular disease states.

2 Structure of the Cardiovascular System

2.1 Heart

The heart is the center of the human cardiovascular system (Fig. 3). The anatomy of the heart is illustrated in Fig. 4. The human heart is a four-chambered pumping device that functions as the central organ for the circulatory, cardiovascular system within the body. The heart can be further divided into the right and left sides where the right side receives used, deoxygenated blood from the various organs of the body and delivers it to the lungs for reoxygenation. The left side receives oxygenated blood from the two lungs and pumps it to the various organs, tissues, and cells of the body [1].

The structure of the heart is composed of four distinct chambers and four valves. The two upper chambers are termed atria and act as receiving chambers, receiving the blood coming in to the heart from outside the heart. The right atrium, receives the deoxygenated blood from the body, whereas the left atrium receives oxygenated blood from the lungs. The atria transfer their contents into the corresponding lower chambers. The two lower chambers are termed ventricles and act as the pumping chambers of the heart. The right ventricle (RV), that receives the contents of the right atrium, pumps deoxygenated blood to the lungs for reoxygenation. The left ventricle (LV), on the other hand, receives blood from the left atrium and pumps this oxygenated blood to the entire body [3,4].

The upper and lower chambers, on each side, are connected to each other through one-way valves. These valves ensure that the blood flows only from the atrium

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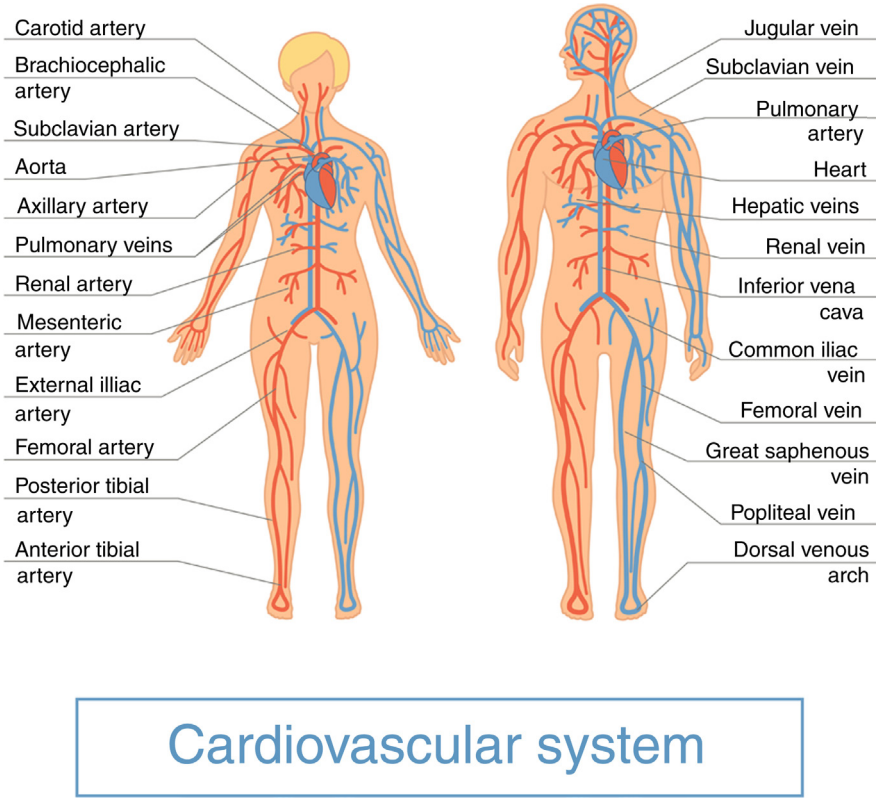

Figure 1 Cardiovascular system.

to the ventricles and there is no regurgitation or leakage. The right atrium is connected to the RV through the tricuspid valve. The left atrium is connected to the LV through the mitral valve. One way valves are also present in the pathway of the blood as the ventricles pump their contents. As the RV pumps the deoxygenated blood to the lungs, the valve that controls this flow is termed the pulmonary valve. As the oxygenated blood makes it way to the rest of the body with the pumping action of the LV, this flow is regulated by the aortic valve [1,3].

The oxygenated blood is pumped by the LV through the blood vessels to all organs, tissues, and cells of the body. The used, deoxygenated blood travels back to the heart for the RV to pump this into the lungs to reoxygenate the blood. This entire circuit is the cardiovascular system of the body. The blood vessels that transport blood away from the heart are termed arteries and the ones that take blood toward

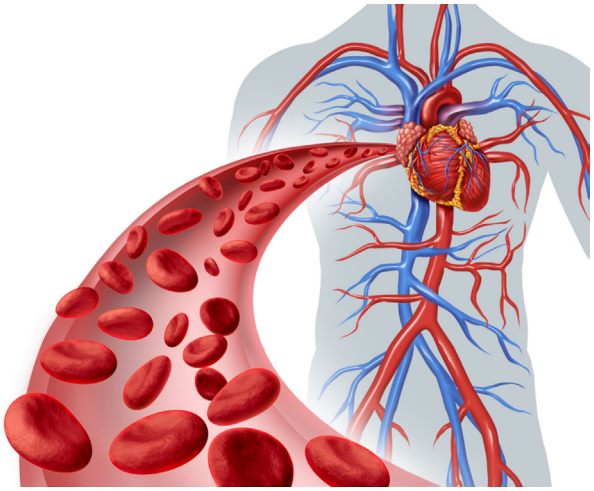

Figure 2 Blood.

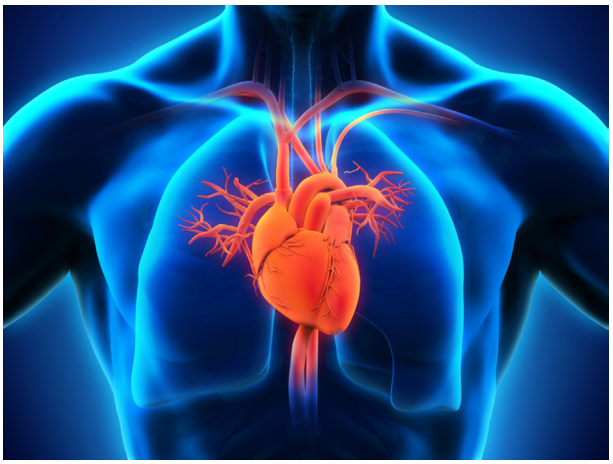

Figure 3 Heart.

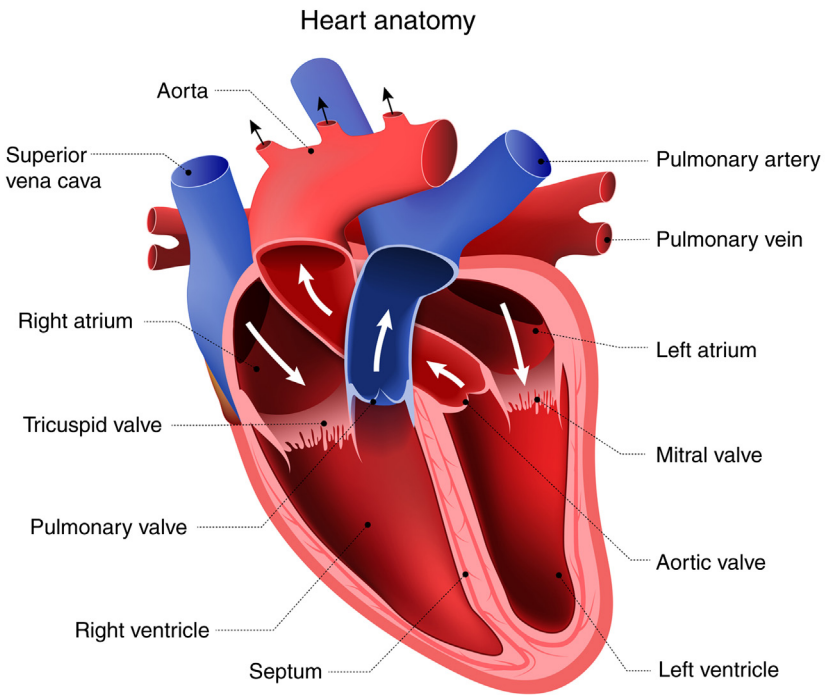

Figure 4 Anatomy of the heart.

the heart are called veins. From the LV blood is pumped into the main artery called the aorta. The aorta branches into numerous smaller arteries. When the blood from the arteries reaches its destination, the arteries are further divided into smaller arterioles and then into capillaries measuring 5–10 μm in diameter. It is in the capillaries that the exchange of substances occurs between the blood and the cells. Blood flows out of the organs and returns to the heart by the way of veins. The blood returns to the heart from the lower part of the body with the vein called the inferior vena cava, and from the upper part of the body with the superior vena cava (SVC) [1,3].

2.1.1 Functioning of the Heart

Circulating within the human body, the total quantity of blood contained in the heart and the cardiovascular system is approximately 5.6 L (6 quarts). The entire volume circulates through the body 3 times every minute. The circulation of blood around the body is governed by the function of the heart muscle and its contractile motion or the heartbeat. The heartbeat can be divided into the actions of contraction and expansion known as the systole and diastole, respectively. Systole is the contraction period of the cardiac cycle, generally referring to ventricular contraction. Systole is associated with the first heart sound; "lub," this sound signifies the closing the atrioventricular (AV) valves preventing backflow of blood into the atria. Diastole refers to the period that is the opposite of contraction of the heart. This relaxation, specifically ventricular, releases blood through the semilunar valves and these valves under the influence of the high flow pressure press the leaflets downward and snap shut. The second characteristic sound of the heart; the "dub," is caused due to this shutting of the valves [1].

The entire cardiac cycle is described as one complete heartbeat. This cycle is illustrated in Fig. 5. Ventricular contraction results in the ejection of blood through the aorta, the amount of blood ejected in one contraction is known as the ejection fraction. Ejection fraction is an important measure of cardiac function and it is a comparison of stroke volume to the end-diastolic volume. The overall cardiac contractile state is expressed as follows:

$$\text{Ejection fraction}\,(\%) = \frac{\text{Stroke volume}}{\text{End diastolic volume}}$$

The ejection fraction is thus, the ratio between the stroke volume and end-diastolic volume for the LV. At rest, the end diastolic volume typically ranges from 120 to 130 mL and the end-systolic volume ranges between 50 and 60 mL. This leads to the stroke volume being 70 mL and an ejection fraction greater than 50%.

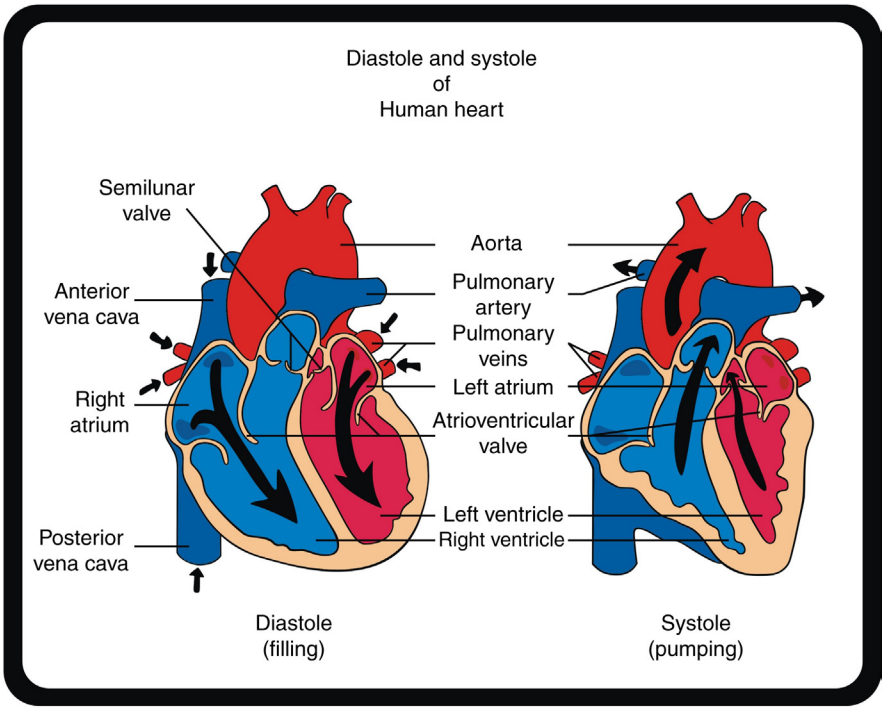

Figure 5 Heart systole and diastole.

Cardiac output is the volume of blood measured in liters, ejected by the heart per minute. It is calculated by the product of the stroke volume and heart rate. At rest, the cardiac output varies from 4 to 6 L/min in a healthy person. Measurement of the cardiac output can help evaluate the overall cardiac status of the person as well as determine their left ventricular function and valve performance [3,4].

2.1.2 Coronary Circulation System

The supply of oxygenated blood to the heart is vital in the functioning of the organ as the center of the cardiovascular system. The blood supply to the heart tissue with oxygenated blood is known as the coronary circulation system. The arteries that supply blood to the heart are the arteries that branch off the aorta. The two openings in the aorta that lead to the two main blood vessels supplying the heart are known as the coronary ostia. From the coronary ostia, the two main vessels that feed the heart are the right coronary artery (RCA) and the left main (LM) coronary artery. The RCA is the main source of fresh blood to the RV, in addition, the RCA supplies 25–35% of the blood to the LV. The LM artery arises from the ascending aorta just above the aortic valve. It further branches into the left anterior descending (LAD) coronary artery and the circumflex (CIRC) artery. The deoxygenated blood is then returned to the right atrium through the coronary venous system [1]. The coronary circulation system of the heart can be seen in Fig. 6.

2.1.3 Structure of the Heart

The heart is surrounded by the rib cage, directly in front of it is the sternum and behind it is the vertebral column. The sternum is also known as the breastbone and it is the flat narrow bone running in front of the thoracic cavity. The heart rests on the diaphragm and is between the two lungs. The position of the heart

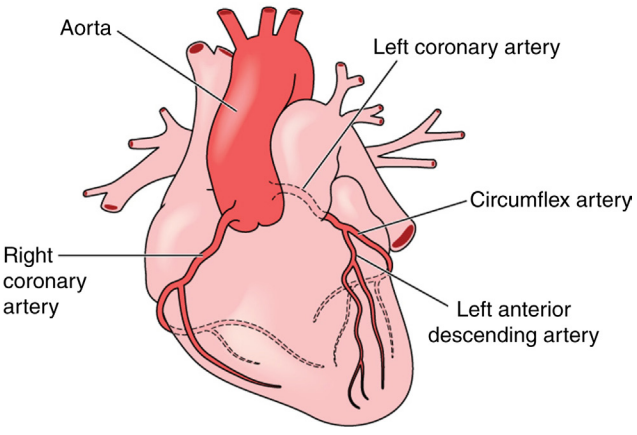

Figure 6 Heart coronary arteries.

Figure 7 Location of the heart.

is slightly titled and this causes the lower tip of the heart to occupy the area between the fourth and fifth ribs on the left side of the chest (Fig. 7). Hence, the left side of the chest is where the heart beat is heard the loudest.

The heart muscle sits in a sac known as the pericardium. The pericardium is a two-layered membrane structure wherein the membranes are separated by pericardial fluid and the presence of this fluid allows the formation of a flexible sac enabling movement of the inner layer as the heart beats. The heart wall is divided into three layers,

- epicardium
- myocardium
- endocardium

The outer most layer is known as the epicardium, this layer is thin, tough, and fibrous. The coronary arteries and nerves are found in this layer. The myocardium forms the middle layer of the heart; it is also the muscular layer that provides the main power of the heart. Its muscular nature apart from being the main source of the contractile power of the heart is also its main mass component. The innermost layer of the heart is composed of endothelial cells and is called the endocardium. The endothelial cells provide an extremely smooth surface to prevent the formation of any blood clots [1,3].

The two upper chambers in the heart are called the atria. The right atrium receives deoxygenated blood from the venous system through the superior and inferior vena cava. The left atrium, on the other hand, receives oxygenated blood from the pulmonary system. The size of the atria is similar to that of a golf ball with their walls being approximately 3-mm thick.

The two lower chambers are called the ventricles and they are the pumping chambers of the heart. The RV receives deoxygenated blood from the right atrium and pumps it to the pulmonary system for infusion with fresh oxygen. The LV receives oxygenated blood from the left atrium and pumps it out of the heart to the rest of the body through the aorta. As the LV has to work harder to pump the blood for a longer distance through the body, the wall of the LV is about 16-mm (0.63-in.) thick as compared to the wall of the RV which is around 6-mm (0.24-in.) thick [5].

Each of the four valves of the heart is surrounded by a complete or partial fibrous ring. These rings join together to form a connective tissue layer forming a fibrous skeleton frame of the heart muscle. This fibrous skeleton plays an important role to electrically and physically isolate the atria from the ventricles. In fact, the bundle of His, explained later, is the only electric connection between the atria and the ventricles. The skeleton also provides a certain degree of rigidity to the heart muscle and thus helps in the prevention of the individual valve and outflow tracts from dilation [4].

2.1.4 Heart Valves

The heart has four major valves that help regulate the flow of blood within the muscle and to the rest of the body (Fig. 8). All valves are made up of leaflets or cusps that open and close effectively regulating the flow of blood in only one direction. Valves separate the atria from the ventricles and these are called AV valves. The AV valves have fibrous tissue, chordae tendineae, attached to papillary muscles that help prevent leaflet prolapse and regurgitation of blood into the atria. The valve between the right atrium and the RV is called the tricuspid valve. The tricuspid valve has three leaflets and is situated on the floor of the right atrium. The valve between the left atrium and the LV is called the mitral valve. Mitral valve forms an essential part of the LV and is bicuspid in nature, that is, composed of two leaflets. The leaflets

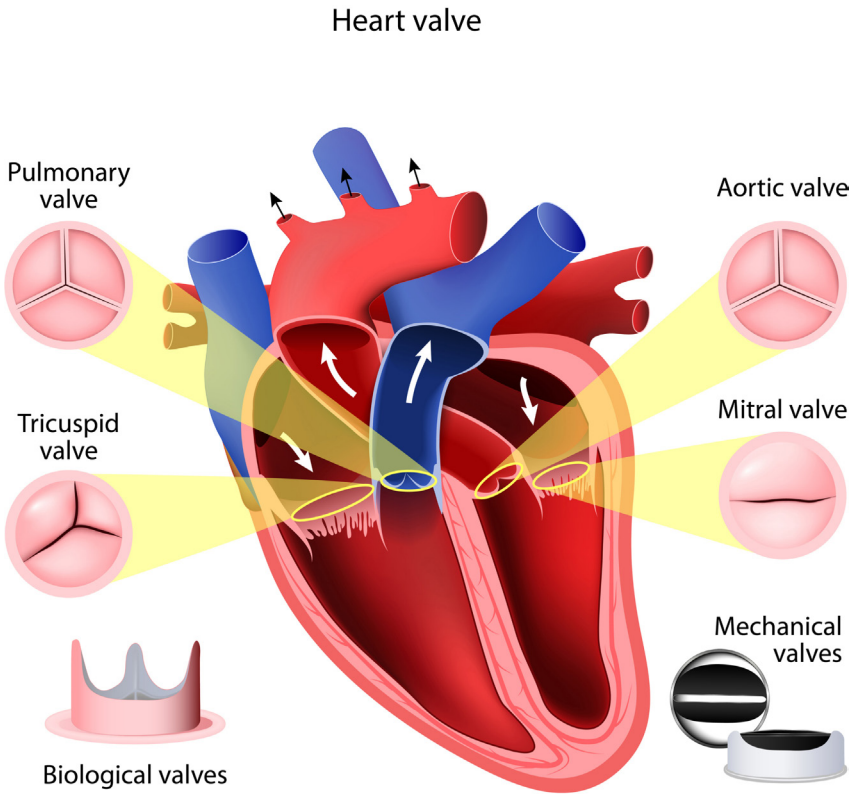

Figure 8 Heart valves.

are unequal in size and are known as the anterior and posterior leaflets [1].

The valves connecting the ventricles to the arteries leaving the heart are called semilunar valves. The pulmonary valve connects the RV to the pulmonary artery as the RV sends deoxygenated blood to the lungs for oxygenation. The aortic valve is between the LV and the aorta. The aorta is the main artery of the cardiovascular system and the blood is distributed to the rest of the body through branches arising out of the aorta.

2.1.5 Conduction System of Heart

The electrical system of the heart plays a crucial role in the functioning of the pumping action of the heart. The electrical system's conduction begins at the sinoatrial (SA) node. From the SA node the impulse is transmitted to the AV node. From the AV node the impulse travels through the bundle of His and specialized Purkinje fibers to the ventricular muscle. This conduction pathway is illustrated in Fig. 9. The sustenance of this conduction system is through the blood supply to the conduction system and this blood supply is mainly through the RCA [1].

The cardiac electrical system is based on the ability of cardiac cells to contract in response to the depolarization of the cells. At rest, the cardiac cell has less positive charge inside than outside so the net electric potential in the cell is negative. As the cell is stimulated, it goes into an excited state and in response it allows sodium ions (Na^+), among a series of other positively charged ions, to diffuse into the cells, this entry of positive ions creates a positive charge inside the cell. This permeation process is known as depolarization and as depolarization occurs, the cardiac cell contracts. There is selective permeability of ions back and forth through cardiac tissue which have special ion channels. To repeatedly depolarize, cardiac tissue must return to its resting state, this return is called the repolarization. The continuous cycle of depolarization and repolarization is the essential part of the cardiac electrical system. This cycle is conducted from cell to cell, causing an electric current to generate. There are certain cells of the heart that have the ability to undergo spontaneous depolarization, this property of the cells is known as automaticity and the SA and AV node cells have the greatest automaticity [6].

The entire depolarization–repolarization cycle is known as the action potential of the cell. The action

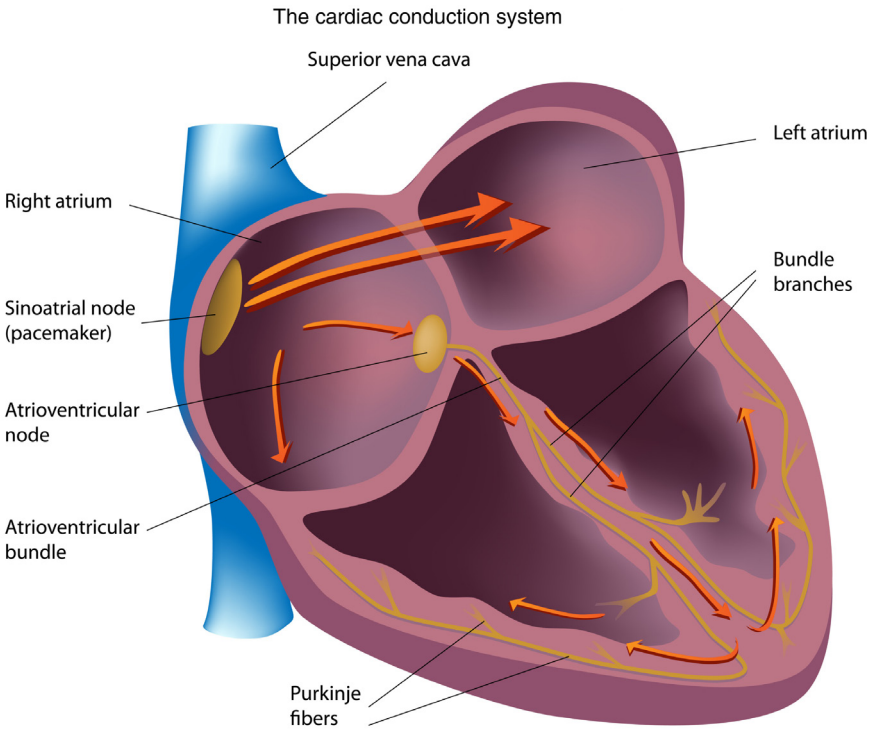

Figure 9 Heart conduction system.

potential begins with the cell in a resting state, selective permeability allows primarily Na^+ ions to enter into the cells, lifting the ionic state of the cells to a net positive potential. Repolarization causes the positive ions to move out of the cells and the cell conductivity passes on this cycle to adjacent cells and the entire muscle goes through the cycle and associated contractions.

Depolarization of the atria and ventricles creates the contraction of the atria and ventricles. This wave of depolarization goes through the heart in the following path (Fig. 9):

- SA node
- AV node
- bundle of His
- Purkinje fibers

As the cycles of depolarization and repolarization happen, an electric current is generated and spread within the heart. This electrical activity can be measured by the placement of electrodes on an individual's heart. This measurement generates what is known as the electrocardiogram (ECG). The ECG is also referred to as the EKG. Different parts of the ECG record can be related to the different electrical activities of the heart as shown in Fig. 10. The ECG curve is an important tool for the physician to diagnose heart electrical activity. ECG is dealt with in greater detail in the following section on cardiac assessment and diagnosis.

In summary one can say the rhythm of the heart is crucial to the proper functioning of the heart muscle and the resultant circulation of blood throughout the body. This rhythm is regulated by electrical activity in the heart. An electrical signal is generated in the right atrium of the heart in the SA node, this signal causes the atrium to contract and pump blood to the RV. This signal then travels to the AV node, the AV node functions as a relay station. The signal is delayed in this travel, by a fraction of a second, allowing the atrium to completely fill the ventricle with blood. The signal then travels through the Purkinje fibers, this leads to the contraction of the ventricles, in the process squeezing the blood out of the heart. The contracted RV supplies oxygenated blood to the organs of the body whereas the LV squeezes deoxygenated blood to have it refreshed in the lungs [1,6].

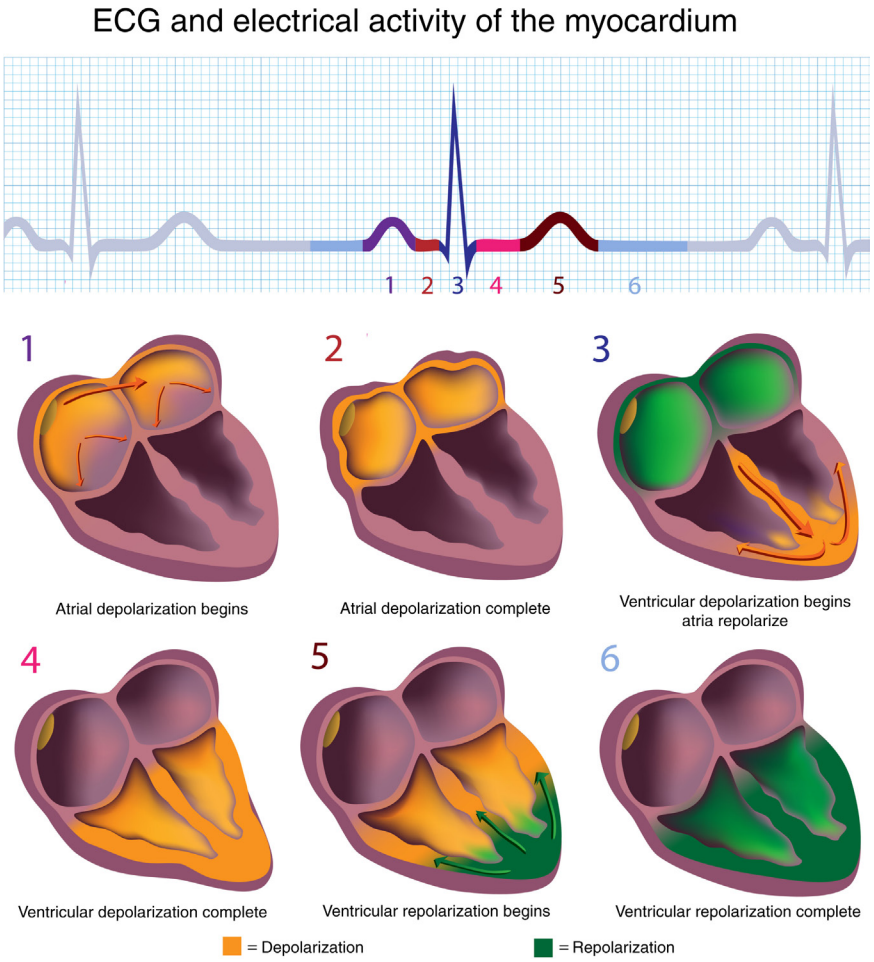

Figure 10 Heart depolarization and ECG.

2.2 Systemic Circulation

The cardiovascular system comprises the heart, arteries, capillaries, and veins. Blood flow from the LV trough the arteries to the different organs and then back to the heart is referred to as systemic circulation. In systemic circulation, the blood is transferred to the aorta. The aorta is the main artery that is connected to the heart; the aorta carries oxygenated blood from the heart to different arterial branches throughout the body.

2.2.1 Arterial Network

The aorta originates from the LV of the heart and extends to the bottom of the abdomen before it is divided to two smaller arteries. The aorta is the largest artery in the body; it is about 12 in. (~300 mm) in length and measures about an inch (~25 mm) in diameter. The aorta is divided into sections, in one system of classification; the division is based on the direction of blood flow. As oxygenated blood emerges from the LV, the flow of blood in the aorta is upward and this section is the ascending aorta. Then the aorta makes a sharp, hairpin, bend over the heart and the blood flow is downward, this section is the descending aorta. The hairpin bend is referred to as the aortic arch. The descending aorta is further divided according to the position of the blood vessel, as the aorta passes through the thoracic cavity it is known as the thoracic aorta and as it passes through the abdominal region, it is known as the abdominal aorta [1].

A few arteries emanate from the different sections of the aorta. The main arteries coming out of the ascending artery are the ones that supply oxygenated blood to the heart, that is, the RCA and the left coronary artery. The arteries branching out from the aortic arch supply blood to the upper part of the body, head, neck, and the chest, as well as to the arms. The descending aorta begins from around the region of the fourth intervertebral spinal disc and arterial branches coming out of the thoracic descending aorta supply blood to the esophagus, pericardium, diaphragm, and the lungs. Lumbar and renal regions receive oxygenated blood from arteries branching out from the

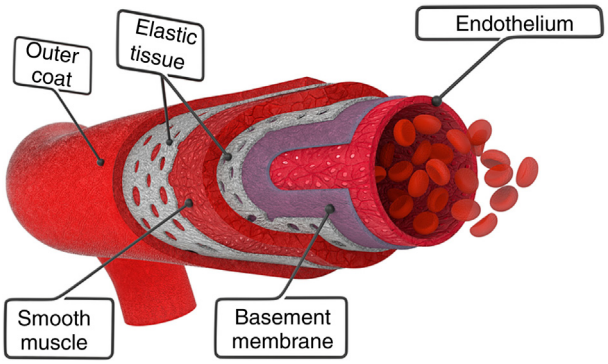

Figure 11 Structure of the artery.

abdominal aorta that then descends to the lower portion of the abdomen and bifurcates into smaller right and left iliac arteries. The iliac arteries originate at around the fourth vertebra of the lumbar spine and the right left iliac artery travel down the respective sides for about 2 in. or 5 cm to the edge of the pelvis. There they split again into the internal and external iliac arteries. The internal iliac artery provides blood to the pelvic region whereas the external iliac artery provides the main blood supply to the lower limbs [1,4].

2.2.2 Structure of Arteries

The wall of the aorta is composed of several layers [1] (Fig. 11):

- The tunica intima, the innermost layer, provides a smooth surface for blood to flow across. The smooth lining is made up on endothelium cells covered by elastic tissues.
- The tunica media, the middle layer with muscle and elastic fibers, allows the aorta to expand and contract with each heartbeat.
- The tunica adventitia, the strong outer layer, provides additional support and structure to the aorta. It is composed of connective tissue as well as collagen and elastic fibers. These fibers allow the arteries to stretch to prevent overexpansion due to the pressure that is exerted on the walls by blood flow.

2.2.3 Microcirculation

The arteries carry blood to the various organs in the body and through the smallest blood vessels embedded in the vasculature of the organ tissues. This circulation through the small blood vessels is known as microcirculation. Arterioles, capillaries, and venules form the main constituents of microcirculation. The arteries narrow down into thinner sections and these thinner blood vessels are called arterioles and the arterioles eventually transport the blood into capillaries. Capillaries are the smallest blood vessels in the body and measure between 5 and 10 μm (0.0002–0.0004 in.) in diameter. The capillaries are present as a network of capillaries and is referred to as a capillary bed. The capillaries are composed of endothelial cells and the lining of these cells is only one-layer thick. Through the capillaries an exchange of oxygen and essential nutrients occurs to the surrounding tissue, the nutrient exchange and the flow of blood in the capillary has been a source of many investigations [1,4,5]. The exchange of substances occurs as a result of the combination of the hydrostatic pressure differential, that is, the pressure difference between the blood in the capillary and the tissues, and the diffusion through the capillary wall. Nutrients are transferred to the tissue in the initial part of the capillary whereas the wastes from the tissue enter the capillary toward the latter part. The capillary then widens to venules, the venules are between 10 and 50 μm (0.0004–0.002 in.) in diameter and form the connection between the capillary bed and the veins. The deoxygenated blood is now carried back to the heart through the veins. This microcirculation circuit is illustrated in Fig. 12.

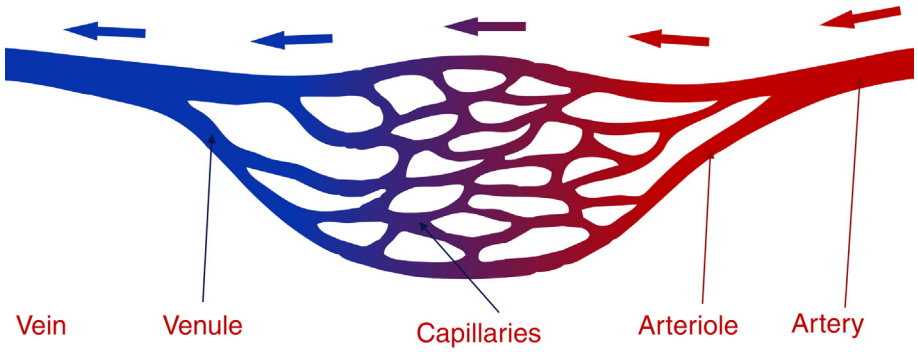

Figure 12 Microcirculation.

2.2.4 Venous Network

The system of veins is responsible for the passage of deoxygenated blood back to the heart. The network of veins largely parallels that of the arteries, however there are smaller veins that do not parallel the arteries and branch off in different directions. These branched veins sometimes form superficial veins that are visible under the skin and very often are used to pump blood by deeper veins for temperature regulation of the body [4,5].

The largest veins in the human body are called the venae cavae. The SVC carries blood from the upper body above the diaphragm, the arms, the neck, and head to the right atrium of the heart. The SVC is typically an inch in diameter and is the normal site for access to many cardiovascular minimally invasive surgical procedures. The inferior vena cava carries blood from below the diaphragm, legs, and abdomen back to the heart. The inferior vena cava runs to the right and roughly parallel to the abdominal aorta along the spine.

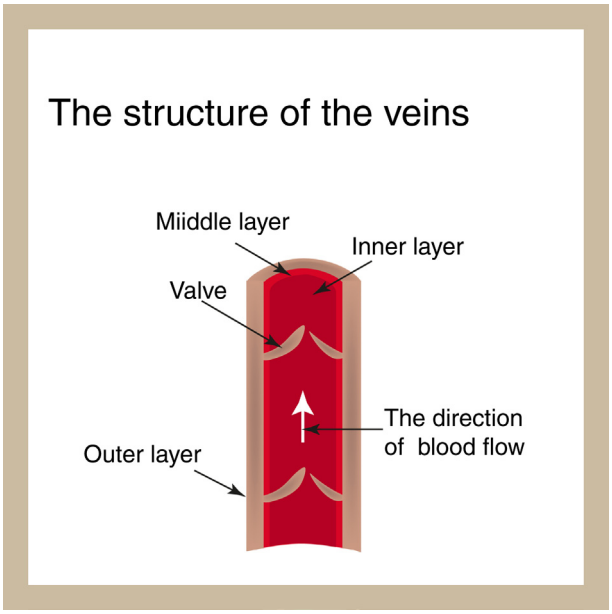

Figure 13 Vein.

2.2.5 Structure of Veins

The structure of a vein is similar to that of the artery in that it consists of three main layers. The outer layer is composed of connective tissue, called tunica adventitia, a middle layer of smooth muscle called the tunica media, and the inner layer lined with endothelial cells called the tunica intima. They differ from the arterial structure with respect to the thickness of the middle layer or tunica media. The tunica media is much thinner in the veins as the blood in the veins is not subject to high pressures it encounters in the arteries. Another major point of difference between the veins and the arteries is the presence of valves within the veins (Fig. 13). These valves are one-way valves that prevent the backflow of the deoxygenated blood. The motion of these valves is dependent on the relaxation and contraction action of skeletal muscles [4,5].

2.3 Pulmonary Circulation

After the systemic circulation, the right atrium receives the deoxygenated blood, transfers it to the RV and the RV pumps it through the pulmonary valve into the pulmonary artery. The pulmonary artery branches into the right and left pulmonary arteries carrying blood to the lungs. Blood is oxygenated in the lungs and returns to the heart through the pulmonary veins. The pulmonary veins take the blood to the left atrium. The circulation of blood between the heart and the lungs is termed as pulmonary circulation [1].

Pulmonary circulation is the process of pumping of the deoxygenated blood from the right side of the heart to the lungs. The deoxygenated blood flows into the right atrium and transfers to the RV through the tricuspid valve. The RV then pumps the deoxygenated blood through the pulmonary valve into the pulmonary artery where the transfer from the heart to the lungs occurs. The pulmonary artery divides above the heart into two branches and these two branches go to the right and left lungs. In the lungs the arteries further subdivide into smaller and smaller branches until the capillaries in the pulmonary air sacs (alveoli) are reached. In the capillaries gas exchange happens, that is, blood takes up oxygen from the air breathed into the air sacs during respiration and releases carbon dioxide. The reoxygenated blood then flows into progressively larger blood vessels until the pulmonary veins are reached. The pulmonary veins transport the oxygenated blood into the left atrium of the heart and from the left atrium blood is transferred to the LV through the mitral valve. The pumping mechanism of the heart then pumps the oxygenated blood from the LV through the aortic valve to the aorta and from there to all parts of the body [1,6].

The heart can very often be looked upon as two separate pumps. The left side receives oxygenated blood from the lungs and pumps this blood out through the aorta to all parts of the body. Therefore, the left side is considered a part of the systemic

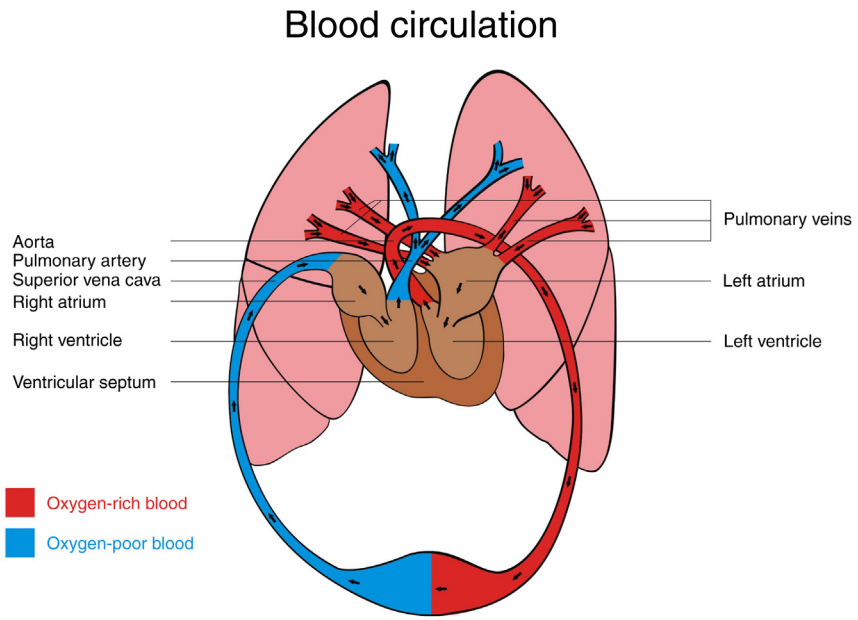

Figure 14 Pulmonary circulation.

circuit. On the other hand, the right side receives deoxygenated blood from the body and pumps this blood to the lungs for oxygenation. The right side is thus considered a part of the pulmonary circuit. The pressure of the blood in the pulmonary circuit is lower than in the systemic circuit, this is reflected in the size of the ventricles and the construction of its walls. The pulmonary circulation is depicted in Fig. 14.

3 Cardiovascular Assessment and Diagnostic Procedures

3.1 Physical Examination

Auscultation is the often the first procedure that a physician employs in the examination of a patient. The origin of auscultation is the Latin word "auscultare" which literally means to listen. Auscultation requires only a stethoscope and good listening skills; however, it is an art that takes substantial degree of practice to develop. In listening to the sounds of the heart, the physician concentrates on noting the heart rate, looks for any abnormal sounds such as heart murmurs or gallops and any extra sounds coinciding with heartbeats. Heart sounds are the noises generated by the beating heart and the resultant flow of blood through it. Specifically, the sounds reflect the turbulence created when the heart valves snap shut. In healthy adults, there are two normal heart sounds often described as a *lub* and a *dub*, which occur in sequence with each heartbeat. These are the first heart sound (S_1) and second heart sound (S_2), that correspond to the closing of the valves, the AV valves and the semilunar valves, respectively. In addition to these normal sounds, a variety of other sounds may be present including heart murmurs, adventitious sounds, and gallop rhythms S_3 and S_4.

3.2 Electrocardiogram

The electrocardiogram (ECG or EKG) measures the electrical activity of the heart over a period of time. Several tiny electrodes are placed at several strategic positions over the heart. The electrodes detect the tiny electrical changes that occur as a result of the depolarization of the heart muscles during each heartbeat. The output from these electrodes is recorded over a period of time and the output graph of electrical voltage (y-axis) versus time (x-axis) is the electrocardiogram [7]. As we have seen earlier, the electrical conduction begins in the SA node in the right atrium; from here it is transferred to the AV node and down the bundle of His and into the Purkinje fibers, spreading throughout the ventricles. This cellular depolarization and subsequent conduction is recorded as the ECG.

The ECG helps the physician monitor and evaluate a number of conditions of the heart and its electrical conduction system. Among other things, an ECG can be used to measure the rate and rhythm of heartbeats,

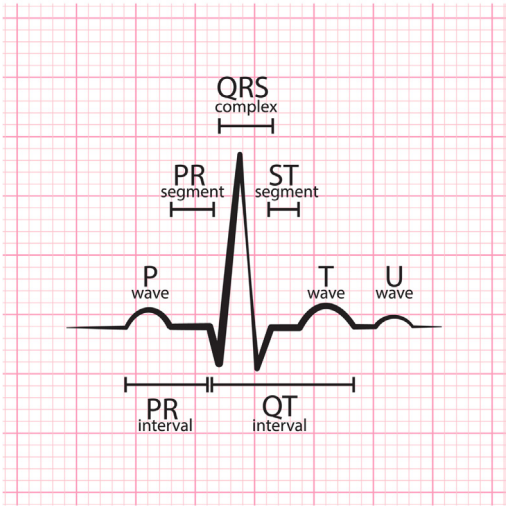

Figure 15 Normal ECG.

the size and position of the heart chambers, the presence of any damage to the heart's muscle cells or conduction system, the effects of cardiac drugs, and the function of implanted pacemakers [8].

A typical ECG is depicted in Fig. 15 and the description of the features of the ECG is tabulated in Table 1.

3.3 Echocardiogram

An ultrasound image of the heart is known as the echocardiogram. Ultrasound images, also known as sonograms, are formed when high frequency sound waves, greater than 20,000 Hz in frequency and inaudible to the human ear, reflect off tissues and the image of the reflected waves is recorded. The echocardiograph has several advantages in that it is relatively inexpensive, portable, records live images and does not use harmful radiation. Echocardiogram is also noninvasive and no known risks or side effects are associated with it. It, however, also has several limitations such as requiring a skilled operator and having a limited field of view. Despite these limitations, echocardiogram is one of the most widely used diagnostic tests in heart function evaluation. It provides a lot of helpful information, including the size and shape of the heart (internal chamber size quantification), pumping capacity, and the location and extent of any tissue damage. An echocardiogram can also give physicians other estimates of heart function such as a calculation of the cardiac output, ejection fraction, and diastolic function (relaxation of the heart).

The standard echocardiogram is the transthoracic echocardiogram; this is a noninvasive technique where the probe is placed on the wall of the chest of the individual and the images of the heart are taken though the chest. In a transesophageal echocardiogram, a probe, containing an ultrasound transducer, is inserted into the esophagus of the individual. A variation of the ultrasound is the stress echocardiogram where the image is recorded with the individual performing action such as walking on a treadmill. Stress echocardiogram is recorded at the target heart rate of the individual that varies according to the age of the individual. The stress echocardiogram can help in the assessment of coronary artery disease (CAD); CAD causes an abnormality in the motion of the heart wall that can be picked up by the stress echocardiogram image, a three-dimensional (3D) image of the heart using a modified ultrasound probe and a specialized image processing system. The 3D image enabled detailed assessment and diagnosis of valvular conditions and certain myopathies [9]. Another technique based on echocardiography is the use of contrast to produce a contrast enhanced ultrasound image [10]. An ultrasound contrast made up of microair bubbles is injected into the bloodstream; the microbubbles return the ultrasound to produce a sharp image.

3.4 Cardiac Catheterization

Cardiac catheterization is a minimally invasive diagnostic procedure that depends upon the insertion of the catheter into the vasculature. The catheter may be inserted from the femoral artery in the patient's thigh or through the radial artery in the patient's arm (Fig. 16). Cardiac catheterization allows the physician to visualize the circulatory system around the heart muscle and in the areas of interest. Coronary catheterization is a subset of cardiac catheterization looking specifically at the coronary arteries surrounding the heart. Coronary catheterization can be used to study the coronary arteries for blockages, occlusion, stenosis, or restenosis. The aorta can be checked for the presence on aneurysmal defects. The heart chamber sizes can be evaluated as well as certain functions of the heart valves. Catheters with pressure sensors can help accurately determine heart and lung blood pressures, values that cannot be measured from outside the body [11].

Cardiac catheterization requires the use of fluoroscopy to visualize the path of the catheter as it enters the heart or as it enters the coronary arteries. Fluoroscopy can be conceptually described as continuous

Table 1 Description of Features in the Output of an Electrocardiogram (ECG)

Feature	Description	Duration
RR interval	The interval between an R wave and the next R wave; normal resting heart rate is between 60 and 100 bpm.	0.6–1.2 s
P wave	During normal atrial depolarization, the main electrical vector is directed from the SA node toward the AV node and spreads from the right atrium to the left atrium. This turns into the P wave on the ECG.	80 ms
PR interval	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. The PR interval reflects the time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles. The PR interval is, therefore, a good estimate of AV node function.	120–200 ms
PR segment	The PR segment connects the P wave and the QRS complex. The impulse vector is from the AV node to the bundle of His to the bundle branches and then to the Purkinje fibers. This electrical activity does not produce a contraction directly and is merely traveling down toward the ventricles, and this shows up flat on the ECG. The PR interval is more clinically relevant.	50–120 ms
QRS complex	The QRS complex reflects the rapid depolarization of the right (RV) and left ventricles (LV). The ventricles have a large muscle mass compared to the atria, so the QRS complex usually has a much larger amplitude than the P wave.	80–120 ms
J point	The point at which the QRS complex finishes and the ST segment begins. It is used to measure the degree of ST elevation or depression present.	N/A
ST segment	The ST segment connects the QRS complex and the T wave. The ST segment represents the period when the ventricles are depolarized. It is isoelectric.	80–120 ms
T wave	The T wave represents the repolarization (or recovery) of the ventricles. The interval from the beginning of the QRS complex to the apex of the T wave is referred to as the absolute refractory period. The last half of the T wave is referred to as the relative refractory period (or vulnerable period).	160 ms
ST interval	The ST interval is measured from the J point to the end of the T wave.	320 ms
QT interval	The QT interval is measured from the beginning of the QRS complex to the end of the T wave. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. It varies with heart rate and, for clinical relevance, requires a correction for this, giving the QTc.	Up to 420 ms in heart rate of 60 bpm

X-rays. Thus, the presence of radio opaque agents in the catheter helps with the positioning of the catheter and guidance with the location of the catheter at any point of time. In certain procedures, such as angiography, where the physician looks for the presence of occlusion in the coronary arteries, a radiocontrast agent, commonly called an X-ray dye, is injected through the catheter into the bloodstream. The flow of this radiocontrast agent enables the physician to visualize the blood flow path in the artery and establish the presence of any blockages. Cardiac catheterization can be of the left part of the heart or of the right part. Left heart catheterization allows the physician to look for occlusions in the arteries. Right heart catheterizations allow the physician to estimate the cardiac output, the amount of blood that flows from the heart each minute, and the cardiac index, a hemodynamic parameter that relates the cardiac output to a patient's body surface area. Determination of cardiac output can be done by releasing a small amount of normal saline in one area of the heart and measuring temperature changes over time in another area of the heart. A couple of newer techniques that are used successfully in cardiac catheterization are optical coherence tomography (OCT) and fractional flow reserve technique (FFR). OCT can be looked upon

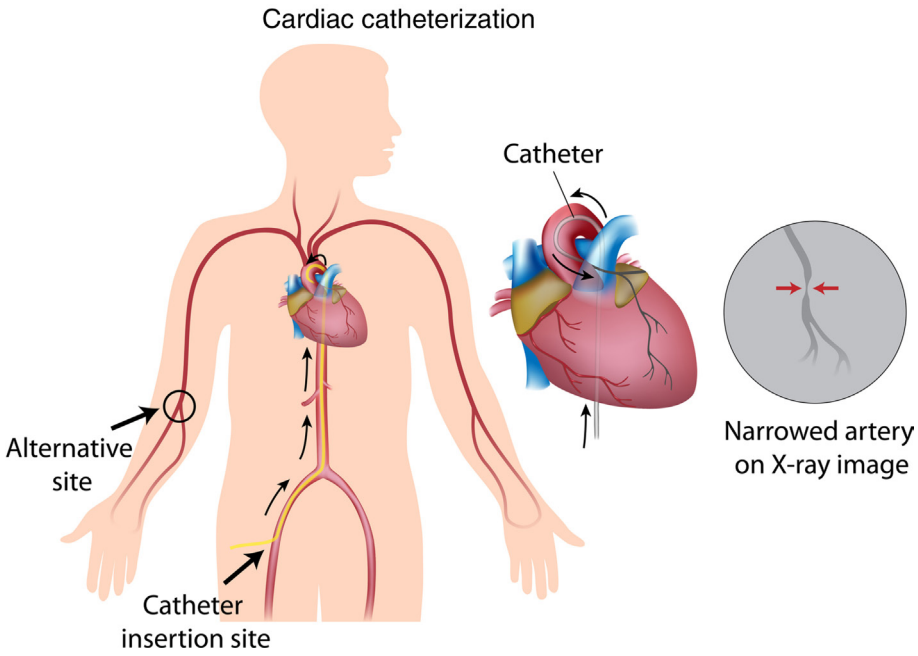

Figure 16 Catheterization.

as optical echocardiograph; OCT is a technique that is capable of obtaining subsurface images of translucent or opaque tissue at a resolution equivalent of images from a low power microscope. The use of OCT in catheterization enables very accurate diagnosis and location especially of CAD [12,13]. FFR is a technique that uses pressure differences in the blood flow through a coronary artery to detect stenosis. FFR uses a small sensor on the tip of the wire (commonly a transducer) to measure pressure, temperature, and flow to determine the exact severity of the lesion. A pullback of the pressure wire is performed and pressures are recorded across the vessel [14].

4 Cardiovascular Diseases

As we have seen the criticality of the entire cardiovascular system, any deviation from the normal conditions can lead to a diseased circulatory system and subsequent development of cardiovascular diseases. Cardiovascular diseases are the leading cause of death globally. This is true in all areas of the world except Africa [15]. Together they resulted in 17.3 million deaths (31.5%) in 2013 up from 12.3 million (25.8%) in 1990 [16].

As a result of being the leading cause of mortality, the risk factors for cardiovascular diseases have been thoroughly investigated in many studies [17–20]. Several risk factors that are associated with cardiovascular disease; these are identified and listed in several studies as:

- age
- gender
- tobacco use
- physical inactivity
- excessive alcohol consumption
- unhealthy diet
- obesity
- genetics or family history of cardiovascular disease
- raised blood pressure (hypertension)
- raised blood sugar (diabetes mellitus)
- raised blood cholesterol (hyperlipidemia)
- psychosocial factors or increased mental stress levels
- poverty and low educational status
- air pollution

It is said that more than 90% of the deaths caused by cardiovascular diseases are preventable [21].

The management of the risk factors mentioned earlier through proper diet, exercise, eliminating tobacco and limiting alcohol intake is shown to be successful in reversal of cardiovascular diseases in many patients in several studies [22,23].

Cardiovascular diseases can be broadly classified as the diseases affecting the heart and the diseases affecting the blood vessels.

Diseases directly affecting the heart include:

- valvular disease
- heart failure
- cardiac arrhythmias

The diseases affecting primarily the blood vessels in the cardiovascular system include:

- CAD
- peripheral arterial disease
- aortic aneurisms

4.1 Valvular Heart Disease

A disease affecting one or more of the heart valves in the human heart is termed as valvular heart disease. The aortic and mitral valves on the right side of the heart and pulmonary and tricuspid valves on the left side of the heart constitute the four valves of the heart. Collectively the valves form a part of the connective tissue frame of the heart which is otherwise known as the cardiac skeleton [4,5]. Valve diseases are either congenital, present at birth or become an issue with advancing age. Old age is a major factor and an estimate puts about 10% of the people above the age of 75 tend to have heart valve disease [21].

4.1.1 Aortic Valve

The aortic valve is present between the RV and the main artery, the aorta. It is a valve composed of three leaflets and performs the primary function of pumping oxygenated blood from the LV into the aorta that distributes it to the rest of the body [1]. Two defects of the aortic valve that can cause serious issues with blood flow through the cardiovascular system are aortic stenosis (AS) and aortic insufficiency (AI). When the exit passage from the valve opening narrows due to a buildup of deposits either within the valve or above and below the valve, it is known as aortic stenosis (AS). This narrowing of the exit causes a decrease of blood supply from the heart to the rest of the body. This decrease in blood supply can lead to primary symptoms of shortness in breath, inability to exercise and fluid retention with swelling of the legs. In severe situations, loss of consciousness and heart failure may occur. Valve stenosis effects are depicted in Fig. 17. When blood begins to flow in the reverse direction during ventricular diastole, that is, from the aorta into the LV, this leakage is called aortic insufficiency, also known as aortic regurgitation (AR). With AI, there is leakage of the blood from the aorta back into the LV due to the improper closure of the aortic valve. The leakage occurs during the early part of ventricular diastole as the pressure in the LV falls below the pressure in the aorta and the aortic valve does not offer a good enough seal. AI can cause an increase in the volume of blood in the LV and that can lead to thickening of the walls of the LV, left ventricular hypertrophy (LVH) and in severe cases further lead to pulmonary edema and congestive heart failure (CHF).

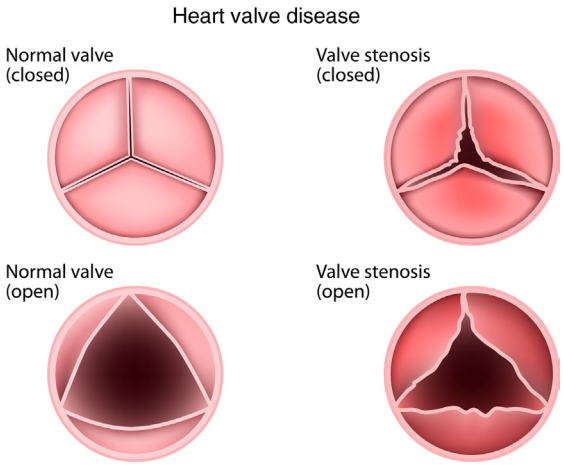

Figure 17 Valve stenosis.

There are three primary causes of AS: it can be a birth defect, that is, congenital, it can be caused due to an incidence of rheumatic fever or it can be a result of aging. In terms of a birth defect, people may be born with a bicuspid aortic valve. This congenital heart valve defect can occur in 1–2% of the world population [24]. Rheumatic fever usually follows a strep throat infection; repeated incidences of strep throat especially if untreated can lead to inflation of the heart and rheumatic heart disease (RHD). This RHD leads to AS. RHD is more common as a path to AS in the developing world. Aging can also cause AS with hardening of the valve tissue over time [25].

AI is caused by two main factors; aortic root dilation and RHD [26]. Aortic root dilation is said to be mainly idiopathic in nature, that is, its causes are unknown. It is also seen that most of the AI cases tend to have the cause of aortic root dilation in developed countries as opposed to RHD being the main cause of AI in developing countries.

For the development of AS over time, the risk factors are similar to the risk factors for CAD and these

include smoking, high blood pressure, high cholesterol, and diabetes. AS manifests as heart murmurs and this can be easily picked up using ultrasounds. Repeated ultrasound tests allow the physician to assess the severity of the AS and decide on the course of action.

The human aortic valve normally consists of three leaflets and in an open position, the total area amounts to between 3 and 4 cm^2. As the LV contracts, it forces oxygenated blood down the aorta and subsequently to the rest of the body. In AS, the surface area of the aortic valve opening narrows, this narrowing can occur mainly due to the calcification of the tissues either surrounding the valve or in the valve itself. This narrowing results in the LV exerting extra pressure to force blood through the aorta. This increased pressure results in a thickening of the muscular walls of the LV [27]. As a consequence of the thickening, extra oxygenated blood is required by the muscle walls of the LV. The requirement for the extra blood is not fulfilled by the normal supply as the arteries supplying the blood to the LV have not increased in diameter or length. This leads to ischemia and eventually to LVH. The LVH and ischemia is first visible during exercise but eventually the heart muscle requires more blood than the arteries can supply even at rest.

The diagnosis of AS can be achieved in a few ways. Physical examination can give one clues about the existence of AS without providing conclusive evidence. Sounds as recorded by the physician with a stethoscope can point to differences between AS and a healthy heart. With AS, a noticeable delay is observed between the two sounds, of the first heart sound (on auscultation) and the corresponding pulse sound in the carotid artery. Also clearly audible is a heart "murmur." The murmur happens during the systolic cycle, is best heard at the right upper sternal border and is seen to radiate to the carotid arteries. The electrocardiogram (ECG) also points to the existence of AS without offering any conclusive proof. Cardiac catheterization provides a more definitive diagnosis when pressure measurement is effected on both sides of the aortic valve. The best diagnosis for AS, however, is achieved by the use of heart ultrasound. The heart ultrasound output also known as an echocardiogram, is a noninvasive tool to evaluate the anatomy of the aortic heart valve and examine its function. The echocardiogram also provides the best diagnosis for AI, transthoracic echocardiography can provide two-dimensional (2D) views of the regurgitated blood stream; it allows measurement of the speed of the blood stream using Doppler techniques, and estimates the blood stream volume.

The management of AS depends upon the severity of the condition. Early and moderate cases of AS are treatable with medications such as beta blockers and statins, however, the effectiveness of medications in treating or slowing down the progression of AS is as yet unproven [28,29]. Aortic valve replacement is seen as the therapy for severe cases of AS. Aortic valve replacement is most commonly replaced using a surgical procedure with either a mechanical or a tissue valve. The procedure for aortic valve replacement is usually an open heart surgical procedure; however, in a growing number of cases a minimally invasive surgical procedure is used. In the minimally invasive procedure, valve replacement is done through the blood vessels rather than through open heart surgery.

Open heart surgery is a surgery in which the chest is opened and surgery is done on the heart muscle, valves, arteries, or other parts of the heart (such as the aorta). The term "open" means that the chest is "cut" open. The cardiac surgeon makes a 5–8 in. incision (Fig. 18) in the patient's chest; the breastbone of the individual is surgically sawed off to expose the heart [30]. A heart–lung machine is often used when open heart procedures are carried out. The heart–lung machine takes over the basic function of blood circulation away from the heart and keeps the circulatory system in the body functioning. These heart–lung machines are termed as cardiopulmonary bypass.

There are two basic types of artificial aortic heart valves, the mechanical heart valve and the tissue heart valve. Mechanical valves have a metallic structure and are designed to replicate the performance of a natural human heart valve. To perform the action of a one-way valve, that is, to efficiently pump blood from the ventricle to the aorta without significant regurgitation, mechanical heart valves are designed in different ways of which two designs, tilting disc and bileaflet valves, are the most popular [24]. Mechanical heart valves are extremely durable and they far exceed the lifetime of a human, however, regular use of an anticoagulant medication such as warfarin is necessary. Tissue heart valves, on the other hand, do not require the use of anticoagulants due to the improved blood flow dynamics and less clotting experienced with these systems. The main limitation of tissue valves is their lifespan, traditional tissue valves typically last 15 years. Tissue valves are fabricated from porcine and bovine tissue [24].

The minimally invasive procedure is known by a few different names, percutaneous aortic valve

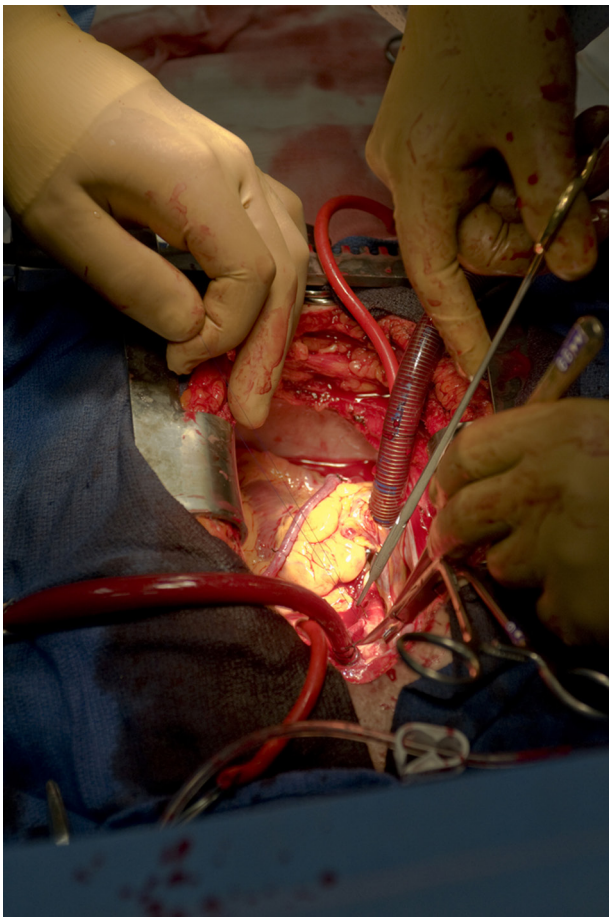

Figure 18 Open heart surgery.

replacement (PAVR), transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) [31]. In this procedure, several access methods can be used to heart, transfemoral, transapical, subclavian, transcaval, or direct aortic. Transfemoral uses the femoral artery in the individual's thigh. The transapical approach sees the catheter and valve inserted through the tip of the heart and into the LV. The transaortic approach sees the catheter and valve inserted through the top of the right chest, subclavian approach goes beneath the collar bone and the transcaval approach uses a puncture in the aorta near the belly button to gain access to the heart [31]. The main advantage of TAVI devices are that they are implanted without open heart surgery [32]. Studies have shown the TAVI procedure is as safe and as effective as open heart surgery [33,34]. In the TAVI procedure, the valve delivery system is inserted in the body, the aortic valve folded and fitted into the delivery catheter and delivered to the heart. The aortic valve is then positioned and implanted inside the diseased aortic valve, and subsequently the delivery system is removed.

4.1.2 Mitral Valve

The mitral valve is a bicuspid valve that lies between the left atrium and the LV. The mitral valve supplies oxygenated blood from the left atrium to the LV. This transfer happens during the diastole cycle and as the atrial pressure increases relative to the ventricular pressure. At the end of the diastole cycle, the mitral valve closes to prevent any reversal of blood flow. A valvular heart disease characterized by the narrowing of the mitral valve of the heart is mitral stenosis. Another valvular heart disease of the mitral valve is mitral regurgitation or mitral incompetence. Mitral regurgitation occurs when the mitral valve does not close properly at the end of the diastole cycle and there is regurgitation of blood back into the left atrium [28].

Almost all cases of mitral stenosis are due to disease in the heart secondary to rheumatic fever and consequent RHD. Mitral stenosis as a result of calcification or congenital conditions is relatively rare [35]. The normal mitral valve orifice is 4–6 cm^2. With the progress of mitral stenosis this opening is restricted and can reach up to areas less than 1 cm^2. As a result there is drastic increase in the left atrial pressure, which increases from a normal value of 5 mm Hg to about 25 mm Hg. This increase in pressure causes an increase in the hypertension in the lungs and leads to an imbalance of pressures which leads further to buildup of fluid in the lungs. This pulmonary edema can cause CHF. The increasing atrial pressure also leads to an increase in the size of the atrium and this increase in the size can lead to atrial fibrillation (AF). The AF can eventually cause a decrease in the cardiac output and sudden CHF. Symptoms associated with mitral regurgitation depend on the severity of the regurgitation. Individuals with acute MI are typically severely symptomatic and will have the signs and symptoms of acute decompensated CHF, as well as shortness of breath even at rest. On the other hand, individuals with chronic and low level mitral regurgitation may be asymptomatic for long periods of time. The mitral valve comprises two valve leaflets, when one leaflet abnormally thickens; the leaflets are prevented from fully coming together during valve closure. Therefore the action of the valve closure is not complete and this leads to regurgitation. This abnormal leaflet thickening is called mitral valve prolapse and is the most common cause of mitral regurgitation

[36]. CAD and RHD are among the causes for mitral regurgitation [37].

Similar to AS, mitral stenosis can also be detected by physical examination. The sounds detected by the physician using a stethoscope are good indications of mitral stenosis. A louder second heart sound corresponds to an increasing force required to close the mitral valve and therefore is a definite indication of mitral valve stenosis. A mid-diastolic rumbling murmur is also heard. Cardiac catheterization is also a method to detect mitral stenosis. Simultaneous measurement of pressures in the left atrium and the LV allows the physician to detect abnormalities. As in AS, echocardiography is the best indicator of mitral stenosis. The echocardiogram shows left atrial enlargement, a calcified mitral valve and signs of any ventricular failure. The echocardiogram also shows a decreased opening of the mitral valve and increased blood flow velocity during diastole [38]. The echocardiogram also is used to confirm the diagnosis of mitral regurgitation. The Doppler image reveals any leakage from the LV into the left atrium during ventricular systole.

The treatment options for mitral stenosis include medical management through medications, mitral valve replacement by surgery, and percutaneous mitral valvuloplasty by balloon catheter [39]. Mitral valve replacement is a cardiac surgical procedure in which the patient's diseased mitral valve is replaced by either a mechanical or tissue valve. Since a mitral valve replacement is an open heart surgical procedure, it requires placing the patient on cardiopulmonary bypass. The valves used are very similar in construction to the valves used in aortic valve replacement surgery. The mechanical valves are made from metal and pyrolytic carbon and designed to last longer than a person's lifetime. Mechanical valve do require a continuous intake of blood thinning medication to prevent clotting. The tissue valves are made from porcine or bovine tissue and do not require the intake of blood thinners but can only last 10–15 years in the body before needing replacement. As the surgery for mitral valve replacement is quite involved, management of the symptoms can also be tried using percutaneous mitral valvuloplasty by a balloon catheter. Mitral valvuloplasty is a minimally invasive therapeutic procedure where the catheter containing the expandable balloon is passed from the femoral vein up the inferior vena cava and into the right atrium. The wall of the tissue separating the right and left atrium is punctured and the catheter passed into the left atrium using a transseptal technique. The balloon on the catheter is then inflated; the inflation is divided into three stages. The three stages of balloon inflation occur at different times so as to not obstruct the functioning of the valve at one time. For individuals with acute mitral regurgitation, two surgical options recommended are mitral valve replacement and mitral valve repair [40]. Mitral valve repair is preferred in cases where such a repair is not only feasible but seen as being effective. The mitral valve repair approach can be either resection of a section of the valve leaflet or the addition of sutures to strengthen leaflets. The suture-strengthened leaflets corrects the anatomy of the leaflets and allows for proper closure.

4.1.3 Pulmonary and Tricuspid Valves

The pulmonary and the tricuspid valves are on the right side of the heart. The pulmonary valve regulates the flow of blood from the RV to the lungs whereas the tricuspid valve regulates the flow of deoxygenated blood from the right atrium into the RV. Both tricuspid and pulmonary valves deal with the blood at a much lower pressure as compared to the valves on the left side of the heart [41]. As a result the diseases affecting these valves are less common than aortic or mitral valve diseases. Pulmonary valve diseases are the least common among all heart valve diseases.

The inability of the tricuspid valve to close completely creates inefficiencies in the flow of blood into the RV. This condition is known as tricuspid regurgitation or tricuspid insufficiency. The signs and symptoms of tricuspid regurgitation are not apparent till the condition is severe, at that point, the symptoms are similar to symptoms for heart failure conditions, that is, fatigue, shortness of breath, swelling of the legs, and the inability to exercise. One of the causes of tricuspid regurgitation can be birth based or congenital, another cause could be rheumatic fever. However, the main reason for tricuspid regurgitation is the dilation of the right side of the heart. This dilation can be a result of many causes including left heart failure, pulmonary hypertension, or infection of lining of the heart, endocarditis [42].

Tricuspid regurgitation can be picked up in the initial auscultatory examination. Auscultation reveals the presence of a pansystolic heart murmur and a third heart sound. A chest X-ray can point to the dilation of the right side; an echocardiogram will assess the chambers of the heart, as well as, right ventricular pressure. Cardiac MRI may also be used as a diagnostic tool, and finally, cardiac catheterization may determine the extent of the regurgitation.

Surgical treatment of tricuspid valve by installing a prosthetic replacement is possible. The replacement

may either be tissue based or mechanical [43]. However, surgical treatment is not recommended when the cause of the regurgitation is the dilation of the right heart, medication is primary treatment in those circumstances.

4.2 Heart Failure

Heart failure, sometimes referred to as CHF, occurs when the heart muscle is unable to pump blood quantities as required by the various parts of the body. Typical symptoms are shortness of breath, excessive tiredness, and leg swelling [44]. Congestion is one major symptom of this disease, as CHF is frequently accompanied by a buildup of fluid in the tissues and veins of the body. This leads to water retention and swelling especially in the limbs. Common risk factors include previous incidences of CAD, AF, valvular heart disease, high blood pressure, and alcohol use [44].

Heart failure mainly occurs with the inability of the heart muscle to either contract or relax efficiently. Heart failure due to the inability of the LV to contract fully is also known as systolic heart failure. Systolic heart failure occurs as a result of a reduced ejection fraction, as the reduction in the ejection fraction increases, failure occurs when the ejection fraction decreases below 40% of the normal ejection fraction [45]. On the other hand, heart failure with preserved ejection fraction is also known as diastolic heart failure. In diastolic heart failure, the LV contracts well but the ventricle does not fill completely with blood during the relaxation phase. A reduced stroke volume may result as a failure of systole, diastole or both. A common finding among heart failure patients is that a symptom of failures of the systolic or diastolic system is accompanied by an increase in the activity of the autonomic nervous system or the sympathetic system. Initially this increase in the sympathetic system activity contributes to compensate for heart failure by maintaining blood pressure and perfusion, however, over the long term; it leads to worsening of ischemia and sometimes fatal irregularities in the rhythm of the heart.

The general effect of heart failure is an increased strain on the heart and a reduced cardiac output as shown in Fig. 19. This greatly increases the risk of cardiac arrest due to irregular rhythms of the heart and significantly reduces supply of blood and nutrition to the rest of the body.

Diagnoses of CHF includes techniques such as echocardiography, electrophysiology, chest X-rays, and blood tests. Echocardiography utilizes 2D, 3D, and Doppler ultrasound techniques to create detailed images of the heart. The output from echocardiography, echocardiogram, can be used to calculate cardiac output, ejection fraction, and diastolic function. An electrocardiogram (ECG) generated from the electrophysiological analysis maybe used to determine the presence of an abnormal heart rhythm. A prolonged QRS complex duration is common among patients with systolic dysfunction and indicative of mechanical dyssynchrony in ventricular action.

Depending on the results from the diagnostic tests, the physician can decide the best course of action for the treatment of the heart failure symptoms. Lifestyle

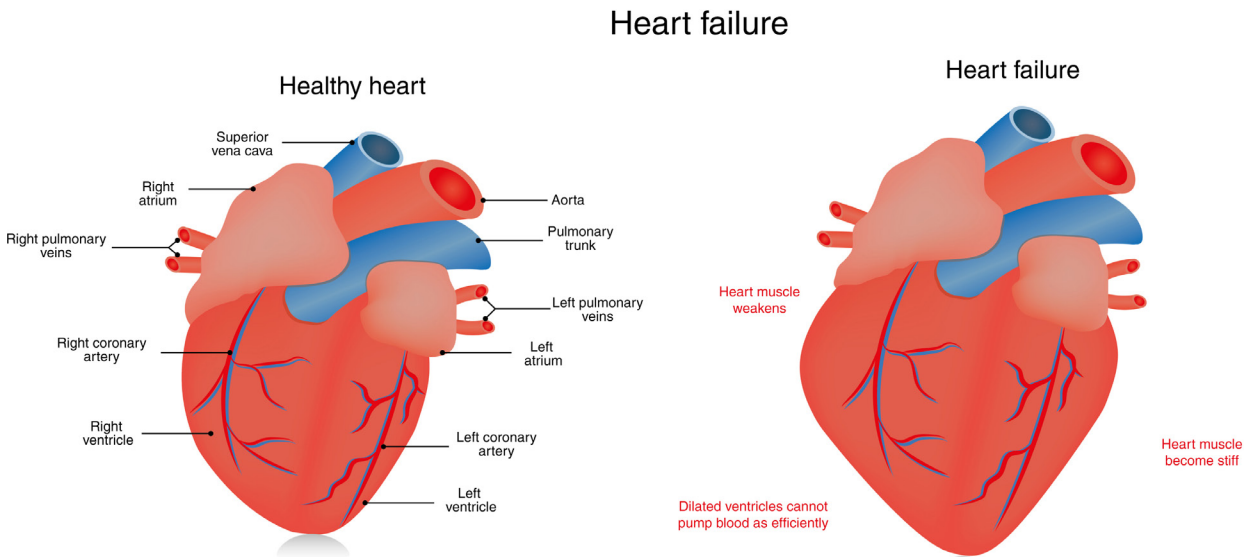

Figure 19 Heart failure.

changes and medications, as with other cardiovascular diseases, are the first course of action. Minimally invasive procedures such as the implantation of cardiac rhythm management devices are recommended for correction of cardiac rhythm abnormalities. The rhythm management treatment known as cardiac resynchronization therapy (CRT) is useful when heart failure is caused by a lack of synchronization in the heart function as identified by a prolonged QRS duration in the electrocardiography output. CRT helps resynchronize the contractions of the heart's ventricles by sending small electrical signals to the heart muscle, which can help them beat together in a more synchronized pattern. This synchronized beating helps the heart pump blood and oxygen throughout the body more efficiently. The primary objective of CRT is restoration of a more normal ventricular activation pattern. Secondarily, CRT allows optimization of the AV interval for patients in sinus rhythm [46].

People with more severe heart failure are candidates for surgical treatment such as the implantation of left ventricular assist devices (LVAD) or total artificial hearts (TAH). LVADs and TAH have traditionally been seen as a bridge therapy for a donor heart but recent advances point to the use of these devices for the long term and as a destination therapy [47].

4.3 Cardiac Arrhythmia

Cardiac arrhythmia is also known as cardiac dysrhythmia or irregular heartbeat. Cardiac arrhythmia is the disruption of the normal electrical activity of the heart. This disruption leads to abnormal electrical signals in the heart and irregular heartbeats. Cardiac arrhythmia is of two main types [48]:

- bradycardia, where the heartbeat is slower than 60 beats/min,
- tachycardia, where the heart beats at faster than 100 beats/min.

Atrial fibrillation (AF), which is characterized by random flutters of the heartbeat, can be classified under tachycardia. Quite often, arrhythmia does not present itself with symptoms, when present mild symptoms include light headedness and palpitations whereas serious symptoms include shortness of breath, chest pain, and fainting that may lead to severe conditions of stroke and cardiac arrest. Mild symptoms of arrhythmia are not serious as such but left untreated arrhythmia can predispose a person to complications such as stroke and heart failure.

Arrhythmia affects millions of people worldwide with almost half of the deaths caused due to cardiovascular disease attributable to electrical dysfunctions of the heart.

4.3.1 Bradycardia

Bradycardia is derived from Greek, "brady" means slow and "cardia" means heart. Bradycardia, also known as bradyarrhythmia, is defined as the heart rate below 60 beats/min in a regular adult. Typically no symptoms are visible till a heart rate of about 50 beats/min. At lower rates, fatigue, weakness, and dizziness are experienced and very low rates can cause fainting. Low heartbeat rates are common during rest and also among certain highly trained athletes. The heart muscle of athletes has become conditioned to have a higher stroke volume and, so, requires fewer contractions to circulate the same volume of blood [48].

Bradycardia may be caused by a defect in the electrical generation and conduction system. This may occur at the atria, the AV node or the ventricles. The atrial bradycardia, referred to as the sick sinus syndrome, occurs due to a malfunction in the heart's natural pacemaker, the sinus node [48]. The AV bradycardia occurs when the rate of depolarization of the sinoatrial node falls below the rate of the AV node. The AV bradycardia may occur as a result of the malfunction of the sinus node or a block impeding the electrical impulse from traveling to AV node. A lack of electrical impulse or stimuli from the atrium may result in ventricular bradycardia.

Bradycardia can be caused either by noncardiac factors or cardiac factors. The noncardiac factors include metabolic issues, electrolyte imbalance, neurologic factors, and drug abuse. Cardiac factors include CAD, peripheral artery disease, and valvular heart disease. These cardiac and noncardiac factors can lead to disorders of either the SA node or the AV node leading to bradycardia. Bradycardia is less likely to be congenital and older patients are most often affected. Shortness of breath, fatigue, and dizziness are common symptoms associated with bradycardia, severe cases may result in fainting. Bradycardia is diagnosed using output from electrocardiography, many times frequent monitoring of the individual may be required to establish bradycardia. ECG outputs from a normal, healthy heart is compared to different cardiac rhythm disorders in Fig. 20. When medications are not effective and bradycardia is seen to be nonreversible then the implantation of a pacemaker is indicated [48].

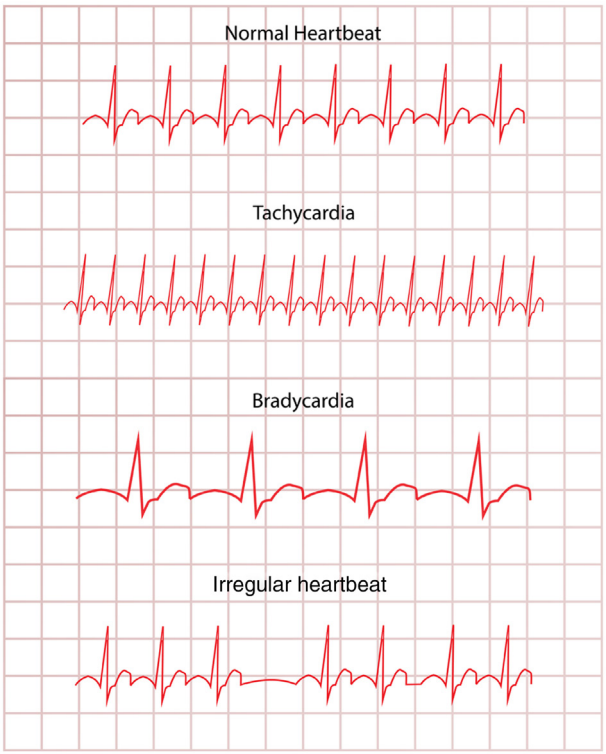

Figure 20 ECG traces in different arrhythmia related conditions.

4.3.2 Tachycardia

"Tachys" in Greek is quick or rapid, hence, tachycardia, also called tachyarrhythmia, and is a heart rate that is faster than the normal resting rate. In general, a resting heart rate over 100 beats/min is classified as tachycardia in regular adults. As the heart rate is controlled by electrical signals sent across heart tissues, tachycardia occurs when an abnormality in the heart produces rapid electrical signals. When the rate of the heart is too rapid, it may not effectively pump blood to the rest of your body, due to this low efficiency of the heart, it provides less blood flow to the body, including the heart itself. This ends up depriving an individual's organs and tissues of oxygen. The high heart rate or tachycardia can cause symptoms such as, dizziness, shortness of breath, lightheadedness, rapid pulse rate, heart palpitations, chest pain, and fainting or syncope. Some people with tachycardia have no symptoms, and the condition is only discovered during a physical examination or with a heart-monitoring test, electrocardiogram [48].

There are many different structural abnormalities that can alter electrical signals and lead to faster heart rates. The common types of tachycardia include the following:

Ventricular tachycardia: Ventricular tachycardia is a rapid heart rate that originates with abnormality of electrical impulses in the lower chambers or ventricles of the heart. This rapid heart rate does not allow the ventricles to completely fill with blood as well contract fully to pump enough blood to the body (Fig. 21). Ventricular tachycardia is often a life-threatening medical emergency.

Ventricular fibrillation: Ventricular fibrillation occurs when rapid, chaotic electrical impulses cause the ventricles to quiver ineffectively and do not function effectively as pumping chambers. This lack of pumping means the body does not receive

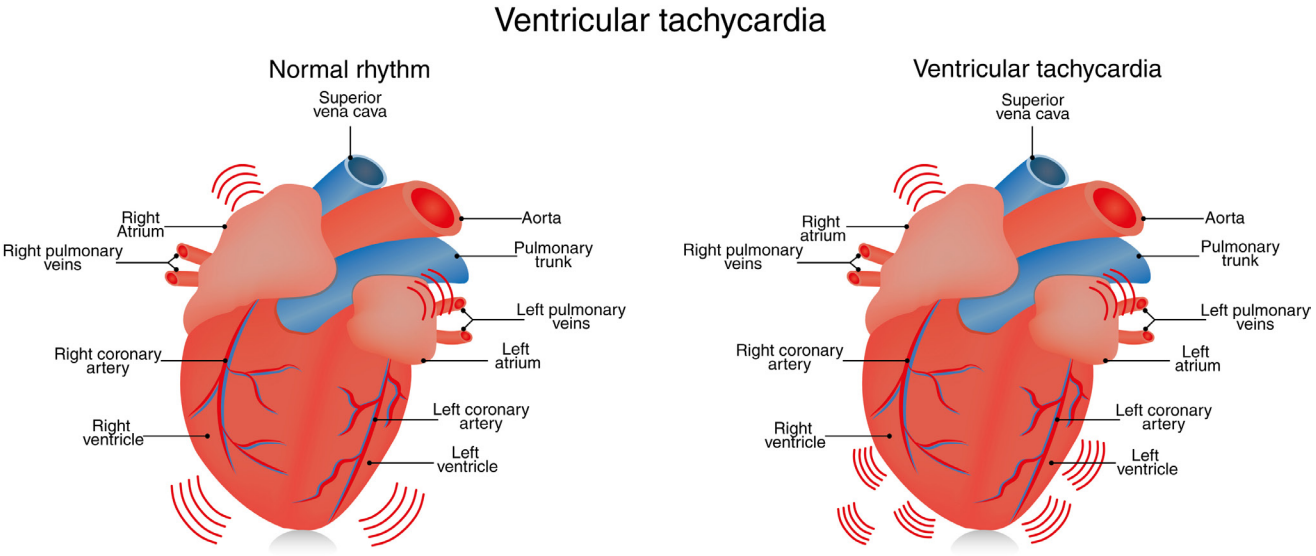

Figure 21 Ventricular tachycardia.

sufficient blood in time. Tachycardia brought on by ventricular fibrillation can be very serious and can even be fatal unless treated very quickly. Most people who experience ventricular fibrillation have an underlying heart disease or have experienced serious trauma.

Supraventricular tachycardia (SVT): SVT, as the name suggests, originates from somewhere above the ventricles such as the atria. It is sometimes known as paroxysmal atrial tachycardia (PAT). SVT is caused by abnormal circuitry in the heart and this abnormality maybe present at birth. The abnormal circuitry creates a loop of overlapping electrical signals. In one form of SVT, a normal electrical impulse coming from the sinoatrial node is split into two due to an abnormality present in the AV node. This splitting sends one signal to the ventricles and the other returns to the atria. Another common abnormality is the presence of an extra electrical pathway from the atria to the ventricles that bypasses the AV node. This may result in a signal going down one pathway and up the other. Wolff-Parkinson-White syndrome is one disorder featuring an extra pathway. SVT is usually less dangerous as compared to the ventricular tachycardias.

Atrial flutter: Atrial flutter is a fast heart rate originating in the atria of the heart. In a sense it can be classified as a SVT as it occurs outside and above the ventricles. In atrial flutter, the heart's atria tend to beat faster than 100 beats/min but at a regular rate. Atrial flutter is caused by irregular circuitry within the atria. The fast rate results in weak contractions of the atria. The rapid signals entering the AV node cause a rapid and sometimes irregular ventricular rate. Episodes of atrial flutter may get better without any intervention, or the condition may persist unless treated. People who experience atrial flutter often experience AF at other times.

Atrial fibrillation: AF is the most common serious form of tachycardia. In Europe and North America alone, about 3% of the population are affected by AF [49]. AF is a rapid heart rate caused by the presence of chaotic electrical impulses in the atria (Fig. 22). These haphazard signals result in rapid, uncoordinated, and weak contractions of the atria. The chaotic electrical signals also affect the AV node and this usually results in an irregular rhythm of the ventricles. The origin of this chaotic activity is around the pulmonary veins. The recovery of the atria from this chaos causes spatially distributed breakup and fragmentation in a process known as fibrillatory conduction [50]. AF can be distinguished from atrial flutter in the lack of regularity of the heart rate pattern and this can be observed in the electrocardiograms. AF may be temporary, however, some episodes will not terminate unless treated. Most people with AF have some structural abnormalities of the heart related to such conditions as heart disease or high blood pressure. Other factors that may contribute to AF include a heart valve disorder, hyperthyroidism or heavy alcohol use.

All diseases and conditions that put a strain on the heart muscle or damage heart tissue increase the

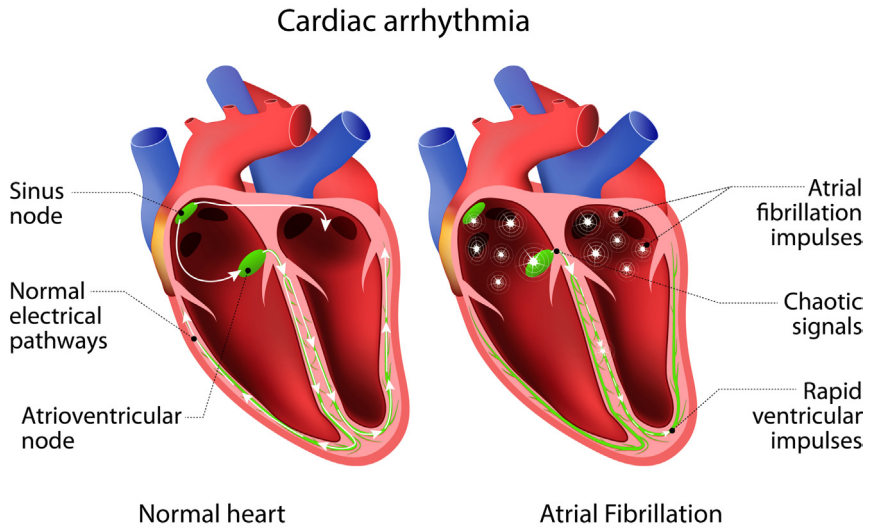

Figure 22 Atrial fibrillation (AF).

risk of tachycardia. Typical risk factors include heart disease, high blood pressure, smoking, heavy alcohol use or caffeine use, use of recreational drugs, psychological stress or anxiety, anemia. Lifestyle changes or medical treatment may decrease the risk associated with the aforementioned factors. Genetic factors are also a big risk factor in tachycardia, a family history of tachycardia puts an individual at greater risk of having tachycardia. Age also plays a role as a risk factor with tachycardia typically occurring in older individuals.

The complications due to tachycardia depend on factors such as, the severity of the disease, the type of tachycardia and the existence of other heart conditions. Possible complications include:

- thrombus formation that can cause a stroke or heart attack,
- causation of edema leading to heart failure due to the inability of the heart to pump enough blood,
- frequent fainting spells, and
- ventricular tachycardia or ventricular fibrillation can cause sudden death.

An electrocardiograph (ECG) is the primary tool for the diagnosis of tachycardia (Fig. 20). The electrical signal output can help the physician not only diagnose tachycardia but also help determine the type of tachycardia. Determination of the type of tachycardia can be made based on the shape of the ECG curve, more specifically, the shape of the QRS complex in the curve [7]. Depolarization of the heart ventricles occurs almost simultaneously, via the bundle of His and Purkinje fibers. If they are working efficiently, the QRS complex is 80–120 ms in duration. This is represented by three small squares or less at the standard paper speed of 25 mm/s. Tachycardia may be classified as either narrow complex tachycardia (SVT) or wide complex tachycardia. Narrow and wide refer to the width of the QRS complex on the ECG. The origin of narrow complex tachycardia tends to be in the atria, while wide complex tachycardia tends to originate in the ventricles of the heart [7].

Portable ECG systems such as a Holter monitor may be useful for diagnosis. A Holter monitor is a wearable device and records the heart rate continuously. Continuous record of the heart rate over a 24-h period provides the physician a prolonged look at the heart rhythm and aid in making the diagnosis. Cardiac catheterization may be recommended as the test to confirm initial diagnosis.

The treatment of tachycardia and the method of cardiac rhythm management depend on the severity of the condition and the stability of the individual as a result. Treatments may include physical maneuvers, medications, cardiac ablation, or electricity conversion. Physical maneuvers, collectively known as vagal maneuvers, can help with certain cases of SVTs. The vagus nerve is a part of the parasympathetic nervous system within the body and affects the muscles of the heart. Stimulation of this nerve can help in the stoppage of unnecessary electrical impulses through the AV node. Several medications can target arrhythmia conditions, these medications act with different mechanisms and exist under different classes of drugs [51]. Cardiac conduction can be accurately mapped using catheterization focusing on the electrical activity within the heart. These electrical activity mapping catheters have specialized tiny sensors on the tip of the inserted catheter. Once the exact spot of electrical disturbance is located, this spot is subsequently destroyed or ablated. The ablation is done via the use of an ablating mechanism attached to the tip of an inserted catheter. The ablating action could be the use of heat, cryogenic temperatures or laser [49]. The application of electrical shocks to the heart's electrical system is an effective treatment of tachycardia. The shock can be applied internally through implanted electrodes. Depending on the nature of tachycardia, different kinds of shock treatments are advised. Cardioversion and defibrillation are the two different shocks. Cardioversion is used for SVT, it uses a therapeutic dose of electric current to the heart at a specific moment in the cardiac cycle. Defibrillation, on the other hand, is more suited for ventricular tachycardia. Defibrillation differs in that the shock is not synchronized. It is needed for the chaotic rhythm of ventricular fibrillation and is also used for pulseless ventricular tachycardia. Defibrillation or cardioversion may be accomplished by an implantable cardioverter-defibrillator (ICD) device.

4.4 Coronary Artery Disease

CAD is the biggest part of the spectrum of cardiovascular diseases. In 2013 CAD resulted in more than 8 million deaths on a global scale [52].

CAD, also known as ischemic heart disease (IHD) is a group of diseases that include angina, myocardial infraction and sudden cardiac death [53]. CAD is caused by the limitation of blood flow and the associated supply of oxygen and nutrients to the muscle cells of the heart or the myocardial cells. CAD is

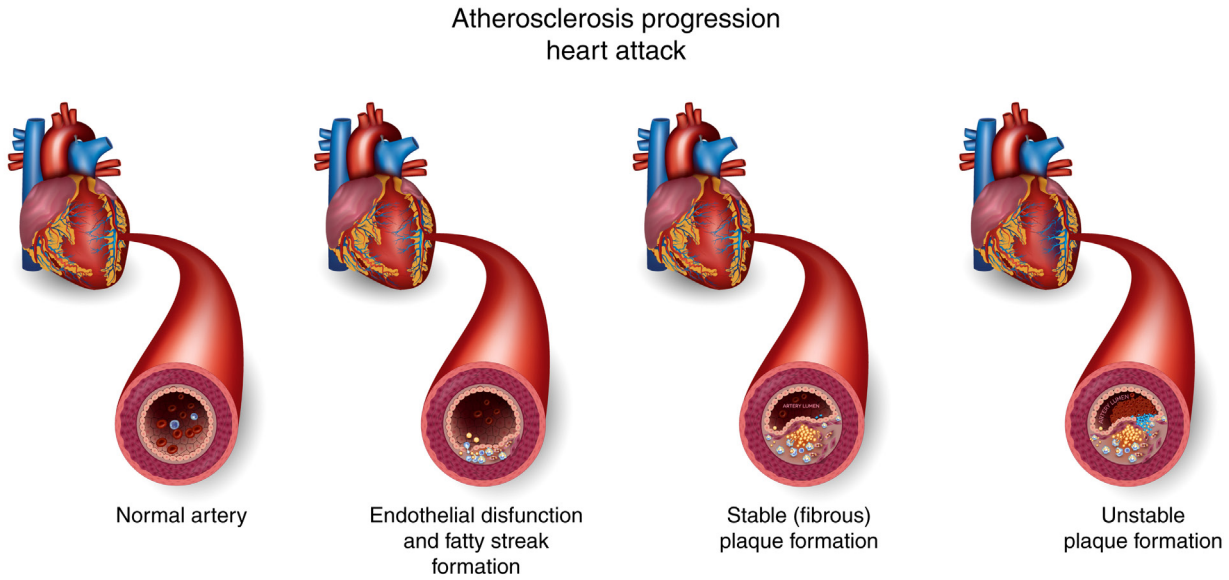

Figure 23 Coronary artery disease (CAD).

usually associated with atherosclerosis which is the thickening of arteries mainly due to fatty deposits. These fatty deposits are also known as plaque. The plaque comprises mainly of cholesterol.

This blood supply limitation causes cell starvation known as ischemia. Myocardial cells may die from lack of oxygen and this is leads to heart muscle damage, heart muscle death, and later myocardial scarring. The muscle death occurring under these circumstances is not reversible and the muscles will not regrow [54].

The unobstructed supply of blood to the heart muscle through the coronary arteries is crucial to the functioning of the heart. Whenever there is some form of restriction to the flow of blood within these arteries, it is termed as coronary artery disease (CAD). CAD can be caused by the buildup of plaque along the inner walls of the arteries around the heart. This buildup narrows the vessels and reduces the flow of blood to the heart (Fig. 23). Subsequently, when the plaque builds up to a degree where it causes the entire vessel to be blocked, the blood and oxygen supplied to the heart is cut off causing a heart attack. Plaque can also be dislodged by blood flow and transported to another part of the anatomy. This dislodging of a piece of thrombus due to the flow of blood in the vessel is known as embolism. When this embolism reaches a vessel smaller than its own size, it can create a blockage of blood in that area and lead to ischemia.

Angina pectoris, commonly known as angina, is one of the issues caused by atherosclerosic obstruction affecting the arteries feeding the heart. Angina pectoris is derived from the Latin "angere" meaning "to strangle" and "pectus" meaning "chest" that can be translated as "a strangling feeling in the chest." Angina is further divided into stable angina and unstable angina. Stable angina is also known as effort angina with chest discomfort and associated symptoms seen as being brought on by activity. Unstable angina, on the other hand, occurs when the patient is at rest and the associated symptoms are more severe and occur with a crescendo pattern [55]. Unstable angina is sometimes also known as crescendo angina. The existence of a fibrous cap protecting the severity of atherosclerosis is what distinguishes stable from unstable angina pectoris.

Chest discomfort and pain is the main symptom of angina pectoris and this pain is usually accompanied by pain in the back, neck, jaw, or shoulders in a phenomenon known as referred pain. Major risk factors for angina pectoris include cigarette smoking, diabetes, high cholesterol, high blood pressure, sedentary lifestyle, and family history of premature heart disease [56].

Electrocardiogram (ECG) is usually is good indicator for angina. The ECG shows a normal pattern under no pain or discomfort conditions while under exercise conditions, that is, a treadmill ECG test, ECG shows abnormality. A coronary angiogram may be performed as a confirmation of the noninvasive tests.

Exercise, diet, and medicine are the first line of treatment of angina pectoris. A potent vasodilator

such as nitroglycerin is traditionally prescribed as an effective treatment for angina. More severe forms of angina, where occlusion is confirmed with an angiogram, are treated with balloon angioplasty followed by the placement of a metallic stent. Coronary bypass surgery, a more invasive form of treatment, may be prescribed in certain cases.

CAD, in general, occurs when the arteries that supply blood to the heart, the coronary arteries, start to develop atherosclerosis. Atherosclerosis is the thickening of arteries mainly due to fatty deposits. These fatty deposits are also known as plaque and this plaque comprises of cholesterol. Plaque deposition renders the artery harder and stiffer and limits the flow of blood to the muscle. Over time, plaque may develop to such an extent that the artery is completely occluded. A patient suffering from CAD may have just one or two plaques or may have many depositions distributed along the coronary artery [57].

The diagnosis of coronary disease underlying particular symptoms depends largely on the nature of the symptoms. The first investigation usually is the recording of an electrocardiogram (ECG/EKG) of the patient, additional blood tests and X-rays may also be advised.

Once the existence of CAD is confirmed, depending upon the severity several lines of treatment are followed. Medications and lifestyle changes are usually the first line of treatment for less severe cases. From an interventional point of view, angioplasty combined with the placement of a coronary stent may be performed. Coronary artery bypass grafting can also be recommended for the most severe cases. In situations where more than one artery of a patient is partially or completely occluded, coronary bypass grafting is seen to be effective than percutaneous coronary interventions such as angioplasty and stent placement [58].

4.5 Peripheral Artery Disease

Peripheral artery disease (PAD) is also known as peripheral vascular disease (PVD). PAD is the development of atherosclerosis or the narrowing of arteries other than the ones supplying blood to the heart and the brain [59]. PAD mainly affects the legs of a person (Fig. 24), however, other arteries are also known to be affected. The classic symptom of PAD is leg pain when walking and this pain resolves with rest, known as intermittent claudication [60]. Claudication is the condition where a cramping pain is induced in the leg during exercise. Various serious complications can result from PAD and these include infection or tissue death that may lead to amputation of the limb, PAD may lead to CAD or could lead to obstruction of blood supply to the brain and result in a stroke.

Cigarette smoking, diabetes, high blood pressure, high cholesterol are known risk factors, out of which cigarette smoking is the leading factor [60]. PAD is mainly diagnosed using the measurement of blood pressure, specifically the ratio of the systolic blood pressure at the ankle and the systolic blood pressure at the arm. This ratio is known as the ankle–brachial index (ABI) [61]. Normal ABI range of a healthy individual is between 1.00–1.40. The patient is diagnosed with PAD when the ABI is ≤ 0.90. ABI values of 0.91–0.99 are considered "borderline" and values >1.40 indicate noncompressible arteries. PAD is graded as mild to moderate if the ABI is between 0.41 and 0.90, and an ABI less than 0.40 is suggestive of severe PAD [62].

Lifestyle changes and medications are the initial lines of treatment for PAD. Persistence of PAD symptoms and severity of the disease lead to surgical intervention. This intervention can be in the form of angioplasty, atherectomy, or vascular bypass. Angioplasty or specifically percutaneous transluminal angioplasty (PTA) is suitable in treatments where larger arteries such as the femoral artery are affected. Atherectomy is another minimally invasive technique that is employed for the treatment of PAD, instead of a balloon pushing the plaque to the sides and walls of the artery like in angioplasty, atherectomy utilizes special tools to cut the plaque buildup in arteries. These different tools utilized in atherectomy to remove the plaque buildup include laser devices, rotational and orbital mechanical devices [62]. In each case the tool is placed at the point of treatment with aid of a catheter. Vascular bypass can also be used as an effective treatment and similar to CAD the diseased area of the arterial vasculature is bypassed using either a natural vein or an artificial conduit as a bypass.

4.6 Aortic Aneurysm

Aneurysm or aneurism is derived from the Greek word "aneurysma" meaning "dilation." Aortic aneurysm is the formation of a blood-filled balloon-like bulge in a blood vessel at a localized spot. The enlargement of a blood vessel to 1.5 times its normal size is termed as aortic aneurysm [63]. Aneurysms lead to the accumulation of blood in the section of the thinned wall into a pool or sac. Aneurysms can be the result of a weakened blood vessel wall due either

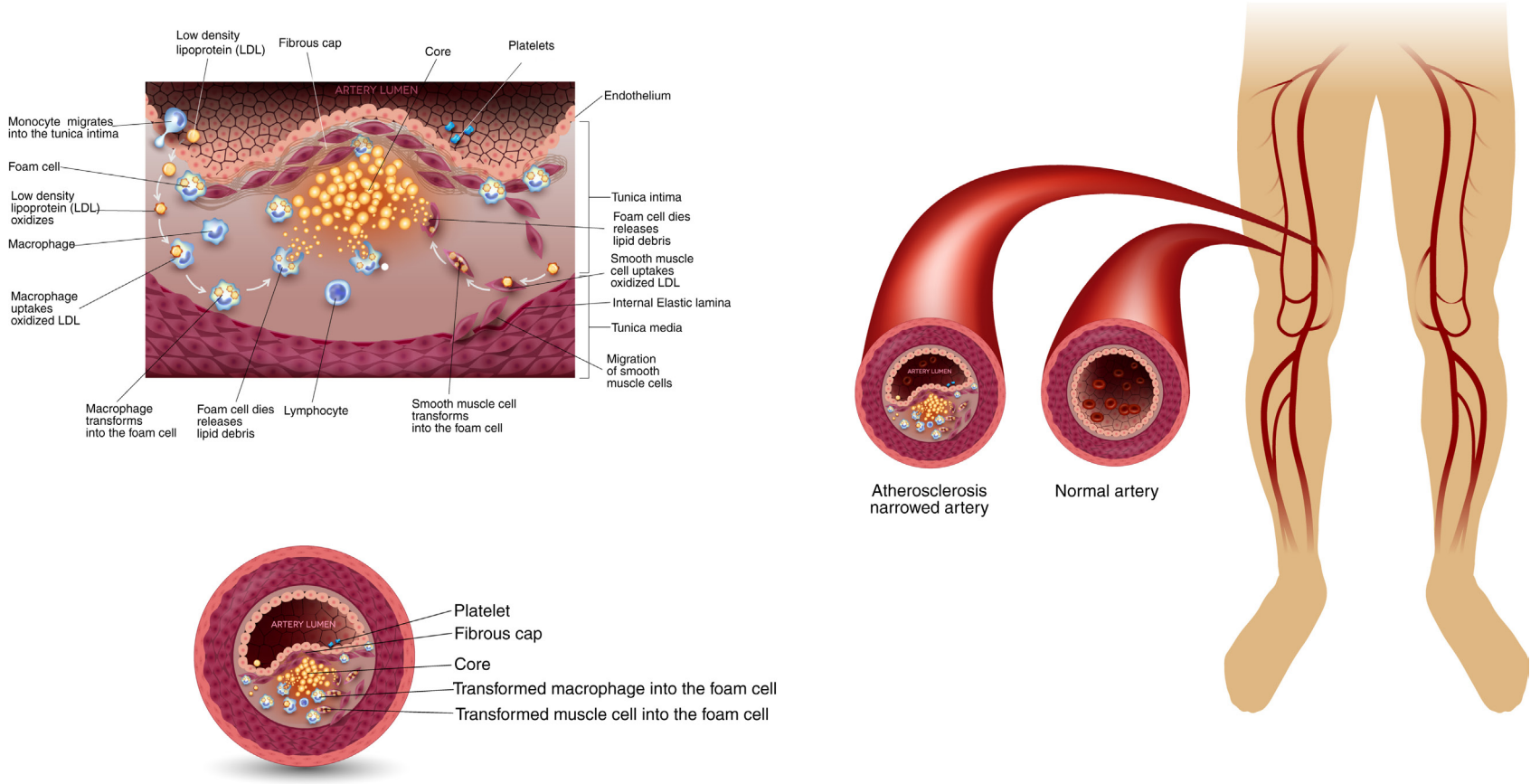

Figure 24 Peripheral artery disease.

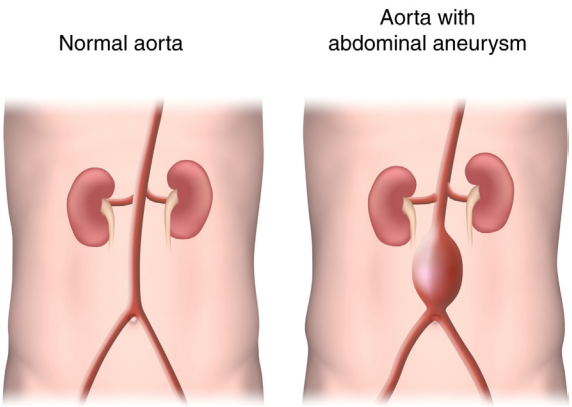

Figure 25 Abdominal aortic aneurysm (AAA).

to a hereditary condition or acquired disease. Ruptured aneurysms can lead to heavy internal bleeding and can be fatal. Aneurysms can also be the focus for thrombosis and embolization.

Aneurysms can occur in any blood vessel but are most often found in the abdominal aorta and sometimes in the thoracic aorta. Abdominal aortic aneurysms also known as AAA are the most common form of aortic aneurysm and involve the segment of the aorta within the abdominal cavity (Fig. 25). Thoracic aortic aneurysm (TAA) occurs in the thoracic section of the aorta and is further classified according to whether it occurs in the ascending or descending aorta. Abdominal aneurysms are more common than thoracic aneurysms due to the reduced level of the principal load bearing protein present in the walls of the aorta, elastin. Another reason is that the abdominal aorta in contrast to the thoracic aorta doesn't possess the nutrient supplying blood vessels, vasa vasorum, within the walls of the aorta [63].

Aortic aneurysms cause weakness in the wall of the aorta and increase the risk of aortic rupture. The risk of rupture of an AAA is related to its diameter, rupture risk is also related to shape; the longer aneurysm, "fusiform" aneurysms are considered less rupture prone than the shorter and bulbous, "saccular" aneurysms, the saccular aneurysms have more wall tension in a particular location in the aneurysm wall than the fusiform aneurysms. When rupture occurs, massive internal bleeding results and, unless treated immediately, shock and death can occur. Unfortunately, in many occasions, rupture is the first sign of an aneurysm.

Already existing coronary or peripheral arterial diseases is a significant risk factor in the development of aortic aneurysm. Other risk factors associated with arterial diseases such high blood pressure, tobacco usage, and high cholesterol levels are also aneurysm risk factors. Along with these certain genetic risk factors play an important role.

It is very important to identify aneurysms and treat them prior to rupture. High risk individuals are recommended for regular ultrasound examination to help identify any developments. The first indication of an aneurysm is with physical examination. In auscultation, a physician can pick up a whooshing sound emanating from the abdomen. Further tests using echocardiography, angiography and X-rays are advised. Contrast enabled X-ray computed tomography (CT scan) is seen to be the most definitive tool for the confirmation of aneurysms.

Surgery is the only way to treat an aneurysm. The decision in going for surgical treatment depends on several factors and a balance of the risks involved with the aneurysm and the surgical procedure. Generally, if the size or the diameter of the aneurysm exceeds 5 cm (2 in.), the risks of rupture are greater than the risks of surgical intervention [64]. The surgical procedure itself could be an open surgery or a minimally invasive technique. Several factors including the location and size of the aneurysm as well as the age of the patient have to be taken into consideration before deciding upon the surgical technique.

The open surgical technique involves exposure of the dilated artery and the insertion of a plastic graft. In the open surgical technique, extreme care has to be taken to ensure continuation of nutrition to the rest of the organs including the spine. The use of a minimally invasive technique avoids the complications of open surgery. The minimally invasive technique relies on the delivery of the plastic graft through a small incision at the top of each leg into the aorta. This technique is known as the endovascular aneurysm repair (EVAR). EVAR is most commonly used to treat the AAA, when the technique is used for the treatment of the thoracic aorta disease, it is termed as TEVAR. In 2010, EVAR accounted for 78% of the AAA treatments in the United States [64].

References

[1] M.M. Madani, E. Golts, Cardiovascular anatomy, Reference Module in Biomedical Sciences, Elsevier, (2014) http://dx.doi.org/10.1016/B978-0-12-801238-3.00196-3.

[2] M. Moreno, T.J. Wiegand, Blood, Encyclopedia of Toxicology, Elsevier, Academic, Amsterdam, (2014) pp. 526–532.

[3] K.L. Moore, A.M.R. Agur, A.F. Dalley, Essential Clinical Anatomy, Lippincott Williams & Wilkins, Baltimore, MD, (2011).
[4] J.E. Hall, A.C. Guyton, Guyton and Hall Textbook of Medical Physiology, Elsevier, Philadelphia, PA, (2015).
[5] G. Betts, et al., Anatomy and Physiology, Open Stax College, 2013, pp. 787–846.
[6] M. Antz, et al. Electrical conduction between the right atrium and the left atrium via the musculature of the coronary sinus, Circulation 98 (17) (1998) 1790–1795.
[7] A. Kumar, ECG IN 100 STEPS By Dr. S. Aswini Kumar MD—Documents. Docslide.us. N.p., 2016. Web.
[8] E. Braunwald, Heart Disease, Saunders, Philadelphia [u.a.], (1997).
[9] K.K. Poh, et al. Assessing aortic valve area in aortic stenosis by continuity equation: a novel approach using real-time three-dimensional echocardiography, Eur. Heart J. 29 (20) (2008) 2526–2535.
[10] G. Maurer, Contrast echocardiography: clinical utility, Echocardiography 17 (s6) (2000) s5–s9.
[11] D.L. Longo, Harrison's Principles of Internal Medicine, McGraw-Hill, New York, NY, (2012).
[12] H.G. Bezerra, et al. Intracoronary optical coherence tomography: a comprehensive review, JACC 2 (11) (2009) 1035–1046.
[13] L. Di Vito, et al. Comprehensive overview of definitions for optical coherence tomography-based plaque and stent analyses, Coronary Artery Dis. 25 (2) (2014) 172–185.
[14] N.H.J. Pijls, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses, N. Engl. J. Med. 334 (26) (1996) 1703–1708.
[15] S. Mendis, P. Puska, B. Norrving, Global Atlas on Cardiovascular Disease Prevention and Control, World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization, Geneva, (2011).
[16] Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. The Lancet 385 (9963) (2015) 117–171.
[17] B.V. Howard, Sugar and cardiovascular disease: a statement for healthcare professionals from The Committee on Nutrition of the Council on Nutrition, Physical Activity and Metabolism of the American Heart Association, Circulation 106 (4) (2002) 523–527.
[18] S.W. Finks, et al. Key articles of dietary interventions that influence cardiovascular mortality, Pharmacotherapy 32 (4) (2012) e54–e87.
[19] R. Micha, G. Michas, D. Mozaffarian, Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes—an updated review of the evidence, Curr. Atheroscler. Rep. 14 (6) (2012) 515–524.
[20] S. Mendis, Global Atlas on Cardiovascular Prevention and Control, World Health Organization, Geneva, (2011).
[21] H.C. McGill, C.A. McMahan, S.S. Gidding, Preventing heart disease in the 21st Century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, Circulation 117 (9) (2008) 1216–1227.
[22] S.S. Gidding, et al. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score in young adults predicts coronary artery and abdominal aorta calcium in middle age-clinical PERSPECTIVE, Circulation 133 (2) (2015) 139–146.
[23] S. Mendis, P. Puska, B. Norrving, Global Atlas on Cardiovascular Disease Prevention and Control, World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization, Geneva, (2011).
[24] M. Czarny, J. Resar, Diagnosis and management of valvular aortic stenosis, Clin. Med. Insights Cardiol. 8 (Suppl. 1) (2014) 15–24.
[25] M.G. Barderas, Valvular aortic stenosis: a proteomic insight, Clin. Med. Insights Cardiol. 4 (2010) 1–7.
[26] S.S. Agabegi, E.D. Agabegi, A.C. Ring, Valvular heart disease, Step-Up to Medicine, Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia, PA, (2013).
[27] W.J. Manning, Asymptomatic aortic stenosis in the elderly, JAMA 310 (14) (2013) 1490.
[28] B. Iung, Management of the elderly patient with aortic stenosis, Heart 94 (4) (2007) 519–524.
[29] F. Rogers, Aortic stenosis: new thoughts on a cardiac disease of older people, JAOA 113 (11) (2013) 820–828.
[30] Updated by: Dale Mueller, and the A.D.A.M. Editorial team. Open Heart Surgery: Medlineplus Medical Encyclopedia. Nlm.nih.gov. N.p., 2016.
[31] S. Agarwal, et al. Transcatheter aortic valve replacement: current perspectives and future implications, Heart 101 (3) (2014) 169–177.

[32] C.R. Smith, M. Leon, M.J. Mack, PARTNER Trial Investigators, Transcatheter versus surgical aortic-valve replacement in high-risk patients, N. Engl. J. Med. 64 (2011) 2187–2198; Br. J. Cardiac Nursing 6 (11) (2011) 564.
[33] M.I. Tomey, U.K. Gidwani, S.K. Sharma, Cardiac critical care after transcatheter aortic valve replacement, Cardiol. Clinics 31 (4) (2013) 607–618.
[34] L. Weinrauch, Heart Surgery, U.S. National Library of Medicine, Washington, DC, (2012).
[35] S.S. Agabegi, E.D. Agabegi, Step-Up To Medicine, Lippincott Williams & Wilkins, Philadelphia, PA, (2008).
[36] D. Kulick, Mitral valve prolapse, Medicinenet.com. N.p., 2010.
[37] F.C. Wells, L.C. Shapiro, Mitral Valve Disease, Butterworth-Heinemann, Oxford, (1996).
[38] H. Boudoulas, C.F. Wooley, Mitral Valve, Futura Pub. Co., Armonk, NY, (2000).
[39] R. Hetzer, J.S. Rankin, A.C. Yankah, Mitral Valve Repair, Springer, Berlin, (2011).
[40] Y. Iba, Mitral valve prolapse associated with accessory mitral valve, Circulation 111 (8) (2005) e107–e1107.
[41] E.D. Grech, D.R. Ramsdale, Practical Interventional Cardiology, Martin Dunitz, London, (2002).
[42] J.H. Rogers, S.F. Bolling, The tricuspid valve: current perspective and evolving management of tricuspid regurgitation, Circulation 119 (20) (2009) 2718–2725.
[43] M.J. Antunes, J.B. Barlow, Management of tricuspid valve regurgitation, Heart 93 (2) (2005) 271–276.
[44] ACC/AHA 2005 Guideline update for the diagnosis management of chronic heart failure in the adult, ACC Curr. J. Rev. 14 (11) (2005) 41–45.
[45] C. Andersson, R.S. Vasan, Epidemiology of heart failure with preserved ejection fraction, Heart Failure Clinics 10 (3) (2014) 377–388.
[46] S.A. Strickberger, Patient selection for cardiac resynchronization therapy: from The Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and The Quality of Care and Outcomes Research Interdisciplinary Working Group, In Collaboration With The Heart Rhythm Society, Circulation 111 (16) (2005) 2146–2150.
[47] T. Carrel, et al. Continuous flow left ventricular assist devices: a valid option for heart failure patients, Swiss Med. Wkly. 142 (2012) w13701.
[48] What is arrhythmia?, National Heart, Lung, And Blood Institute (NHLBI)—NHLBI, NIH, Nhlbi.nih.gov. N. p., 2016.
[49] M. Zoni-Berisso, et al. Epidemiology of atrial fibrillation: European perspective, Clin. Epidemiol. 6 (2014) 213–220.
[50] R.S. Vasan, D. Levy, Defining diastolic heart failure: a call for standardized diagnostic criteria, Circulation 101 (17) (2000) 2118–2121.
[51] H.P. Rang, Pharmacology, Churchill Livingstone, Edinburgh, (2003).
[52] Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden Of Disease Study 2013. The Lancet 385 (9963) (2015) 117–171.
[53] N.D. Wong, Epidemiological studies of CHD and the evolution of preventive cardiology, Nat. Rev. Cardiol. 11 (5) (2014) 276–289.
[54] J. Ambrose, M. Singh, Pathophysiology of coronary artery disease leading to acute coronary syndromes, F1000Prime Rep. 7 (2015).
[55] V. Hombach, et al. Pathophysiology of unstable angina pectoris—correlations with coronary angioscopic imaging, Eur. Heart J. 9 (Suppl. N) (1988) 40–45.
[56] R.V. Milani, J. Myers, A.L. Ries, Psychosocial interventions for patients with coronary artery disease: a meta-analysis, J. Cardiopulmonary Rehab. 16 (4) (1996) 259.
[57] S. Aziz, Chronic total occlusions—a stiff challenge requiring a major breakthrough: is there light at the end of the tunnel?, Heart 91 (Suppl. 3) (2005) iii42–iii48.
[58] I. Sipahi, et al. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease, JAMA Internal Med. 174 (2) (2014) 223.
[59] What is peripheral artery disease?, National Heart, Lung, And Blood Institute (NHLBI)—NHLBI, NIH. Nhlbi.nih.gov. N. p., 2011.
[60] H. Tran, Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease, JAMA 292 (15) (2004) 1867.
[61] M. Ruiz-Canela, M.A. Martínez-González, Lifestyle and dietary risk factors for peripheral artery disease, Circulation J. 78 (3) (2014) 553–559.

[62] J.L. Anderson, et al. Management of patients with peripheral artery disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force On Practice Guidelines, Circulation 127 (13) (2013) 1425–1443.

[63] K.W. Johnston, et al. Suggested standards for reporting on arterial aneurysms, J. Vasc. Surg. 13 (3) (1991) 452–458.

[64] A. Dua, et al. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010, J. Vasc. Surg. 59 (6) (2014) 1512–1517.

PART III

Applications of Plastics in Cardiovascular Devices

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1 Introduction

The cardiovascular system is the central circulatory system for the supply of blood, oxygen, and nutrients to the various organs of the body. It is critical to the efficient functioning of the human body; any abnormalities in the behavior of this system can have significant consequences on the health and lifestyle of an individual.

Abnormalities in the functioning of the cardiovascular system can result from many conditions including the following:

- Defects in the heart valves
- Deviation in the rhythm of the heart pumping action
- Blockages in blood supply to the heart or other parts of the body
- Dilation or aneurysms of the blood vessels

Heart valve defects mainly affect the aortic and mitral valves on the left side of the heart and the two primary issues with heart valve defects are stenosis and regurgitation. Stenosis causes a narrowing of the blood passage within and out of the heart and that can cause a decrease in the blood supply to the body. Regurgitation causes a leakage of blood due to the improper closure of the valves, aortic regurgitation, for example, can result in an increase in the volume of blood in the left ventricle leading to thickening of the walls of the left ventricle and eventual heart failure. A proper rhythm of the heart pumping and filling actions is essential for the maintenance of a coordinated blood flow in the entire cardiovascular system. The heart rhythm could be disturbed due to the diseases of the electrical system of the heart causing a heart beating too slowly, too quickly or the chambers of the heart not acting in a coordinated fashion. Cardiac rhythm issues can lead to palpitations, dizziness to more serious heart failure issues. Blockages in blood supply can occur as a result of plaque deposits in the blood vessels; these blockages can occur in the arteries supplying blood to the heart or elsewhere in the peripheries of the cardiovascular system. The limitation of the blood supply to the heart can result in heart attacks. The dilation of blood vessels, occurring mainly in the aorta, can lead to the formation of a balloon-like bulge at a localized spot in the aorta and can potentially lead to heavy and fatal internal bleeding.

There are a variety of treatments that exist for dealing with these abnormalities and the nature of the treatment depends upon the severity of the disease. Many of these treatments involve the use of different medical devices. Plastics are a big component of these devices and this part of the text explores their application in different cardiovascular devices. Catheters play a major role in the diagnoses and treatment of many cardiac diseases; they also play a significant role in the delivery of many medical devices. Therefore, a section describing the catheters, their design, manufacture, materials, and application forms a separate part of the following text. Devices such as prosthetic heart valves, cardiac rhythm management (CRM) devices, ventricular assist devices (VADs), angioplasty balloons, and aortic aneurysm tackling stent grafts are covered and the role of plastic components in the devices is explored.

2 Cardiovascular Devices Market

With increasing patient population, newer medical technologies, growing medical coverage, and governmental support, it is estimated that cardiovascular medical devices market will enlarge to a value of up to $67.5 billion by 2019 [1]. North America accounts for the largest share of the market with 47.1% of the market share in 2013, Europe had a share of 22.6% and emerging markets such as India, China, Brazil, Mexico, South Africa, and Russia had a share of 30.3% in 2013; the worldwide market is expected to grow at greater than 10% annual growth rate with majority of the growth coming from the emerging markets [1].

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Within the cardiovascular market, CRM devices make up the largest share of overall cardiac devices market accounting for nearly 35% of the overall market. The cardiac rhythm devices include ECG devices and cardiac monitors for diagnostic applications, implantable pacemakers, defibrillators, and cardiac resynchronization devices for treatment of cardiac arrhythmia. The overall CRM market is expected to grow at 4.7% per annum [2]. The strongest growth in the CRM sector is expected to be in the diagnostic sector and within the devices sector the fastest growth is expected in defibrillators.

The entire worldwide catheter market is expected to grow at a rate of 7.5% per annum; by 2020 the market size is estimated at $42.5 billion [3]. Cardiovascular catheters make the majority of the overall catheters market in terms of revenue accounting for nearly 40%. It is forecast that the two fastest growing segments of the market during this period will be advanced diagnostics and advanced ablation, with growth rates of 23 and 17%, respectively [4]. These segments will be driven by growth in the number of atrial fibrillation (AF) ablation procedures—AF is the commonest sustained arrhythmia in North American and European patients and was classified as a growth industry in the 21st century by the European Heart Journal even in year of 2000 [4].

The market for prosthetic heart valves is expected to be worth $4.8 billion in 2020 with an annual growth rate of 9.1% [5]. The rise of valvular diseases in an aging population is the main driver for this growth and the introduction of the minimally invasive technique for the heart valve replacement is expected to be the strongest area of growth.

The market for the treatment of coronary heart disease through the use of angioplasty and stent technologies is estimated to grow to $22.5 billion by 2021 [6]. The market for stents is large and is expected to grow to greater than $10 billion worldwide by 2021. The number of patients receiving stent grafts for aneurysm repair is estimated to grow to $1.9 billion by 2020 with a growth rate of between 6.7 and 9.5% per annum [7].

The major companies active in the cardiovascular devices sector and some of the products they manufacture are listed in Table 1.

3 Cardiovascular Catheters

Catheters are thin tubes inserted into the body serving a broad range of functions. Catheter comes from the Greek verb “kathiemai” meaning “let down” as the catheter is let down into the body [18]. Depending on the material used to make the catheter, its manufacture, and design, the catheter can be tailored for use in cardiovascular, neurological, gastrointestinal, urologic, or ophthalmic applications. There are many kinds of cardiovascular or cardiac catheters including electrophysiology catheters, percutaneous transluminal coronary angioplasty (PTCA) balloon catheters, intravascular ultrasound (IVUS) catheters, percutaneous transluminal peripheral angioplasty catheters, guiding catheters, angiography catheters, and pulmonary artery catheters [18].

Cardiac catheters can be used for diagnostic evaluation of a patient or for interventional purposes. Diagnostic catheters are used to determine and evaluate the state of the patient with regard to certain cardiovascular diseases. Interventional catheters, on the other hand, are used for therapeutic purposes, that is for the treatment of an identified disease. Catheters are used in various applications within the cardiovascular sector; these range from the simple intravenous drug delivery to procedures such as ablation and angioplasty. Catheters are also used as delivery systems for the placement and delivery of permanent implants such as pacemakers and defibrillators.

Catheters need to be designed for the specific function that they are intended to perform. Catheters are designed with the following features in mind:

- Mechanical properties: The strength of the material of construction and the mechanical design of the catheter are important characteristics in determining the overall mechanical properties of the catheter. The material of construction decides the catheter’s resistance to bursting, its flexibility, and the ability to steer the catheter through the vasculature. The mechanical design in combination with the material properties significantly impacts the performance of the catheter; the mechanical design includes the basic dimensions of inner and outer diameter and the size of the lumens.
- Radio opacity: The ability of X-rays to locate the catheter through the vascular system is an important property of the catheter. The radio opacity allows accurate placement of the catheter inside the body. Radio opacity can be obtained by compounding the catheter material with radio opaque agents or by the placement of radio opaque strips at different points in the catheter length.
- Surface and friction: The ease of passage of the catheter over the metallic guidewire and the

Table 1 Major Companies and Their Products in the Cardiovascular Medical Devices Sector

Company	Products
Abbott Laboratories, USA [8]	• Guidewires • Cardiovascular catheters • Mitral valve repair device • Stents—bare metal, drug eluting and bioresorbable • Stent graft • Vascular closure devices
Biotronik, Germany [9]	• Guidewires • Ablation catheters • Stents—drug eluting and bioresorbable • Angioplasty catheters • CRM devices • Cardiac monitoring devices
Boston Scientific, USA [10]	• Guidewires • Ablation catheters • Stents—drug eluting and bioresorbable • Angioplasty catheters • Introducer sheaths • CRM devices
Cook Medical, USA [11]	• Guide wires • Cardiovascular catheters • Introducer sheaths • Angioplasty systems • Stent grafts
Edwards Lifesciences, USA [12]	• Cardiovascular catheters • Prosthetic heart valves—bioprosthetic and transcatheter • Heart valve repair devices
Gore Medical, USA [13]	• Vascular grafts • Stent grafts • Suture • Septal occluders
Biosense Webster (Johnson and Johnson) [14]	Cardiovascular catheters
Medtronic, Ireland [15]	• Cardiovascular catheters • Ablation catheters • Angioplasty systems • CRM devices • Stent grafts • Cardiac monitors • Prosthetic heart valves—mechanical, bioprosthetic and transcatheter
Sorin Group, Italy [16]	• Cardiovascular catheters • Prosthetic heart valves—mechanical, tissue and transcatheter • Mitral valve repair systems • CRM devices
St. Jude Medical [17]	• Cardiovascular catheters • Ablation catheters • Septal occluders • CRM devices • VADs • Prosthetic heart valves—mechanical, bioprosthetic and transcatheter

CRM, cardiac rhythm management; VAD, ventricular assist device; VCD, vascular closure devices.

surface of the blood vessels without any undue damage is an important aspect of the catheter. The frictional properties of the catheter are an important measurement for this determination. The behavior of the surface of the catheter is an important consideration in their response to the bodily fluids.

- Atraumatic tip: It is important that the process of catheter insertion and its progress through the vasculature does not cause any damage to the surrounding tissues. This damage is minimized by the careful design of the catheter tip.

3.1 Mechanical Properties of Catheters

3.1.1 Catheter Size

The "French" scale is used to denote the size of a catheter, the Fr (French) number divided by 3 is the diameter (D) of the catheter in millimeters (mm), that is,

$$D\,(\text{mm}) = \frac{\text{Fr}}{3} \tag{1}$$

The French size was devised by Joseph Charriere, a 19th century Parisian surgical instrument maker [18].

$$C = \pi D \tag{2}$$

The circumference of catheters, C, is only slightly (4.7%) greater than its calculated French size. An increasing French size corresponds to a greater diameter of the catheter; however, the size only corresponds to the external size of the catheter so the effective volume of the catheter depends on its wall thickness and the lumens (size and geometry).

Table 2 gives some dimensions of catheters in different units of measurement [18].

In most cases for a diagnostic or interventional catheters, sizes between 5 and 7 Fr are used. A catheter is usually in the range 100–125 cm (40"–50") in length [19]. Cardiac catheters can range from the simplest cylindrical tubes to more complicated structures. The degree of complexity depends upon the nature of the application of the catheter.

3.1.2 Flow Through Catheters

When catheters are used to pump fluids of different sorts through them, as in a catheter used to deliver medicinal fluids, the flow rates that can be achieved

Table 2 Catheter Size Conversion Between French Sizes to Millimeters and Inches

French Gauge	Circumference	Diameter (mm)	Diameter (inches)
3	3.14	1	0.039
4	4.19	1.334	0.053
5	5.24	1.667	0.066
6	6.28	2	0.079
7	7.33	2.334	0.092
8	8.34	2.667	0.105
9	9.42	3	0.118
10	10.47	3.334	0.131
11	11.52	3.667	0.144
12	12.57	4	0.158
13	13.61	4.334	0.170
14	14.66	4.667	0.184
15	15.71	5	0.197
16	16.76	5.334	0.210
17	17.81	5.667	0.223
18	18.85	6	0.236
19	19.9	6.334	0.249
20	20.94	6.667	0.263

becomes important. The Hagen–Poiseuille equation from fluid mechanics describes the flow of a liquid in a circular orifice thus:

$$Q = \Delta P \frac{\pi r^4}{8 \mu L} \tag{3}$$

where Q is the volumetric flow rate, ΔP is the pressure drop along the length of the tube, r is the radius of the tube, μ is the viscosity of the fluid being transported through the tube, and L is the length of the tube.

Since the Hagen–Poiseuille equation applies to flow through rigid tubes, it can be used to describe flow through vascular catheters, and how the dimensions of a catheter can influence the flow rate. The effect of the inner radius of the catheter on the flow rate that can be achieved is significant as the flow is directly related to the fourth power of the radius. A change in the catheter diameter can have a profound influence on the flow rate through it, doubling the inner radius of a catheter, for example, can increase the flow rate through it by 16-fold. According to the equation, the influence of length on the flow rate is significantly less than its radius; however, the flow is inversely proportional to the length of the catheter and it is important to take that into consideration in catheter design. The fluid viscosity is also inversely proportional to the flow rate so increasing viscosity will decrease the flow through the catheter. The viscosity of commonly used infusions used in intravenous injections ranges from 1 centipoise (cP) to 40 cP [20]. The viscosity of water at room temperature is ~ 1 cP, plasma is mostly water but contains other components such as proteins, electrolytes, and other macromolecules, and as a consequence the viscosity of plasma at 37°C is about 1.8–2 times that of water [21]. The viscosity of plasma forms a part of the viscosity of blood which is further determined by red blood cells. The concentration of the red blood cells in the blood, known as hematocrit, has a very strong impact on the viscosity of the blood [22]. At 37°C, the viscosity of blood is estimated to be between 3 and 4 cP [21].

3.1.3 Pushability of Catheters

The ability of the catheter to easily navigate the complexities of the vascular system is expressed in terms of the degree of force required to push the catheter through. This degree of force is expressed as the pushability of the catheter. Catheter pushability refers to the response of a tube upon the placing of a longitudinal force along its axis. Pushability is also related to and sometimes referred to as the columnar stiffness of the catheter. Columnar stiffness is the ability to transmit force or movement from the proximal end to the distal end of a catheter. The proximal end of the catheter is defined as the portion of the catheter close to the point of attachment or insertion, whereas the distal end is the opposite of the proximal end and describes the portion furthest away from the point of insertion. The pushability of a catheter is related to longitudinal stiffness of the tube and for small deflections its behavior can be approximated as a spring system; it can be calculated as [23]

$$k_{\text{long}} = \frac{EA}{L} \tag{4}$$

where k_{long} is the longitudinal spring constant, E is the modulus of elasticity of the material of the catheter, A is the cross-sectional area, and L is the length of the catheter shaft.

For increased pushability, k_{long} must be increased. An examination of the aforementioned equation reveals that the pushability is directly related to the material modulus and the catheter cross-sectional area, whereas the pushability is inversely related to the length of the catheter. Accordingly a maximization of k_{long} can be achieved in the following ways

- Increasing the size of the catheter, that is, increasing cross-sectional area of the tubing.
- Increasing the material stiffness or elastic modulus
- Decreasing the overall catheter length

However, these variables are limited by the actual application, the size of the catheter is limited by the size of the blood vessel to be accessed, the stiffer the material of construction of the catheter the greater is the probability of causing injury to the vasculature and finally the length of the catheter is limited by the type of procedure and the distance between the point of insertion and the target area for diagnosis or intervention.

3.1.4 Torqueability of Catheters

The maneuverability of the catheter through the vasculature depends upon the ability to transmit torque from the proximal end to the distal end of the catheter. Torque is the force that produces or tends to produce rotation. The degree of distal rotation

is divided by the degree of proximal rotation to determine the torque ratio. The torque ratio must be such that the catheter material is able to provide sufficient rotation to the distal end of a catheter, in some cases a lower torque ratio may be desirable as a lower torque ratio may provide better steering ability for the catheter.

The torsional stiffness of a catheter can be expressed by the "Torqueability" of the catheter. Again for small deflections, as previously, the catheter can be approximated as a spring system and the torqueability of a catheter can be expressed as [23]

$$k_{\text{torq}} = \frac{GJ}{L} \tag{5}$$

where k_{torq} is the torsional spring constant, G is the shear modulus, J is the polar moment of inertia, and L is the length of the catheter shaft.

Maximizing the transmission of torque means an increase in the torqueability of the catheter and this can be achieved by maximizing the torsional stiffness value, k_{torq}. One of the ways of increasing the k_{torq} value can be through maximization of the material polar moment of inertia, J.

For a tube, the governing equation for J is [23]

$$J = \frac{\pi}{32}(d_o^4 - d_i^4) \tag{6}$$

where d_o is the outer diameter of the catheter and d_i is the inner diameter of the catheter.

Maximization of J can be achieved through the maximization of the catheter's outside diameter as well as its wall thickness.

As the shear modulus is also directly proportional to the torqueability, an increase in the shear modulus can also result in an increase in the k_{torq} value. The shear modulus is directly related to the elastic modulus of a polymer and generally expressed as [24]

$$E = 2G(1+\nu) \tag{7}$$

where E is the material elastic modulus, G is the shear modulus and ν is the Poisson's ratio.

Poisson's ratio is a dimensionless quantity and is generally between 0.3 and 0.5 for most plastics.

An increase in torqueability can also occur with a corresponding decrease in the part length, L, as it is inversely proportional to k_{torq}. However, as with pushability, the degree of freedom with these variables in increasing the torqueability is limited by the application site and the potential of injury to the blood vessels.

3.1.5 Catheter Flexibility

As the catheter travels within the vasculature to its destination, it has to go through numerous complex channels and therefore the ability of the catheter to traverse the complex pathway without causing any injury to the vasculature is important. This property of the catheter is referred to as its flexibility [25].

Traditionally, material durometer is used as the measure of the flexibility of a catheter. Durometer is a measure of the material's hardness; however, durometer is only an indirect measure of the catheter flexibility. The elastic modulus of the material is a better measure of the stiffness and flexibility of the material. The hardness of a material is related to its modulus, in general, the harder a material, the higher is its elastic modulus. However, this relationship is not direct as can be seen in Fig. 1.

Mathematically, the flexibility or flexural stiffness of a tube can be determined by approximating the catheter as a spring system and calculating its flexural spring constant [25]:

$$k_{\text{flexural}} = \frac{3EI}{L^3} \tag{8}$$

where k_{flexural} is the flexural spring constant, E is the modulus of elasticity, I is the material moment of inertia, and L is the length of the catheter shaft.

Eq. (8) implies that to improve the flexibility of the tube the flexural stiffness value, k_{flexural}, must be minimized by decreasing the moment of inertia (I) of the material of construction making up the catheter. The moment of inertia characterizes the resistance to motion demonstrated by a body subjected to rotational motion. When a body is rotating, or free to rotate, around an axis, a torque must be applied to change its angular momentum. The amount of torque needed for any given rate of change in angular momentum is proportional to the moment of inertia of the body. For a tube, the governing equation for I [24]:

$$I = \frac{\pi}{64}(d_o^4 - d_i^4) \tag{9}$$

where d_o represents the outer and d_i represents the inner diameters of the tube.

Minimization of the moment of intertia, I, can be achieved by decreasing the wall thickness of the catheter. Apart from decreasing I, the overall flexural spring constant, k_{flexural}, can further be reduced by

- By minimizing the modulus of elasticity, that is, by using a softer material.
- By increasing the overall part length.

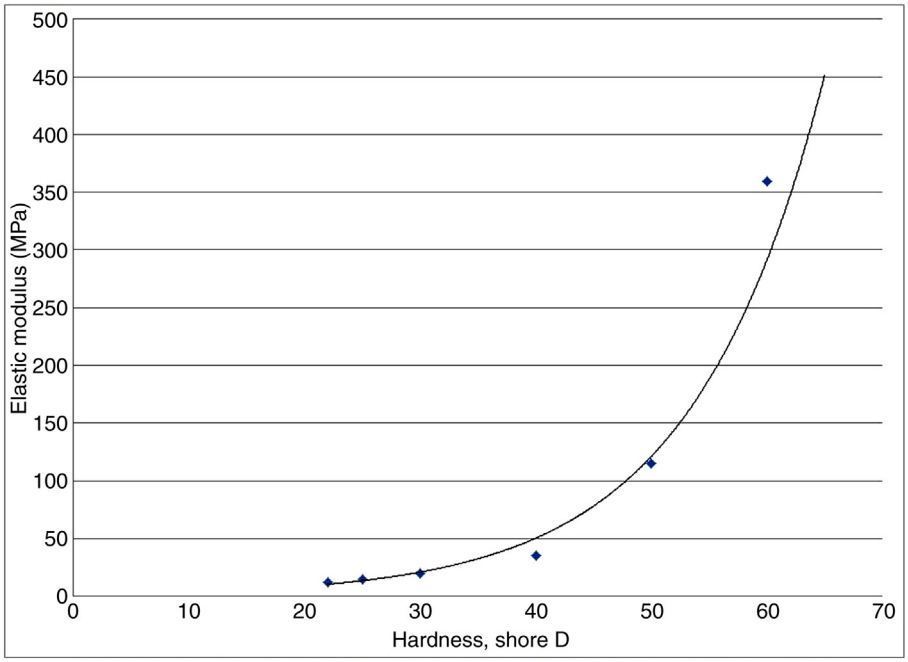


Figure 1 Relationship between polymer hardness and its elastic modulus [data for siloxane-based thermoplastic polyurethanes (TPUs)].

Along with the flexibility of the catheter, another important property of a catheter is its kink resistance. The kink resistance of a catheter can decide to a great degree, the amount of bend that the catheter can withstand without permanent deformation. The maximum bend radius a catheter can withstand is determined by three factors: the catheter diameter, its wall thickness, and the properties of the plastic material making up the catheter. For some applications, bend radius may not be as important as tensile strength, whereas in other applications the opposite may be true. As a general rule, the bend radius is usually half of the catheter outer diameter [25]. Flexibility itself is not however an accurate measure of kink resistance. Data have shown that tubes with a small inner diameter to outer diameter ratio perform better than those with higher inner diameter to outer diameter ratios. That is the catheters with thicker walls have better kink performance than those with thinner walls.

3.1.6 Catheter Burst Pressure

The burst pressure is another important property to consider when designing catheters [26]. This property becomes especially important when the catheter is designed to expand as a balloon in angioplasty procedures or to deliver a stent. A theoretical calculation using tensile strength, outer diameter (d_o), and inner diameter (d_i) values can be used to determine the conditions under which a tube might fail or develop cracks due to pressure from within and can be expressed as in Eq. (10).

$$P = \frac{T(d_o^2 - d_i^2)}{d_i^2\left(1 + \frac{d_o^2}{d_i^2}\right)} \tag{10}$$

where T is the ultimate tensile strength of the catheter, d_o is the outer diameter of the catheter, d_i is the inner diameter of the catheter, and P is the burst pressure of the catheter.

As can be seen, an increase in burst strength is directly proportional to the material tensile strength and materials with higher ultimate tensile strengths are chosen for high performance applications. Increasing the wall thickness and decreasing the overall tube diameter can also increase the burst pressure; however, these dimensions are limited by the application.

The mechanical equations for the design of a catheter (Eqs. (1–10)) represent the material requirements for tensile strength, elastic modulus, durometer, etc. However, in many instances the properties of a plastic are just not adequate to satisfy all the requirements for catheter design. In these cases, catheters are frequently reinforced with metallic, steel or nitinol, braids. Braided catheter shaft designs (Fig. 2) can satisfy requirements for applications that require

Figure 2 A braided catheter. *Courtesy: St. Jude Medical.*

high torque, burst pressure resistance, pushability, torqueability, and kink resistance at the same time.

Catheter design is further complicated by the combination of a small size and the requirement for multiple lumens. Multiple lumens are required for different functionalities that are delivered through each lumen either different fluids or more complicated therapeutic devices. Multiple lumens help achieve the goal of a small and minimally invasive procedure providing multiple activities through a single access point. Three to six or more lumen catheters have been commonly used [25]. The equations provided previously (Eqs. (1–10)) are good approximations for single lumen catheters; however, multilumen catheters can complicate this analysis.

The combination of the catheter design formulae highlights an increasing degree of difficulty for design engineers. The equations indicate that the same material properties that increase pushability and torqueability of the catheter also decrease the flexibility of the catheter and will end up making the catheter stiff. A stiffer catheter will increase the possibility of causing injury to the vasculature. This design challenge is usually overcome by using more than one material of construction. Very often the material variations used are different durometers of the same material. Different durometers of the same material are chosen to facilitate ease of bonding as that can occur with the same base chemistry. A harder durometer is used toward the proximal end whereas a lower durometer is used toward the distal end. As seen earlier, the durometer values correspond to the elastic modulus of the material.

Catheter assembly with material variations can be accomplished by different techniques. Catheters with multiple materials or multiple durometers of the same material, along the length of the shaft, may be manufactured by extruding discrete segments of different materials and subsequently bonding or fusing them together. The bonding can be achieved by different techniques; use of adhesives and thermal bonding or fusion. Adhesives can often be used in the assembly technique to fuse together different materials. The selection of adhesives is important to the manufacturing process as some adhesives, such as epoxies, may display good bonding properties but may need a long cure cycle or high cure temperatures. Adhesives that can be cured at room temperature, for example, moisture curing or light sensitive adhesives can be viable alternatives. Thermal fusion is another technique used in catheter assembly; thermal bonding is done using the "reflow" process. The reflow process relies on the melting of the material and gentle pressure during the melting process forces adjacent layers of material to flow into each other. Reflow ovens and mandrels are used for the melting of the tubes and the exertion of pressure. Upon cooling, the layers form an integral adhesive bond to each other. The reflow technique is quite commonly used for polyurethane and polyether amide (PEBA) catheters.

An intermittent extrusion technology can also be used to produce catheters with variable durometers along their length. Most thermoplastic catheter materials can be utilized in the intermittent extrusion process and both single and multilumen catheters can be produced using this technology [26]. Intermittent tapering during extrusion is another technique to achieve the variable rigidity of the catheter along its length. Tapering is done in a controlled fashion as the material exits the die when the plastic is still hot and malleable. Intermittent tapering is the process which tapers different regions of the extrudate into different draw downs in a variable manner that changes the cross-sectional area of the catheter in different sections. This variation of the cross-sectional area leads to variable flexibility along the length of the shaft. This technique can be used for single lumen catheters as well as for multilumen catheters.

3.2 Catheter Radio Opacity

Radio opacity refers to the inability of electromagnetic radiation, particularly X-rays, to pass through the material. Radio opacity can also be referred to as radio density. The two primary factors that contribute to a material being opaque to electromagnetic radiation are its atomic weight and density. Catheters usually incorporate materials with high electron density contrast to the surrounding tissue material. Visualizing the catheter during a procedure allows the physician to guide and maneuver the device for proper placement or alignment. The materials inducing radio opacity in catheters include titanium, tungsten, bismuth, and barium [27].

X-rays are a form of radiation and consisting of high energy waves with different frequencies and lengths forming a part of the electromagnetic spectrum. Diagnostic X-rays fall in the lower wavelength end of the spectrum with wavelengths between 0.1 and 1 Angstroms (Å). When fast moving electrons emanating from an X-ray source impacts on an anode or target, X-rays are produced. The intensity of an X-ray beam is determined by the number of photons in the beam and the energy of the photons, which is expressed as kiloelectronvolts. X-rays used for medical imaging tend to have photon energies between 5–10 keV [28].

In an X-ray beam different parts of the body can attenuate the X-ray energy in a different fashion. These differences can create differing contrasts of the resultant image. Bones contain calcium, which due to its relatively high atomic number absorbs X-rays efficiently. This reduces the amount of X-rays reaching the detector in the shadow of the bones, making them clearly visible on the radiograph.

The X-ray imaging technique used frequently during cardiovascular procedures is fluoroscopy. Fluoroscopy is an imaging technique commonly used by physicians or radiation therapists to obtain real-time moving images of the internal structures of a patient through the use of a fluoroscope. In its simplest form, a fluoroscope consists of an X-ray source and a fluorescent screen, between which a patient is placed. However, modern fluoroscopes couple the screen to an X-ray image intensifier and a video camera allowing the images to be recorded and played on a monitor.

The material density and its atomic number play an important function in the determination of its ability to act as radio opaque elements. Barium sulfate, bismuth compounds, and tungsten metal are frequently used as radio opaque fillers in catheter tubing [27]. Barium sulfate ($BaSO_4$) is the oldest and most widely used of the radio opaque materials. It has a specific gravity of 4.5 and is generally used as 20–40% loadings by weight in combination with the base plastic. $BaSO_4$ is white in color and can be colored differently using colorants. Its main attraction is its low cost; however, its density implies that a higher loading may be required as compared with other more dense fillers. As the loading of a filler increases, the properties of the base plastic start getting affected and at higher loadings one may see a decrease in the plastic's tensile strength and even its biological stability. Bismuth compounds are considerably more expensive than $BaSO_4$ but are almost twice the density of $BaSO_4$. That implies that one can compound in a greater amount of the radio opaque agent without compromising the physical properties of the base plastic. A higher loading means a clearer image of the catheter is produced during the procedure. Tungsten metal powder has a very high specific gravity of 19.5 and so much higher loadings can be compounded with greater image clarity as a result. However, the use of Tungsten is restricted due to its abrasive nature that affects the compounding extruders. All these radio opaque materials are biocompatible and have no issues in being used in the medical industry [27].

The amount of the radio opaque agent also depends on the application and device design. A catheter that is deployed near the surface of the skin requires a much lower level of the radio opaque filler as compared to the catheter that is used in the coronary artery of the heart. A higher loading of the radio opaque filler is also required for thin walled catheters as compared to thicker walled catheters. A higher level of loading is also used for catheters having discrete radio opaque markers, such as, strips, rather than a uniform distribution of the filler. Sometimes a blend of radio opaque fillers may be used to balance the issues of cost, loading, physical properties, and image clarity.

Compounding radio opaque fillers into the base plastic is a sensitive operation. First of all, correct levels are to be chosen based on the application, device design and the filler type; second, great care has to be taken so as not to over shear and degrade the properties of either the filler or the base plastic. Bismuth compounds, for example, are sensitive to shear whereas Tungsten metal can damage the compounding extruder due to their abrasive properties.

3.3 Frictional and Surface Properties of Catheters

In catheters, the physical property most often used to describe the ease of passage of the catheter through the blood vessels is the coefficient of friction (COF).

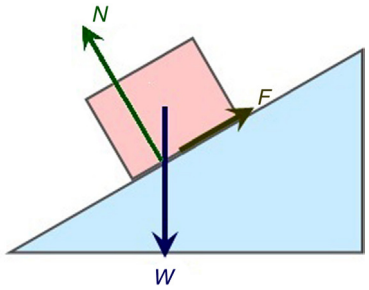


Figure 3 Illustration of the frictional forces on an object.

The COF is also used to describe the ease of insertion of another device through the shaft. A low COF implies better lubricity of catheters. The science of friction, abrasion, and lubrication is called tribology. A tribometer is an instrument used for the measurement of friction.

The measurement of friction is carried out empirically; a tribometer compares the frictional values of a known surface to the one that needs to be measured. The measure of sliding resistance of one material over another is usually used to calculate the COF. The COF can be expressed as (Fig. 3)

$$\mu = \frac{F}{N} \tag{11}$$

where μ is the COF, F is the tangential force, and N is the normal force.

The COF values depend on the material used. For catheter interactions with the blood vessels, COF values of approximately 0.04 are indicative of a low insertion force whereas values of greater than 0.2 indicate a high insertion force [29]. Polytetrafluoroethylene (PTFE) has long been recognized as having the lowest COF of polymers commonly used in medical devices. However, PTFE might not possess other properties such as elastic modulus and thermal processability that are favorable to catheter design; hence PTFE is frequently used as liners in catheters but rarely as the main material of construction in catheters.

The application of coatings on catheters is seen as another way to improve their surface properties. Apart from making catheters more lubricious, coatings can function in numerous other ways to enhance the surfaces of catheters and leading to an improvement in the catheter interaction with the biological environment.

Coatings are often seen as solutions to the problem of the lack of consistency in the surface properties of catheters. Coating processes on polymers were explored in the 1950s, the oldest patent on a hydrophilic coating was published in 1956 [30], and although it did not specifically talk about usage in medical devices, it was important as it described the basic chemistry of coating processes. This basic chemistry was then expanded upon in one form or another by subsequent work in the area of polymeric coatings in general and hydrophilic coatings in particular.

The polymeric systems that were used in the coating of catheters and were patented in the 1960s to 1980s included polyvinylpyrolidone (PVP), polyurethanes, polyacrylic acid (PAA), polyethylene oxide (PEO), and polysaccharides. Most of these systems continue to be used to this day with subtle variations in the actual chemistry. The initial patent from DuPont described a two-layer system, where a bonding layer is first placed over the substrate to provide for consistent binding for a top coat. Work done in later publications differentiated this basic technology into heat-cured and photo-cured coatings [31]. These studies also talked about the use of coating systems with a single layer versus systems with a two-layer structure comprising a bonding layer and a top coat.

Apart from the reduction in the COF, the antifouling property of the coating is also an important determinant of the effectiveness of the coating. Protein adsorption, as noted earlier, is one of the first events that occur upon the introduction of a foreign object into the body. Protein absorption, in many instances, is seen as a precursor to blood clotting and thrombosis [31]. Therefore, if the coating demonstrates an ability to reduce protein adsorption, it will reduce subsequent tendency to thrombosis of the inserted catheter. Reducing the propensity for proteins to stick to a surface is a key approach to making a nonthrombogenic material and an antifouling coating. These coatings were initially utilized in coating guidewires but are increasingly being used to coat introducers and catheters. Some hydrophilic coatings also employ heparin, which is antithrombogenic in that it actively catalyzes a reaction between antithrombin and thrombin, which ultimately affects clotting by reducing the formation of the fibrin protein.

Current coating designs also include drug delivery packages into the coatings. A pervasive problem that exists in numerous procedures is that of operation-related bacterial infections. For example, central venous catheters (CVCs) and peripherally inserted central catheters (PICCs) have serious potential to cause life-threatening infections such as sepsis, and catheter infection rates are 5.3 per 1000 catheter days. Consequently, there is a large push to incorporate antimicrobial materials into hydrophilic

coatings, which can present special challenges depending on the coating system. One effective technique is the incorporation of antimicrobial drugs into the coating. These antiinfection drugs will elute into the body over time and prevent the development of infections after the procedure. Each antimicrobial–catheter coating pair has different requirements that are dependent on the relative chemical relationship between the compounds in the system. Thus each system must thoroughly be tested and verified before being used in practice. The antimicrobial agents used in today's catheter systems are either exclusively or a combination of silver compounds, chlorhexidine, and other antibiotics including minocycline and rifampin in combination [31].

Antimicrobial impregnated catheters have been shown to reduce catheter infection rates [31]. However, the effectiveness of the technology depends not only on the drug combination used but also on the application conditions, the nature of the contact with the tissues, and the duration of the implant.

Another factor that plays a role in the effectiveness of the antiinfection drugs and their elution is the formation of a biofilm on the surface of the implant. A biofilm is described as a group of microorganisms in which the cells stick to each other and adhere to a surface. The biofilm shields the infection from the antimicrobial drug. Thus, another current approach in hydrophilic coating technology is to have surfaces that inhibit biofilm formation and bacterial attachment. By modifying the surface with specific chemical species and charges, protein adsorption can be delayed, which can directly or indirectly affect attachment of bacteria to the surface protein layer. Doing this cuts off the process of colonization, and if the numbers of bacteria in the local area can be kept low, biofilm formation can be reduced or delayed.

The first generation of coated medical devices in general and catheters in particular have succeeded in giving us catheters with increased lubricity, improved biocompatibility due to their antifouling properties, and durability for their applications. The next generation of hydrophilic technologies allows for enhanced functionality such as drug-delivery capabilities and suppressing the formation of biofilm structures. With further advancement in medical devices, there is an increasing identification of issues that the future coating technology needs to solve. A more developed coating in the future will not only retain the functionalities of previous coating technologies but will add on to providing a biomaterial surface that allows specific material–tissue interactions thus allowing for different cell types to cover the device surface in different locations.

3.4 Catheter Tipping

For a catheter to be advanced into its position down the vasculature, it is critical that the advancement does not cause any damage to the cardiovascular system. This is done by ensuring that the tip of the catheter is fabricated in such a fashion that it does not cause any injury during its advancement through the vasculature or in other words, it is atraumatic. The process of fabricating the atraumatic tip is termed catheter tipping or end forming. Tipping is the process of molding a rounded tip on the end of a thermoplastic tube used in the medical industry. Thus, the rounded end of the catheter tube allows the tube to be safely inserted into the human with minimal trauma to body tissue. Various tip geometries are required depending on the application of the catheter; the catheter tips may be open or closed ends, it might also involve transitioning of multiple lumens into a single lumen tip, the tips could be tapered or necked down and a special radio marker band may be placed at the tip as the location of the tip is important to monitor.

3.5 Catheter Extrusion

Thermoplastic melt extrusion with dies designed to produce circular cross-sections is used to produce catheters. Catheters can essentially be looked upon as small versions of pipe and hose manufacture; however, it is not a simple scale down and involves numerous factors for successful manufacture [32].

A typical catheter extrusion line is illustrated in Fig. 4.

Figure 4 A typical catheter extrusion line. *Courtesy: Elsevier Publications; G. Jin, M. Wang, D. Zhao, H. Tian, Y. Jin, Design and experiments of extrusion die for polypropylene five-lumen micro tube, J. Mater. Process. Technol 214 (1) (2014) pp. 50–59 [32].*

Table 3 Acceptable Moisture Levels and Drying Conditions for Common Catheter Materials

Material	Acceptable Moisture level (%)	Drying Temperature	Drying Time
Thermoplastic polyurethane (TPU)	0.02	160–220F	2–8 h
PEBA	0.08	55–80°C	2–8 h
Polyethylene terephthalate (PET)	0.005	140–160°C	4–6 h
Nylon (Polyamide 6)	0.25	70-90°C	4–6 h

The components of a catheter extrusion line are as follows:

3.5.1 Extruder

For medical catheter production, single screw extruders of screw diameters of 1" and below are preferred as the outputs with the production of the small diameter tubes are low [33]. The extruder is a melting and pumping machine and it converts solid plastic pellets into a uniform polymer melt. This melt is then forced through a tubular die at a constant rate. The frictional heat generated from the mechanical work of the screw and heat conducted from the heated barrel of the extruder provide the extruder with sufficient heat to melt the material. The length of the extruders and the screw design utilized depends on the material being used. Longer lengths and intensive screw designs are not suitable for shear sensitive materials. Excessive shear can cause degradation, that is, a reduction in the polymer's chain length and subsequent loss in the mechanical properties of the tubing. Shear rates are affected by the design of the screw, the rpm or speed of the screw, and clearances in the die. The presence of filler also impacts the screw design considerations, radio opaque fillers such as Bismuth-based compounds tend to be shear sensitive. Many tubing lines are equipped with a melt pump, in such a situation, the gear-based melt pump acts as the main flow control mechanism.

Polymer degradation greatly affects the properties of the finished catheter, any reduction in chain length results in a loss of the mechanical properties of the catheter and in extreme cases the catheter may end up completely discolored and brittle. There can be several sources of chain degradation, excessive shear, as explained earlier, can lead to degradation, a similar effect may occur with the use of the wrong temperature, too high a temperature can cause temperature-induced degradation whereas too low a temperature may cause the shear rates to increase to a high enough level to cause shear induced degradation.

3.5.2 Dryer

The presence of moisture in the extruder may also lead to degradation among certain materials, polymers such as thermoplastic polyurethanes (TPUs) and polyethylene terephthalates (PETs) will depolymerize in the presence of moisture especially at high temperatures. Therefore, drying of the polymer pellets, often the first step in most extrusion processes, is a critical step in catheter extrusion.

Drying technology for plastics has advanced through the years and different designs of dryers are available. Desiccant dryers are very commonly used in the catheter extrusion. Inside the desiccant dryer, hot dry air is pumped into the bottom of the hopper containing the resin so that it flows up through the pellets, removing moisture on its way. The hot wet air leaves the top of the hopper and is first run through an after-cooler, because it is easier to remove moisture from cold air than hot air. The resulting cool wet air is then passed through a desiccant bed. Finally, the cool dry air leaving the desiccant bed is reheated in a process heater and sent back through the same processes in a closed loop. The degree of drying is strongly dependent on the material used in the extrusion. Underdrying of some materials may cause degradation of the material in the extruder, overdrying, on the other hand, may cause thermal degradation in other materials. The specification for the drying of different plastics is usually specified by the manufacturer of the plastic. Some general drying conditions are stated in Table 3.

The moisture level also needs accurate measurement to satisfy the material requirements.

Different techniques exist for the measurement of the moisture content in a plastic material. The moisture content determination techniques include loss of weight, chemical reaction, thermogravimetric, and spectroscopic tests. The loss of weight technique or the loss on drying (LOD) technique and the chemical reaction technique of titration are widely used for plastics. When the volatile content of the solid is primarily water, LOD technique gives a good measure of the moisture content. In a typical LOD analyzer,

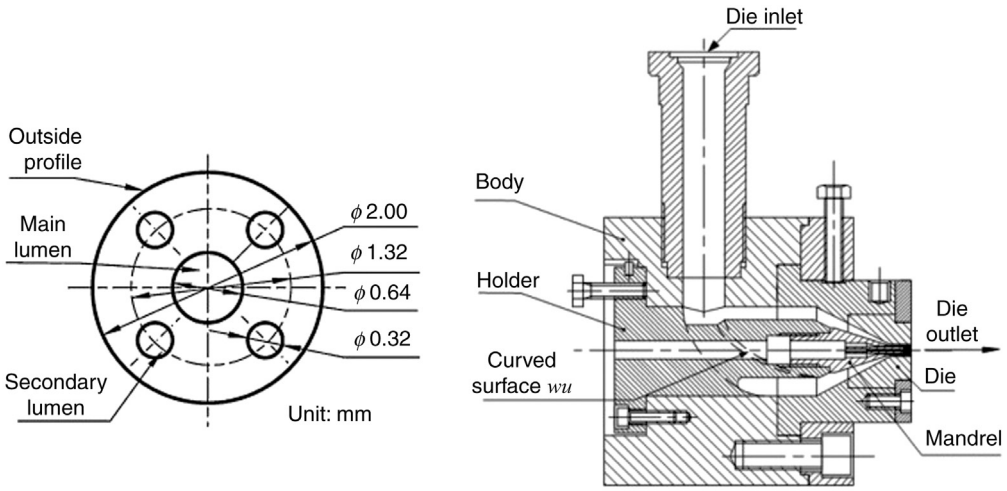


Figure 5 A drawing of the tube and die arrangement. *Courtesy: Elsevier Publications; G. Jin, M. Wang, D. Zhao, H. Tian, Y. Jin, Design and experiments of extrusion die for polypropylene five-lumen micro tube, J. Mater. Process. Technol 214 (1) (2014) pp. 50–59 [32].*

the sample is placed on a sensitive balance within the instrument, the sample is then rapidly heated and moisture content measured as the sample weight drops with the release of moisture [34]. A more accurate method for the measurement of the amount of water content is the use of Karl Fisher (KF) titration. This technique was developed in the 1930s by the German chemist Karl Fischer and is reliant on the reaction of water molecules with the KF titrant and the resultant electrical activity. The KF technique has a high accuracy and precision and in contrast to the LOD technique is selective toward water rather than any other volatile substance [34].

3.5.3 Tubing Die

The flow behavior of the material and it relation to shear and temperature can be accurately measured with rheological studies. It is, therefore, imperative to study the rheology of the polymer prior to its use as a catheter material and selecting a certain screw design. This will ensure that the plastic is extruded under the right conditions and final catheter has optimum physical properties.

An extruder die sits at the end of the extruder and forms the initial shape and dimensions of the extruded tube. Tubing die consists of two major components a mandrel or pin that forms the tube ID, and a die that forms the tube OD. The die and the mandrel constitute the extrusion head. There are a number of die, head and mandrel designs and these designs play a critical role in the extrusion process and the ability to produce precise dimensions of tubes. A drawing of a multilumen tubing die is shown in Fig. 5.

The design of extrusion dies is based on the principles of rheology, thermodynamics, and heat transfer. The quantities to be calculated are pressure, shear rate, and residence times as functions of the flow path of the melt in the die. The pressure drop is required to predict the screw design and its performance, the shear rate calculation in the die shows melt flow is within the normal shear rate range and the residence time of the melt in the dies gives an indication of the uniformity of melt flow.

In general, the relation between volume flow rate and pressure drop of the melt in a die can be expressed as [35]

$$\dot{Q} = KG^n \Delta p^n \tag{12}$$

where $\dot{Q}$ is the volumetric flow rate, G is the die constant, Δp is the pressure drop in the die, and n is the power law exponent.

For a tubular die, the die constant and the shear rate in the die are given as [34]

$$G = \left(\frac{\pi}{6}\right)\frac{(R_o + R_i)^{\frac{1}{n}}(R_o - R_i)^{1+\frac{2}{n}}}{2L} \tag{13}$$

$$\dot{\gamma} = \frac{6.\dot{Q}}{\pi(R_o + R_i)(R_o - R_i)^2} \tag{14}$$

where R_o is the outer radius of the die, R is the inner radius of the die, L is the length of die/pin, and $\dot{\gamma}$ is the shear rate.

Using modifications to these basic set of equations (12–14) accurate simulations of polymer melt flow through the die geometry are made possible by software packages such as Compuplast [36]. These

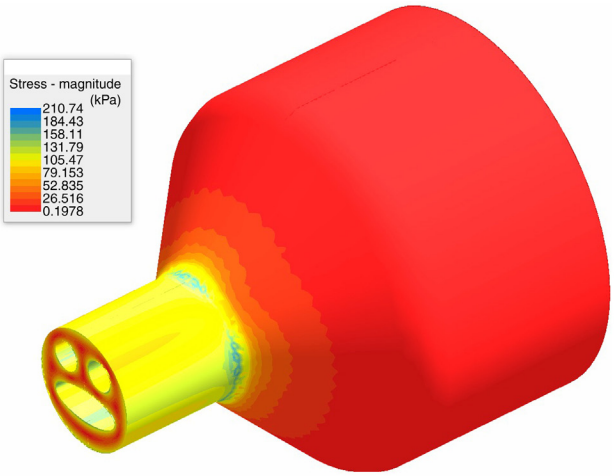


Figure 6 Polymer melt flow simulation through a multi-lumen die—the shear stress distribution. *Courtesy: Compuplast International.*

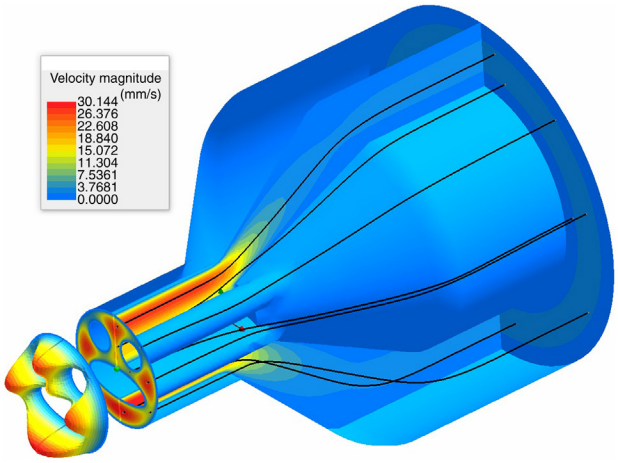


Figure 7 Polymer melt flow simulation through a multi-lumen die—velocity profile and path lines in flow. *Courtesy: Compuplast International*

simulations depend on the correct input of the material's rheological and thermal properties hence the accurate measurement of these properties is critical to the success of these simulations. These simulations can help the equipment designer and the material scientist to design the entire process so as to match the process conditions and the material properties. These simulations can go a long way in the avoidance of common issues arising out of catheter extrusion such as flow balancing, excessive melt temperatures and pressures, polymer degradation, voids, and gels. Representative output of these simulations can be seen in Figs. 6 and 7.

In these representative simulations, a multilumen die with three lumens was used and low density polyethylene was used as the melt. Fig. 6 shows the distribution of shear stress in the flow channel leading to the die; low values of shear stress signify the presence of dead spots and melt flow stagnation that could lead to problems such as degradation and gels in the extruded tubing. Fig. 7 shows the distribution of velocities at the die exit and this could be used to correct for proper mass balancing of the flow. Note that the velocity at the metal–polymer interface is always zero.

3.5.4 Post Extrusion

Polymer melts exhibit an increase in cross-sectional area whenever they emerge from extrusion dies. This phenomenon is called die swell, or more correctly, extrudate swell. Extrudate swell is a result of the extensional rheology of the polymer melt and is attributed to the memory effect that the polymer melt experiences during flow. The relationship between the die dimensions and the final catheter dimensions is known as the draw down ratio (DDR). The DDR can also be said to be the ratio of the area of the die exit and the cross-sectional area of the final annular extruded product. The die exit is formed by the die inner diameter and the pin outer diameter. The DDR calculation does not take the melt die swell into account. In most catheter operations, the value of the DDR is maintained in the range of 1.5–5.0 [33].

The DDR also results in molecular orientation and residual stresses in the tubing. The orientation can result in increase in tensile properties of the material in the machine direction but a corresponding strength decrease in the transverse direction which could result in a decrease of burst pressure of the finished tubing. Stresses can cause problems in the subsequent thermal processing such as sterilization; stresses can also be detrimental to the stability of the material in biological environments and lead to decreased biostability, a concern for longer term implants. The built-up stress is addressed by the use of an annealing process at the end of the extrusion line.

The molten polymer exiting the extrusion die is cooled using a water bath. The cooling process can be critical in the determination of the dimensions, physical properties, and the morphology of the catheter. Many polymers are either semicrystalline or have significant molecular order and the rate of cooling from a melt, that is, an amorphous state, can have a significant effect on the morphology. Rapid cooling can slow down or even eliminate crystallinity and order, slow cooling, on the other hand, can result in large crystal formation. In some applications, such as balloon manufacturing, the extruded tubing must

be amorphous prior to the balloon-forming process [33]. In other applications, increasing the amount of crystallinity may be more desirable as it can improve stiffness and lubricity. Therefore, it is important to verify cooling parameters used for the process.

From the cooling tank, the tube is cut to the appropriate length and subjected to an annealing cycle. The annealing happens in a temperature controlled oven and is designed to relieve the stresses that are stored in the tubing as a result of the manufacturing process. The annealing cycle, time and temperature, is dependent on the material that is used for the manufacture of the catheter.

Once the catheter is extruded, it has to undergo several secondary operations to be ready for its final application. The kind of secondary operations are dictated by the nature of the application.

Machining holes and other profiles into the catheter form an important part of the catheter manufacturing step as these holes perform an important role in the function of the catheter as either a diagnostic or interventionist tool. The catheters are extremely small in size so special machining devices and methods are necessary for successful drilling or punching. Precision micro-machining techniques can achieve this to a certain extent [35]. Laser technology has aided considerably in the development of these machining tools. Lasers have been successful at machining tiny holes with a high degree of precision [37]. Thermal damage is one area that needs careful attention especially when working with parts as small as catheters. A growing trend with laser beam machining (LBM) is the shift toward shorter wavelengths and delivering short laser pulses. Shorter wavelengths are better absorbed by the material and shorter pulses keep the temperature rise of the material in check avoiding instances of thermal damage. Thermal damage is also avoided in standard micro-machining technique by using the appropriate coolants and well-designed machining fixtures. Any damage caused to the part has a big impact on the functionality of the part.

As referred to earlier, a catheter may be subjected to reflow operations to join different parts of the catheter together. Reflow, in general, refers to a catheter construction process whereby the inner and outer jacket materials are "reflowed" (i.e., melted) to build a composite catheter shaft. Plastic reflow involves using heating processes where plastics change state from solid to liquid. One use of the reflow process is press fitting a metal part into a plastic part. The metal part, in the process, is heated to a temperature greater than that of the plastic melting point. Reflow can be done with the polymer material and a metallic braid, braided reflow catheters add strength, kink resistance, steerability, and torsion control to medical device tubing. A typical reflow catheter construction involves a lubricious inner liner (usually PTFE), braid reinforcement, and a polymer outer jacket. The materials are reflowed together on a mandrel using heat shrink tubing to build the desired catheter shaft properties.

3.5.5 Bump Extrusion

In many instances, a varying diameter helps with the catheter design in terms of its flexibility, pushability, and torqueability. A smaller diameter at the distal end of the catheter can be beneficial at the same time a larger diameter is desired at the other or proximal end. Traditionally this variation in diameter would be a secondary operation and involve bonding several pieces together. However, this "tapering" can also be achieved with certain in-line extrusion techniques known as bump extrusion. Bump extrusion is a fairly recent technique that is fast catching on with different manufacturers [26]. Bump extrusion details tend to vary with materials and manufacturers but the basic variables that are controlled in bump extrusion are as follows:

- Tubing line speed: Controlled variation in the line speed can control the degree of drawdown of the tubing and thus the dimensions of the tubing
- Internal air pressure: Variation of the blow-up of the melt can effectively alter the tube dimensions.
- Extruder output: Controlled change in the extruder output by changing the speed of extruder screw can affect the catheter dimensions.

Careful consideration needs to be given to all the catheter dimensions, i.e. the outer and inner diameters, the size and the number of lumens, etc. as all of them might be affected differently with the changes in drawdown ratio, air pressure, and overall output.

3.5.6 Silicone Extrusion

Polysiloxanes or silicones are thermoset in nature and cannot be extruded on standard thermoplastic catheter extrusion equipment. The components of the tubing line are similar to the catheter extrusion line for thermoplastics. However, there are key differences. The silicone extrusion process begins with blending a two-part silicone gum stock on a two-roll mill

Table 4 Properties of Commonly Used Catheter Materials

Characteristic	Silicone	Polyurethane	PTFE (Teflon)	HDPE
Biocompatibility	Excellent	Excellent	Fair	Fair
Heat sensitivity	Excellent	Poor	Excellent	Excellent
Stiffness	Soft	Softens in body	Stiff	Stiff
Ease of insertion	Difficult	Fair	Easy	Easy
Memory	Excellent	Poor	Poor	Poor
Tensile strength	Low	Medium	High	Medium
Flexibility	Excellent	Medium	Poor	Poor
COF	Fair	Medium	Excellent	Good
Coating option	Difficult	Hydrophilic	n/a	n/a
Sterilization	Autoclave or ETO	ETO	Autoclave or ETO	Autoclave or ETO
Biostability	Excellent	Fair to good (depends on nature of components)	Excellent	Good

to produce a homogeneous silicone material. The silicone is then formed into strips and fed continuously into the extruder. The extruder used for extruding thermoset silicones is a single screw with extra flight depth and the screw capable of being cooled [38]. The length-to-diameter ratio of the screw is typically10:1 to 12:1with a compression ratio of 1:1.5–1:2. The variable speed screw feed maintains proper pressure at the pin and die, and a laser micrometer monitors the tube OD throughout the process. Extrusion is carried out at room temperature, temperatures higher than 50°C are avoided to prevent scorching and any loss of the cross-linking agent. The silicone emerging from the extruder die is cured by passing through a hot oven. Hot air curing is the preferred method for initiating cure with free radical curing agents in the formulation.

3.6 Catheter Materials

One of the first materials used in catheters was plasticized polyvinyl chloride (PVC). Toxicity concerns with phthalate-based plasticizers have meant that current usage of PVC in medical devices is very limited and is used only for short-term applications as peripheral venous catheters [39]. TPUs are the key polymers for catheters as they do not need plasticizers. Polyether and polycarbonate-based polyurethanes with aromatic or aliphatic isocyanates have been prepared for catheter application [23,24]. Silicone vascular catheters are inserted for long-term access (weeks to months), frequently as access for hemodialysis. Silicone is softer than polyurethanes; therefore also thick-lumen silicone catheters have lesser risk of vascular injury [39]. However, the mechanical weakness of silicones has meant that fractures in use can occur [40]. Polyamide block copolymers (PEBA) are frequently used as they combine the flexibility of polyurethanes with the strength of nylon [41]. The balloons of interventional catheters are typically made of polyester or polyamides such as nylon 11 and nylon 12 mainly due to their high tensile strength resulting in greater burst pressures.

Many catheters are constructed with inner linings, high density polyethylene or PTFE are usually used as inner lining of interventional catheters to provide lubricious properties and ensure good sliding on the guide wire. Alternatively, other high strength polymers such as polyimide or polyether ether ketone (PEEK) can also be used as inner lining of load bearing catheters [42].

Different materials have several pros and cons associated with them and quite often it is the particular application that dictates the type of material that is used. Some of the characteristics of materials are tabulated as shown in Table 4 [43].

3.7 Catheter Insertion Technique

The process of introduction of a catheter inside the body is termed as catheterization. The introduction of catheters into the body occurs through the commonly known Seldinger technique (Fig. 8).

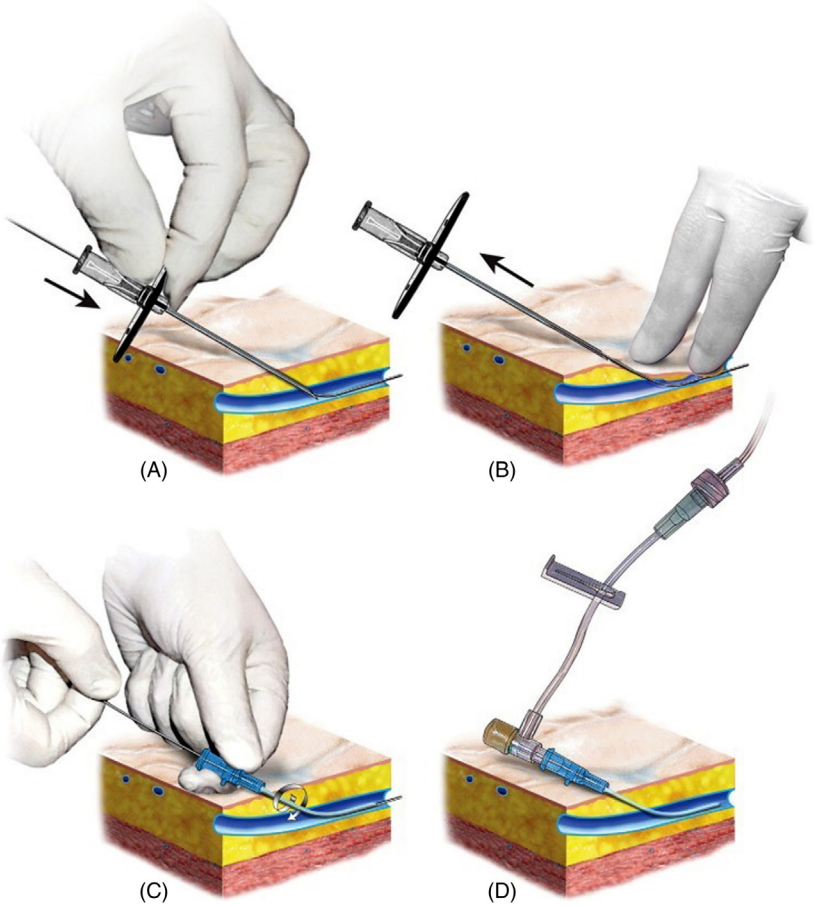


Figure 8 Seldinger technique for catheter insertion. *Courtesy: Elsevier Publications; S.H. Wald, C. J. Coté, Procedures for vascular access, A Practice of Anesthesia for Infants and Children (2009) pp. 1049–1064, Fig. 49-2 [44]).*

This technique is named after a Swedish radiologist who introduced this procedure in 1953. The technique uses a sharp metallic needle to penetrate into a blood vessel. The needle is called a trocar and the blood vessel accessed is most often the femoral artery. The radial artery or the femoral vein can also be used in certain cases. The femoral artery is preferred in many cases due to its size and a less tortuous path to the heart. Once the trocar is inserted, a metallic guide wire is inserted through the lumen of the trocar into the blood vessel. The guidewire is threaded down through the blood vessel and is primarily used to facilitate the placement of a diagnostic or interventional catheter. The guidewire is followed by an introducer sheath, the needle is withdrawn and an introducer sheath with a tapered dilator is introduced into the vessel. The introducer sheath can be made from different materials and the usual materials of construction are polyurethane, PTFE, silicone and high density polyethylene, many times the materials are coated with a hydrophilic coating. The function of the sheath is hold the vessel open and provide access to the eventual catheter into the vessel. Sheaths are primarily used to avoid trauma to subcutaneous tissues. Sheaths range from 6Fr to 7Fr in diameter and around 10 cm in length (Fig. 9).

Insertion of the sheath is performed with a dilator in its lumen. Dilators are short, stiff, thick-walled sections of catheter, available in a variety of sizes, with a long, tapered end that spreads tissues more easily than diagnostic or therapeutic catheter. A catheter is then inserted over the guidewire and threaded all the way to the heart. Once the catheter is in place, the guidewire and the introducer sheath are removed. The punctured vessel is sealed either by manual compression or the use of vascular closure devices (VCDs); VCDs are covered later in this text. During this entire process the placement and progress of the guidewire and catheter is monitored by a continuous X-ray system, fluoroscopy.

Guidewires are either solid or braided and composed of steel or an alloy of nickel and titanium, nitinol. Coiled or braided wires offer a great degree of flexibility, pushability, and kink resistance.

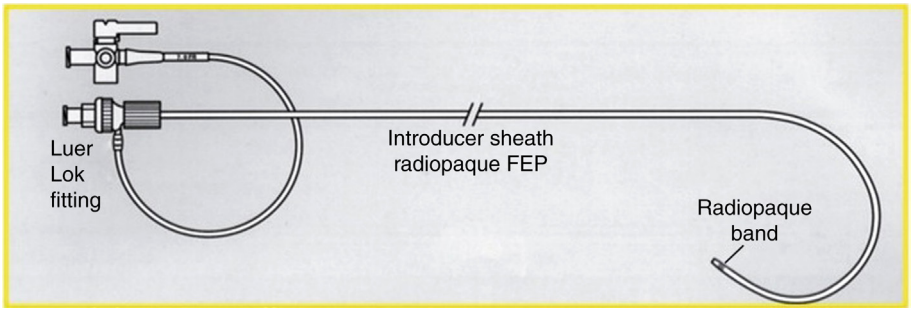


Figure 9 Introducer sheath. *Courtesy: Elsevier Publication; M.B. Silva, Jr., C.C. Cheng, Guidewires, catheters, and sheaths, Endovascular Surgery fourth ed., 2011, pp. 59–69 [45]*

Guidewires range from 0.35 mm up to 1 mm in diameter and are often coated with a hydrophilic coating for greater lubricity for easier movement in the tortuous path within the blood vessels.

Diagnostic catheterization is a useful technique to confirm or exclude the presence of a heart conditions. Noninvasive diagnostic tests such as an electrocardiogram (ECG), chest X-ray, or exercise tests give indications of heart disease in a patient and these lead to diagnostic catheterization. The diagnostic procedure can be used to measure the pressure of the different chambers of the heart, to collect blood samples, or inject a dye that allows visualization of the blood vessels within the heart in X-rays. Unlike a bone, which is clearly visible in X-rays, a special radiographic contrast dye has to be injected into the heart in order for it to be seen in X-rays. The procedure of angiography is an example where this radioactive contrast is used; the procedure relies on this contrast to pick up any obstructions in blood flow especially in the main coronary arteries. X-rays are then taken of the heart arteries indicating the build-up of plaque.

Catheters are also used in techniques of interventional cardiology for treating certain cardiac conditions. The catheters are used in techniques such as balloon angioplasty, stent placement, and AF (Fig. 10). The techniques are described in greater detail in the subsequent sections.

Figure 10 Flexability ablation catheter from St. Jude Medical. *Courtesy: St. Jude Medical.*

4 Heart Valve Devices

As we had seen in the earlier part of this text, the human heart has four valves that maintain the flow of blood within the heart and from the heart to the lungs and from the heart to the rest of the body. The valves ensure the flow of blood in one direction and avoid any flow-back or regurgitation. The operation of these valves, that is, its opening and closing depends on the contraction and expansion of the heart chambers and the resulting pressure differentials. The two atrioventricular (AV) valves are mitral and tricuspid, these AV valves ensure blood flows from the atria into the ventricles. The two semilunar (SL) valves, that is, aortic and pulmonary, are present between the ventricles and the arteries leaving the heart and their function is to regulate blood flow from the ventricles and prevent blood flowing back from the arteries into the ventricles [46].

With valvular heart disease, the functionality of any of the four heart valves in either blood flow regulation or the prevention of back flow is affected. Heart valves can be afflicted by three kinds of problems, back flow or regurgitation, narrowed opening or stenosis and no opening or atresia. There are a number of causative elements that can lead to the development of valvular heart disease, regardless of the cause; the effect of valvular heart disease is to burden the heart with an increased work rate to maintain effective stroke volume. This increased work rate can lead to effects on the heart muscle such as left ventricular hypertrophy subsequently leading to congestive heart failures [46].

The surgical options for valvular heart disease are either heart valve repair or heart valve replacement. Depending on the severity of the diseased state of the valve either heart valve repair surgery is attempted or an artificial valve is used. Artificial valves could be either biologic or metallic in nature; both the valves have their respective advantages and disadvantages

[46,47]. Traditional valve replacement surgery requires open heart surgery; alternatively a newer technique involving delivery of the valve using a catheter is a minimally invasive procedure. An artificial heart valve with a polymeric structure has been attempted by many research teams [48,49]; however, issues with thrombogenicity, calcification, biostability, etc. have prevented the use of this technology in the clinic.

Mechanical heart valves (MHVs) and bioprosthetic heart valves (BHVs) are the two principal designs of artificial heart valves used as replacement heart valves. While almost half of the implanted valves were mechanical in the late 1990s [49], more than 80% prostheses implanted in the industrialized world today are tissue valves [50].

4.1 Mechanical Heart Valves

MHVs are manufactured entirely from artificial biomaterials including metals such as titanium, cobalt, and pyrolytic carbon and polymers such as polytetrafluorethylene (PTFE), polyacetal, PET, and silicone [46]. The primary components of most types of MHVs are a hinge, stent, leaflet, and a sewing ring. To function as effective one way valves, the MHVs typically have a ball or disc to enable their valve mechanisms. MHVs designed and developed over the years have included the ball and cage valve, tilting disc, and the bi-leaflet valve. The design is composed mostly of pyrolytic carbon alloys. Pyrolytic carbon is produced when a hydrocarbon is heated to close to its decomposition temperature and allowing the graphite to crystallize. Pyrolytic carbon has a similar structure to graphite. Graphite consists of covalently bonded carbon atoms stacked in hexagonal arrays. These arrays are held together by weak interlayer binding. In contrast, pyrolytic carbon materials are arranged in disordered layers, resulting in wrinkles or distortions within layers [47]. This gives pyrolytic carbon improved durability compared to graphite. Pyrolytic carbon materials have many unique physical properties in terms of strength, durability, and wear resistance. Their surfaces are very resistant to thrombus formation and they do not elicit any adverse reactions when implanted into human bodies, that is, are very biocompatible.

Although mostly metallic, MHVs do use plastic components in their construction. One of the first heart valves commercialized was the Starr–Edwards valve. The Starr–Edwards valve used a ball-cage design; the ball used was made out of silicone. The silicone used was cross-linked with a peroxide heat-cure system. However, these silicone balls absorbed lipids and swelled, causing premature failure of the valves [46,47]. MHVs have typically a circular geometry; this circular metallic frame is attached to a fabric sewing cuff or ring. This sewing cuff is made from a fabric of PET or PTFE. Tissue integration is a requirement at the sewing cuff and fabric construction helps with tissue ingrowth into the micro-porous structure of the textile. Rapid tissue integration is very important as the sewing cuff may become a site for thrombosis, so tissue integration and endothelial cell coverage prevents thrombus formation and platelet attachment. Apart from trials with silicone as the ball in the Starr–Edwards valve, other plastics such as polyacetal (Delrin) and certain polyolefins especially ultrahigh molecular weight polyethylene (UHMWPE) have been tried as leaflet or disc materials [47] but with limited success and as a result these materials and the related designs are not utilized in any commercial valve at the present. A standard MHV and a Starr–Edwards MHV are shown in Fig. 11.

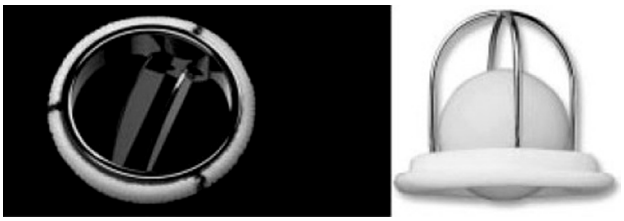


Figure 11 A Standard Mechanical Heart Valve and Starr Edwards Ball and Cage Design. *Courtesy: Elsevier Publications; M. N. H E LMU S, Biomedical Consultant, USA and C. M. C ßWoodhead Publishing Limited, 2011 U N A N A N, Cunanan Consulting, USA [45].*

4.2 Bioprosthetic Heart Valves

BHVs are composed primarily of material that is obtained from living tissue, including porcine aortic heart valve leaflets and bovine pericardium [49]. The porcine heart represents the best anatomical fit for replacement as it is most similar in structure to the human heart. Tissue harvested from the pericardial sac of cows is also used in the manufacture of the leaflets in BHVs. Tissue from the pericardial sac is particularly well suited for a valve leaflet due to its durable physical properties. The tissues, either porcine or bovine pericardium, are chemically treated

and sterilized so that the biological markers are removed, making them more compatible with the patient's immune system. The leaflets used are flexible and durable similar to the patient's natural tissue and therefore the individual with such a replacement valve does not require taking blood thinner medication on a continuous basis; this is a major differential with respect to MHVs. Compared to mechanical valves they have better hemodynamics in view of their similarity to natural flexible leaflet valves, but they have limited durability due to calcification and degeneration processes [50]. The longevity of BHVs is their main drawback as opposed to MHVs. The average expected lifespan of a BHV is between 10 and 20 years [51].

In BHVs the biological tissue is mounted on a frame to form the leaflet structure. This frame is also known as a stent. The stent can be made from a metallic wire frame or a hard plastic such as polyacetal (Delrin). Polyacetal is injection molded to form the shape of the frame. For successful use as a stent, the material has to withstand a degree of mechanical stress and creep. Stent creep testing is a standard test required of any new stent material design. The fixation elements of a BHV are made from materials similar to those used in mechanical valves. To assist in fixation, all valves contain some cloth or fabric that attaches the tissue to the stent of the BHV [46]. The cloth is typically made of PET or PTFE and permits ingrowth of cells into the cloth which helps hold the replacement valve in place minimizing thrombosis at the same time. Some may also contain additional support elements to provide rigidity and integrity to support the sutures that are used to fix the valve in the patient's heart; these include the use of an elastomeric silicone annular ring. Examples of BHVs are shown in Fig. 12.

4.3 Transcatheter Aortic Valve Implantation

The implantation of either MHVs or BHVs requires an open heart surgical procedure. The procedure itself is very involved, it is also reasonably expensive and not suitable for certain classes of patients who are not well enough to be exposed to the procedure such as the elderly. For these reasons, transcatheter valves, that is, valves that can be delivered through minimally invasive techniques, are attractive. Most of the developments of these valves have been in the aortic valve space and hence they are known as transcatheter aortic valve replacement (TAVR) or transcatheter aortic valve implantation (TAVI). TAVI is delivered through a vein, an artery or through the apex of the heart using a specific delivery system. A TAVI available from Edwards Life Sciences, Sapien valve is a trileaflet bioprosthesis made of bovine pericardium that is mounted on a balloon-expandable stainless steel stent (Fig. 13) [52]. The stent frame has an inner PET fabric skirt placed on the ventricular side covering half of the frame.

4.4 Polymer Heart Valves

The use of polymers as the leaflets in the manufacture of heart valves has many attractive possibilities. Polymer leaflets do not have animal origins and therefore are not susceptible to carrying forward embedded diseases such as bovine spongiform encephalopathy commonly known as mad cow disease, polymer leaflets are relatively inexpensive as a material, the requirement for anticoagulation medication is not necessary and the manufacturing process for leaflet production is straightforward. On that basis several

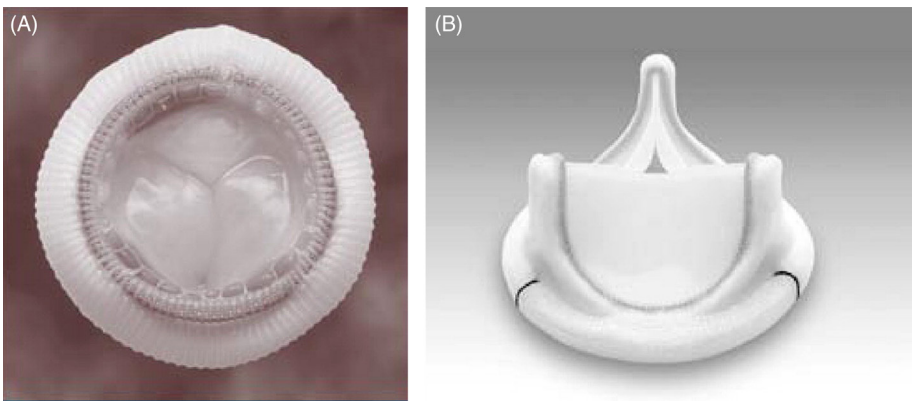


Figure 12 (A) Hancock porcine valve and (B) Carpentier–Edwards pericardium BHVs. *Courtesy: Elsevier Publications; H. Mohammadi, K. Mequanint, Prosthetic aortic heart valves: modeling and design. Med. Eng. Phys. 33 (2) (2011) 131–147 [47].*

Figure 13 Two commercially available TAVI heart valves, Top- Sapien® from Edwards Lifesciences, Bottom- CoreValve® from Medtronic. *Courtesy: Elsevier Publications; M. N. H E LMU S, Biomedical Consultant, USA and C. M. C ßWoodhead Publishing Limited, 2011 U N A N A N, Cunanan Consulting, USA [45].*

polymers have been evaluated as potential candidates to produce flexible valves for incorporation into a new heart valve design. One of the first polymers experimented with was polysiloxanes or silicones. The excellent biological properties of silicone including their biocompatibility and biostability made them an attractive choice for use as leaflets in heart valves. Various designs including different leaflet thicknesses were tried with silicones [48]. All early trials resulted in unsuccessful experiments; the lack of success in these trials was attributed to the failure of the leaflets and resultant embolism. One major drawback of silicones is their inferior physical properties. The mechanical durability of heart valves is an important aspect of their functionality. The inferior physical properties of silicones meant that they were not suitable candidates for manufacturing heart valve leaflets.

Another material that was focused on in many studies has been TPUs [49]. This is in view of their favorable physical and chemical properties combined with its flexibility in processing techniques. TPUs also demonstrate very high biocompatibility and are readily accepted by the body [48]. The biggest concern with polyurethanes was their susceptibility to degradation in the body. The presence of groups that are hydrolytically unstable was addressed by the elimination of ester groups in the soft segment of the polyurethanes. The introduction of carbonate and siloxane groups in the soft segment progressively improved the oxidative stability of TPUs [53]. Heart valves made with polyurethane leaflets typically have a hard plastic stent, using an injection molded frame of PEEK upon which the leaflets are dip molded (Fig. 14). Many groups used this sort of design and had different degrees of success with their trials [49]. However, a combination of mechanical durability and thrombogenicity meant that in spite of promise these polyurethane heart valves have so far not seen commercial applications.

PTFE was tried as a leaflet material in a few trials. In all the trials, a fabric of PTFE was used; in certain cases the expanded form of PTFE, ePTFE was used. In all cases, however, extensive calcification was noted and that resulted in stiffer leaflets and regurgitation. Other materials such as poly(styrene-b-isobutylene-b-styrene),

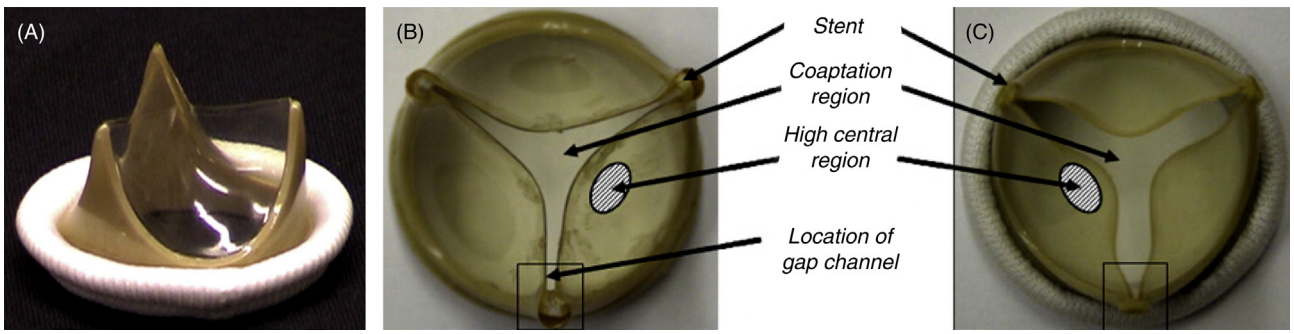


Figure 14 Polyurethane heart valves *Courtesy: Elsevier Publications; D. Bezuidenhout, D. Williams, P. Zilla, Polymeric heart valves for surgical implantation, catheter-based technologies and heart assist devices, Biomaterials 36 (2015) 6–25 [48].*

known as SIBS, and cross-linked ethylene-propylene-dienemonomer (EPR) rubbers have also been tried but with no success.

5 Heart Failure Devices

Heart failure is a major affliction affecting millions of people across the world. Heart failure has high mortality rate with one in every five affected; heart failure accounts for more than 7% of deaths due to cardiovascular disease. Heart failure has many causes including coronary atherosclerosis, hypertension, and congenital issues. Heart failure causes an insufficient supply of blood to the body; this causes a volumetric expansion of the left ventricle to keep up with the requirements of the body. This volumetric expansion weakens the heart muscle and further increases the size of the left ventricle. This leads to a significant increase in the size of the heart and this enlarged heart "congests" the chest; therefore another term for this is congestive heart failure. Transplantation has been the only solution to stop the progress of heart failure. However, transplantation is limited by the number of donor hearts available and as a result many patients in need of transplantation do not receive the hearts in time. An alternative to transplantation led to the development of mechanical circulatory support systems such as VADs and artificial hearts [54–56]. The VADs are used to supplement the functioning of the heart and are used either as a bridge to transplant, that is, waiting for a donor heart or in certain cases as a permanent or "destination" therapy. Artificial hearts, on the other hand, completely take over the functioning of the heart and can be similarly used as bridge to transplant or destination therapies.

5.1 Ventricular Assist Device

A Ventricular Assist Device (VAD) is a mechanical pump that is used to support heart function and blood flow in people who have ventricles that have significantly weakened and can no longer provide adequate blood supply to the entire body. VADs can assist the function of ventricles in general, that is, both right and left ventricles. The two basic types of VADs are a left ventricular assist device (LVAD) and a right ventricular assist device (RVAD) [54]. If both types are used at the same time, they are called a biventricular assist device (BIVAD). The LVAD is the most common type of VAD. It helps the left ventricle pump blood to the aorta. RVADs usually

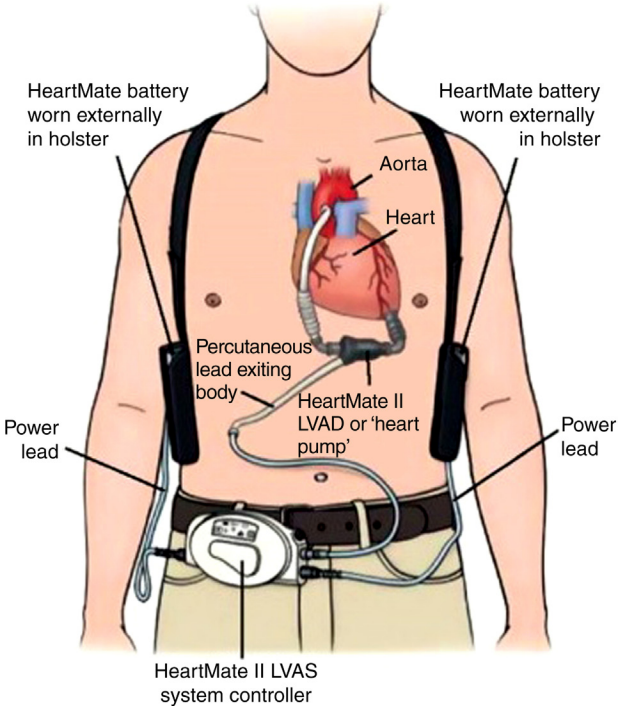


Figure 15 Schematic overview of the HeartMate II™ LVAD design and components. *Courtesy: Elsevier Publications; A.M. McDivit, J.G. Copeland, E.D. Adler, Ventricular assist devices, Ref. Module Biomed. Sci. (2014) 2014)*

are used only for short-term support of the right ventricle after LVAD surgery or other heart surgery. An RVAD helps the right ventricle pump blood to the pulmonary artery.

An LVAD may be implanted in the upper abdomen, chest, or inside the pericardium either extraventricular or transventricular as shown in Figs. 15 and 16. The inflow for long-term LVADs is typically from the apex of the left atrium via a cannula to the pump, and the outflow of the pump is connected to the ascending aorta via a graft.The device takes blood from a lower chamber of the heart and helps pump it to the body and vital organs, and tries to simulate the functioning of a healthy heart.

The central part of an LVAD is its pumping mechanism. The pumps used in LVADs are of two main types: pulsatile pumps and continuous flow pumps. Pulsatile LVADs use positive displacement pumps that mimic the natural pulsing action of the heart. Continuous flow pump use either a centrifugal pump or an axial flow pump for its pumping action. Due to the rotary action of the pump, a continuous flow VAD might not give rise to a normal pulse, but your body gets the required amount of blood. Continuous flow pumps are smaller and more durable than pulsatile

Figure 16 The VentrAssist™ left ventricular assist device (Ventracore, Chatswood, NSW, Australia). *Courtesy: Elsevier Publications; A. Kumar, P.S. Khanwilkar, 6.625 – Long-term implantable ventricular assist devices (VADs) and total artificial hearts (TAHs), Ref. Module Mater. Sci. Mater. Eng. Comprehens. Biomater. (2011) 389–402 [54].*

flow pumps [54]. An important issue with continuous flow pumps is the method used to suspend the rotor. Early versions used solid bearings; however, newer pumps, some of which are approved for use in the European Union, use either electromagnetic suspension ("maglev") or hydrodynamic suspension. Apart from the pump there are two other critical parts of an LVAD system; these are the electronic controller and the power supply. The electronic controller is usually a microprocessor chip–based controller that can adjust functions of the pump, such as pumping speed and provide diagnostic, alarms, alerts, and communications to an external monitoring system. The power supply for the pump is given by two external batteries and that power is transmitted to the electronics in the VAD via a cable inserted through the abdomen. The batteries are carried outside the body usually in underarm holsters or a waist pack.

A VAD itself has several basic parts (Figs. 15 and 16). A small tube or cannula carries blood out of the ventricle into the pump. Another tube carries blood from the pump to the aorta, which delivers the blood to your body. Where the blood flows from the left ventricle into the pump is known as the inflow cannula. As the pump creates suction, the inflow cannula has to have the ability to withstand the suction forces without collapsing. The inflow cannula is, therefore, made from either a semirigid polymer or metallic frame. The outflow cannula is similar in construction to a vascular graft and carries the blood from the pump to the aorta. The inflow cannula and outflow cannula is made in many devices from PET or polytetrafluoroethylene. The pumps are metallic usually titanium-based alloys. The power supply cord does not have any strict mechanical requirements; silicones are typically chosen for the insulation of the power supply cords due to their biocompatibility and biostability [57].

5.2 Total Artificial Heart

An artificial device to take over the complete functions of the heart would eliminate the need for a heart transplant and the availability of a donor heart. However, the development of such a device has been very challenging and so far technology has progressed to the clinical use of these total artificial hearts (TAH) as a temporary device. That means that these devices are used as bridge to transplant devices still requiring a donor heart. Advances in pumping technology, battery design, and biomaterials means that these TAH devices are showing increasing longevity and in certain cases are moving toward use as destination therapies [56]. A TAH is similar in design and operation as a VAD but the fact that it takes on the entire operation of the heart, presents many more challenges than a relatively simpler VAD.

The first clinically used TAH was developed at the University of Utah by a team of researchers lead by Dr. Robert Jarvik; hence the first devices were called Jarvik TAH. The basic concept of the many present day TAHs are similar to the Jarvik device [54]. Jarvik TAH utilized pneumatic pumping mechanisms to drive two ventricular pumps that were joined together and then fastened to the heart's natural atria using a PET-based felt attachment. The ventricles are ellipsoid shaped and constructed of polyurethane that has a sac that pushes the blood from the inlet to the outlet valve. The inflation and deflation of the sacs occur by air acting on the nonblood side of the sac. Air is pulsed through the ventricular air chambers at rates of 40–120 beats per minute (bpm) simulating the natural beating pattern of the human heart. The polyurethane diaphragms are constructed from dip molding into solutions containing polyether-based

polyurethane urea [56]. The diaphragms are connected to the atria by PET-based cuffs. The valves in the conduits tend to be MHVs. The drive lines for the diaphragms are reinforced polyurethane tubes. It is critical that the TAH functions similar to a natural heart, that is, works constantly without stoppage. The main properties that are required of a material for the construction of an effective diaphragm are good blood compatibility, biostability, infection resistance, good flexural properties, and mechanical robustness. Issues with the use of polyurethanes in TAH have been reported, issues such as calcification, degradation, surface cracking and device infections, these issues have so far limited the use of TAH as destination therapies [58–60]. Two representative TAHs are shown in Figs. 17 and 18.

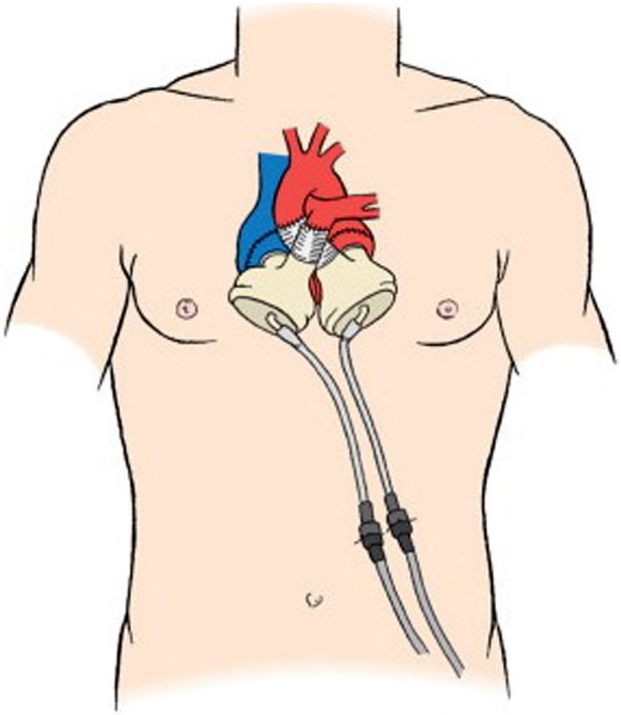
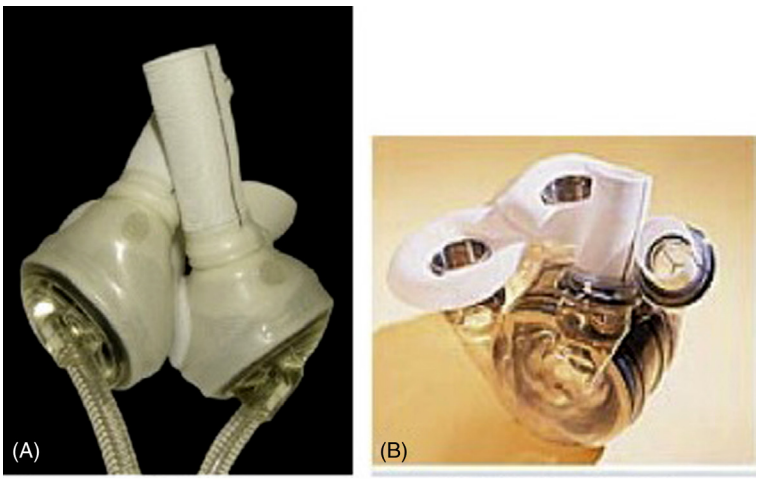


Figure 17 SynCardia total artificial heart (TAH) *Courtesy: Elsevier Publications; A.M. McDivit, J.G. Copeland, E.D. Adler, Ventricular assist devices, Ref. Module Biomed. Sci. (2014) 2014.*

6 Cardiac Rhythm Management Devices

Cardiac arrhythmia is the disruption of the electrical activity of the heart that results in the irregular beating of the heart. Depending on the nature and severity of the arrhythmia, different therapies can be prescribed by the doctor. In many cases, antiarrhythmic drugs are the first option. Cardiac ablation is used for AF cases when antiarrhythmic drugs do not have the desired effect. Implantable devices such as pacemakers and defibrillators are used for bradycardia and tachycardia. These implantable devices apply electrical shocks to maintain the rhythm of the heart and if necessary restart it.



Jarvik-7

AbioCor implantable replacement heart

Figure 18 (A): Total artificial heart—Jarvik-7. (B): The AbioCor total artificial heart. *Courtesy: Elsevier Publications; A. Kumar, P.S. Khanwilkar, 6.625 – Long-term implantable ventricular assist devices (VADs) and total artificial hearts (TAHs) Ref. Module Mater. Sci. Mater. Eng. Comprehens. Biomater. (2011) 389–402 [54].*

Figure 19 Ablation catheter with an irrigated radio frequency head. *Courtesy: St. Jude Medical, Therapy™ Cool Flex™ ablation catheter.*

6.1 Ablation Catheters

Cardiac ablation is a minimally invasive procedure in which the doctor threads a flexible thin catheter through the blood vessels to ablate or destroy the tissues causing abnormal electrical pathways in the heart [61]. Cardiac ablation is done through the use of catheters inserted through a vein in your limb and threaded to the heart. Ablation essentially scars or burns the tissue that causes arrhythmia; this scarring is done with the help of radiofrequency (RFA) or with the aid of very low temperatures (cryoablation) as in Fig. 19.

The ablation catheters are basically single or multilumen extrusions made from primary cardiac catheter materials such as polyurethanes, PEBA, etc. The challenge in designing cardiac catheters is that they need to be relatively inflexible toward the proximal end and flexible enough toward the distal end to be able to maneuver through narrow and winding blood vessels without causing trauma to them [61]. This variation in flexibility, as explained earlier, is obtained as a result of using variable hardness materials at different parts along the catheter length. The different hardness materials are bonded together using either adhesives or a thermal process such as the reflow technique.

6.2 Implantable Devices

Depending on the severity of the arrhythmia, the doctor can prescribe the use of implantable devices. The implantable devices can address the issues of a fast beating heart, tachycardia (heart beats $>$ 100 beats/min) or a slow beating heart, bradycardia (heart beats $<$60 beats/min).

Figure 20 A pacemaker. *Courtesy: St. Jude Medical, Accent™ pacemaker.*

Pacemakers are designed to treat bradycardia whereas implantable cardioverter defibrillators (ICDs) are used to treat tachycardia (Fig. 20). A pacemaker monitors the heart beat and if it detects a slow rhythm, it sends out low voltage electric signals through the insulated leads to the heart to correct the issue. A recent development in the area of pacemakers is the introduction of leadless pacemakers. St. Jude Medical (Nanostim) and Medtronic (Micra) have introduced these leadless devices (Fig. 21) that can be placed directly in the heart and do not need leads to deliver shocks.

An important role of the pacemaker is to be able to provide electrical stimulation to the right portions of the heart at the right time [62]. This is an important aspect of the sensing mechanism of the pacemaker and the avoidance of unnecessary stimulation by sensing

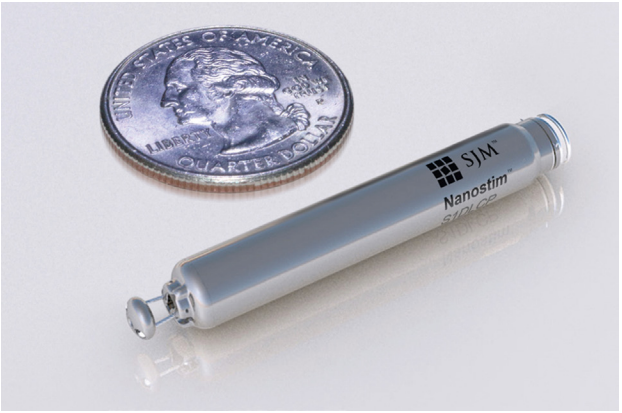


Figure 21 Leadless pacemaker. *Courtesy: St. Jude Medical, Nanostim™.*

of the natural heart rhythm is critical. The function of the pacemaker is the stimulation of a depolarization wave that readily spreads throughout the entire heart. The engineering challenges for these devices include providing or withholding pulses and/or adjusting their timing to make them as physiological as possible [63].

6.2.1 Functioning of a Pacemaker

Cardiac stimulation requires energy and the energy generated by each stimulus is dependent on output parameters that are programmed in the pacemaker's memory. Electrical energy is governed by Ohm's law,

$$V = IR \tag{15}$$

where V is the voltage, I is the current, and R is the resistance.

During pacing or sensing, the voltage always remains constant but the resistance and, as a consequence, the current can vary from patient to patient. The resistance of the device is a function of

- Conductor wires
- Tissue between the electrodes
- Interface between the electrode and the myocardium

An increased resistance results in a lower current in the device and a lower current is associated with a greater longevity of the device.

The programmable characteristics of the pacemaker that decides the amount of energy delivered by the device to the tissue depends upon the intensity of the beats of the heart. The beats, as described by the pulses, are affected by degree of polarization, the resistance of the tissue, and the density of the current. The pulse amplitude and the pulse width define the output of a pacemaker. The pulse amplitude is measured in volts and can be described as the intensity of the output; the pulse width, on the other hand, is a measure of the length of time the output energy is delivered to the cardiac tissue [64].

Every time the pacemaker delivers electrical energy to the heart and initiates depolarization, the reverse effect of polarization occurs near the electrode of the pacemaker. In some cases, polarization may be interpreted by the pacemaker as a signal from the heart and it may respond inappropriately. The polarization is affected by different factors [62]:

- Surface area of electrode tip
- Current flow into the electrode
- Material of construction of the electrode
- Duration of the pulse

The tip of the electrode can contribute not only to the polarization effects but also to the current density of the pacemaker. A high current density tip is therefore considered desirable for efficient pacemaker operation.

Pacing and sensing are the two basic functions of any cardiac device lead. For this to occur efficiently the requirement for the device is the existence of conductors for current flow between the pulse generator and myocardium and insulators over the conductors to prevent short-circuiting of this current. The pacing and sensing function can be set up in a couple of ways; the negatively charged lead electrode tip can act as a cathode whereas the pacemaker can or the pulse generator acts as the positively charged anode [64]. In such a case, the electrons from the electrode tip flow from electrode tip through the myocardium and the thoracic cavity to the positively charged pulse generating metallic can. Such an arrangement is called a unipolar lead circuit. The basic drawback of the unipolar system is the distance between the cathode and anode. The distance can cause issues with oversensing of myocardial signals. Signal oversensing can lead to major consequences in the performance of the device. This oversensing can be avoided by the use of a bipolar configuration (Fig. 22). In a bipolar arrangement, there are two electrodes on the lead and hence the pulse generator does not act as the anode in the circuit. The bipolar lead is primarily used in the current construction of pacemaker leads.

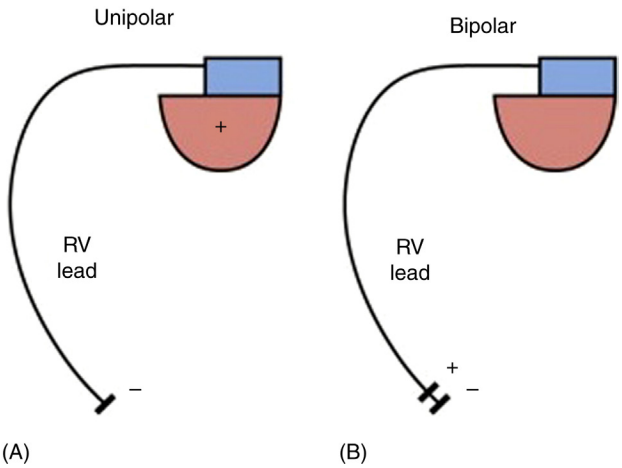


Figure 22 Unipolar and bipolar arrangement in a pacemaker. *Courtesy: Elsevier Publications; Haqqani et al. Engineering and Construction of Pacemaker and ICD Leads [63]*

The minimum amount of electrical energy required to consistently trigger depolarization in the heart through a given electrode is known as cardiac stimulation threshold. After the implantation of the pacemaker, there is resulting inflammation and tissue growth around the newly implanted electrode. This results in a variation of the energy requirements of the pacemakers and may take weeks or months to stabilize. To minimize this inflammation and to keep the cardiac stimulation threshold from rising, pacemakers tend to have a steroid eluting plug placed at the tip of their electrodes. The elution of steroid, such as dexamethasone sodium phosphate, helps with the control of inflation and keeps the cardiac stimulation threshold at a stable value [64].

6.2.2 Pacemaker Implant Technique

The subclavian vein is most often used for implantation of the pacemaker, occasionally; other veins such as the cephalic and auxiliary vein may be used. An incision is made beneath the collar bone and a pocket is created to house the pacemaker can. In addition to creating a pocket for the can, the incision also provides access to the vein for lead placement (Fig. 23). The vein is accessed and using the Seldinger technique the leads are placed into position [65].

For placement of the lead into the right ventricle, the lead enters the right atrium through the superior vena cava and descends to the bottom of the right ventricle. The leads could have an active or passive fixation technique. In active fixation, the tip of the lead is screwed on to the myocardium whereas in a passive fixation technique, the lead is placed in contact with ventricular tissue and fibrotic tissue grows on it over a 6 to 8 week time period [65]. The placement of the lead in the right atrium can be similarly active or passive and follows a similar delivery route to the lead meant for the ventricle but ends earlier in the atrium. A fluoroscopic X-ray is used to confirm the correct placement of the leads.

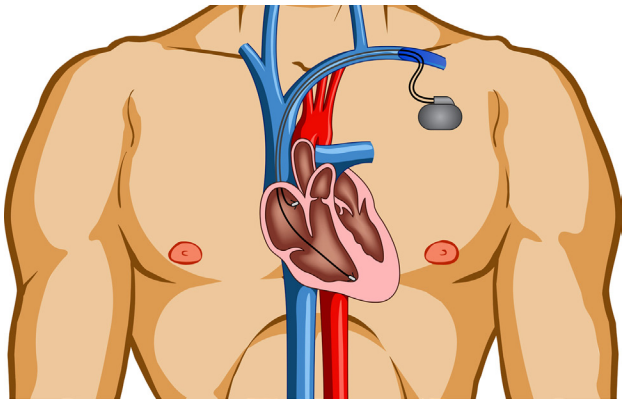


Figure 23 Insertion of the leads of the pacemaker into the heart.

6.2.3 Implantable Cardioverter Defibrillator

ICD, on the other hand, is implanted to treat cases of tachycardia or fast heart rate. An ICD monitors the heat and if it detects a fast rhythm, it sends out a low to high voltage electrical signal to restore normal heart beat. An ICD is therefore very useful for all cases of ventricular fibrillation and ventricular tachycardia. ICDs are very similar in construction to the pacemaker as described earlier. The ICD contains the electronic circuitry inside a titanium can; it is connected to the wires or leads through a plastic connector or header. The leads are passed through a vein to the right chambers of the heart. The lead is usually anchored in the apex of the right ventricle. Just like pacemakers, ICDs can be made to stimulate just the right ventricle (single lead), the right atrium, and right ventricle (two leads) or have three leads to stimulate the right atrium, right ventricle, and another lead present on the walls of the left ventricle [66]. ICDs, however, can stimulate the heart at a much higher voltage as compared to a pacemaker, the maximum voltage an ICD can achieve is ~800 V as opposed to 8 V in a pacemaker system [66]. The implantation technique for an ICD is similar to the implantation technique for a pacemaker. A newer development in the field of ICDs is the use of a subcutaneous device (S-ICD), in the S-ICD, the leads are inserted subcutaneously obviating the need for their insertion through the veins and into the heart [10].

6.2.4 Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is used in cases where there is a lack of synchronization between the pumping actions of the chambers of the heart. This often means that the right and left ventricles of the heart do not pump together and can lead to the left ventricle not pumping enough blood as required by the body. This can eventually lead to heart failure. Even though this lack of synchronization of the heart's pumping action is a cause for heart failure, CRT is frequently classified with the CRM devices. The CRT device is a special kind of pacemaker and using biventricular pacing to achieve

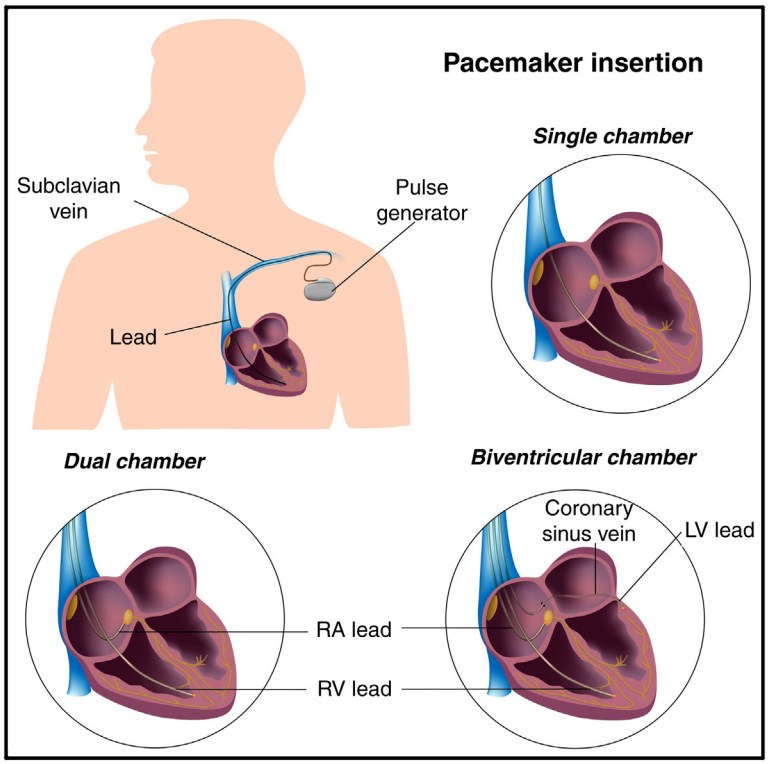


Figure 24 Placement of the leads of the pacemaker into the heart.

synchronization. Biventricular pacemakers add a third lead to help the left ventricle have a normal contraction (Fig. 24). The construction of CRT devices is similar to the pacemaker and ICD devices, in that they are made up of a metallic can, plastic header, and insulated leads.

6.3 CRM Device Construction

Both pacemakers and ICDs consist of a metallic can and wires that go along the blood stream inside the heart muscle. The can is implanted subcutaneously usually below the collar bone. The metallic can, usually made out of titanium, houses the main electronic circuit and the battery for the operation of the circuit. A plastic cap is joined on to the top of the can; this cap also known as the header acts as the link and connects the electrical signals from the wires to the electronics in the can and vice versa.

6.3.1 Device Header

The header needs to have certain hardness and also be transparent. These properties are essential as the connectors from the wires are metallic. A hard header is required so as to be relatively inflexible with respect to the inserted conductors. Transparency is desirable to visually ensure the correct placement of these conductors [67]. The can with the header is placed in a pocket under the collar bone; the wires that travel inside the heart are then joined to the can (Fig. 25).

The header is usually made out of epoxy or a harder grade (>70D) polyurethane. Epoxy headers are molded from a reactive mixture and then glued on the can using silicone-based medical adhesives. Polyurethane headers are injection molded and

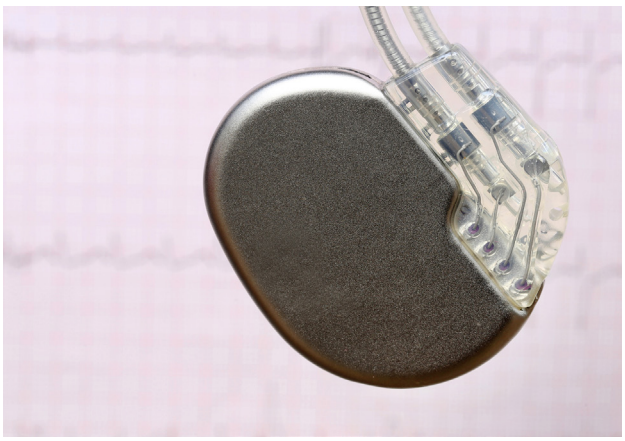


Figure 25 CRM device header.

joined to the cans using both mechanical interlocks and silicone adhesives.

Epoxy headers can be directly molded on to the titanium can. Prior to molding, the can is primed, usually with a silane-based primer, to aid the adhesion of the epoxy header to the can. The connectors from the electronics in the can are fed through and protected with screws and metallic inserts so as to ensure their conductivity. The can is placed in a silicone mold with a cavity in shape of a header; suitable inserts are placed to protect the conductive connectors coming from the can as well as for the creation of holes for the placement of leads. Once the injection step is complete, the header is inspected for any defects or bubbles [68]. Any bubbles observed are pulled out with the aid of vacuum before the header is cured into a solid. The mold is then placed in a curing oven with circulating inert nitrogen. After the cure is complete, the header is further polished, adhered to the can with a silicone-based adhesive and finished for final use with the device. The entire epoxy header molding process is labor intensive and time consuming. The use of injection molding, using thermoplastic polyurethanes, is a more automated process reducing the labor and time from the epoxy header molding process. The high temperatures and pressures involved in the thermoplastic injection molding process mean that the header cannot be directly molded onto the can of the device. The injection molded header is fixed to the can with the use of mechanical locking mechanisms and the use of a silicone adhesive. The material used in the injection molding process is high hard block polyurethane. The hard block percentage levels are greater than 60% resulting in a material hardness of higher than 70 Shore D. As the hard block levels are so high using a polyether-based polyol for the soft segment does not create any issues with biostability.

6.3.2 Device Leads

The wires, also referred to as leads, are delivered into place inside the heart with aid of a catheter-based delivery system. The leads have metallic conductor coils made out a nickel – titanium alloy, and these are covered with a plastic insulation. There are two main types of bipolar lead designs for pacemakers. The coaxial lead design and the co-radial lead design (Fig. 26). Coaxial leads have an inner conductor that extends down to the to the tip electrode at the end of the lead, the cathode [63]. The inner conductor is covered with an inner insulation; this coil and insulation arrangement is wrapped by another coil which is connected to the anode. Another layer of insulation

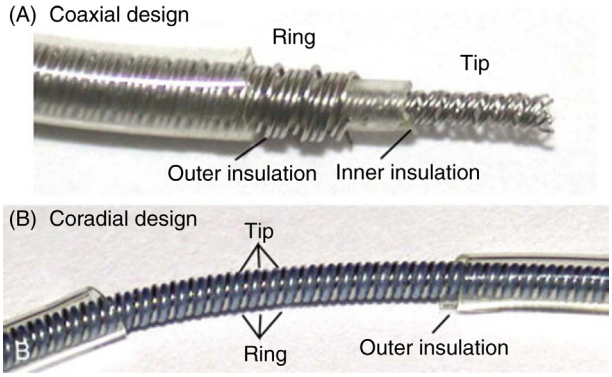


Figure 26 Coaxial and co-radial lead design for CRM devices *Courtesy: Elsevier Publications; Haqqani et al. Engineering and Construction of Pacemaker and ICD Leads.*

covers the outer coil and protects it from the environment. The coaxial designs have been widely used in the industry; however, their four layer design makes them bulky and stiff. The coradial design addressed some of these concerns by using two parallel, alternating conductor strands one connecting the cathode and the other connecting the anode. Each conductor strand is individually insulated. The concepts of the coradial design have also been successfully used in ICD lead design [63]. ICD leads have a greater complexity with multiple coils connecting to the pacing/sensing electrodes as well as to the high voltage shocking coil. A depiction of an example of the ICD lead is shown in Fig. 27, here each individual coil is wrapped in a separate insulation layer (PTFE based), all the coils are surrounded by another layer of insulation (silicone based), and finally polyurethane insulation encapsulates the entire lead.

The materials used for the insulation of pacing leads are a very important component of the pacemaker or defibrillator device. Any issues with the material in the application can lead to failure of the lead to sense and regulate the current flowing through it and subsequently lead to device failure with serious consequences. A combination of desired properties for lead insulation such as flexibility, toughness, abrasion resistance, and strong insulation for electrical conductors is required of the materials used. Elastomeric polymers offer this combination and as a consequence have had a history of use in implantable cardiac applications [69,70]. The medical device industry has primarily used two elastomeric polymers for decades—silicones and TPU. Silicone rubber (polysiloxanes) is typically available in low durometers offering excellent flexibility and biostability. The biological properties of silicones are very favorable

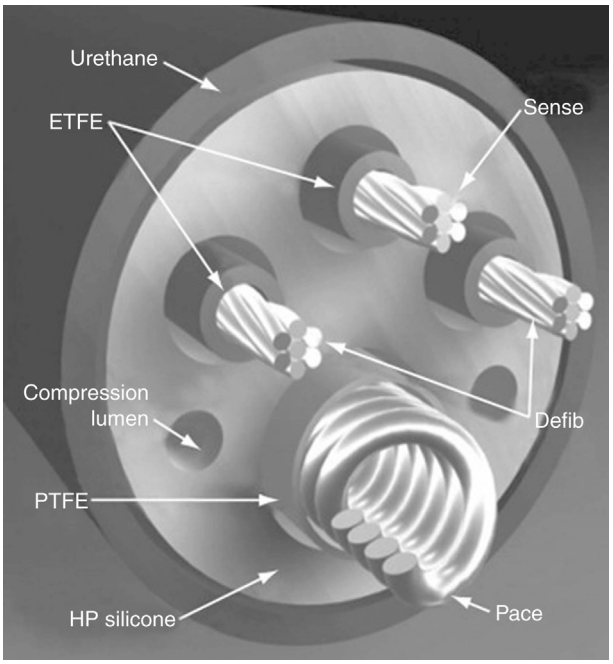


Figure 27 ICD lead insulation structure. *Courtesy: Elsevier Publications; Haqqani et al. Engineering and Construction of Pacemaker and ICD Leads.*

as they have a high degree of biocompatibility and biostability. However, they possess relatively poor mechanical strength, tear, and abrasion resistance. This poor mechanical strength means that silicone insulations are more prone to abrasion failures and tears. The inadequate mechanical strength combined with high surface friction make silicone leads more susceptible to damages during implantation. Traditional TPUs can offer mechanical robustness with superior toughness and tear resistance; however, they have been shown to be vulnerable to biostability as demonstrated in studies by Stokes et al. and Wiggins et al. [72,73].

TPUs obtain their elastomeric properties through the use of a combination of hard and soft polymer block segments. It is seen that the chemical composition of the soft blocks is susceptible to the hydrolytic and oxidative degradation pathways within the body. TPUs made of soft segments comprising polyesters are widely used for industrial applications and were used early on in the medical device industry but deemed unsuitable for long-term implants due to hydrolytic degradation of the aliphatic polyester soft segment [70,71]. Polyether-based TPUs replaced polyester TPUs as the ether groups in them offered superior hydrolytic stability. These changes, however, did not address oxidative stability which is of much greater concern in pacemaker and defibrillator lead applications [73,74]. In the 1980s, large numbers of pacemaker lead failures were noted that resulted from oxidative degradation involving metal ion oxidation (MIO) and environmental stress cracking (ESC) of polyether-based PU (Pellethane 80A) [69,70]. The environment for pacing lead insulation is very challenging as in addition to the standard hydrolytic conditions, the oxidative degradation conditions are exacerbated due to the presence of metal ions as a result of the conductors present inside the lead. The metal ions tend to catalyze oxidation and so for a polymer to survive in a lead insulation application, exceptional oxidative resistance is paramount.

The use of hydroxyl terminated siloxane as the soft segment in TPUs was attempted as an answer to combining the advantageous properties of both materials, silicones and urethanes; however, early attempts at synthesizing these materials were challenging due to the thermodynamic dissimilarity between the nonpolar siloxane soft segment precursors and the polar isocyanates. This resulted in low molecular weight polymers with inadequate mechanical properties as a result of premature phase separation during polymerization. Later, it was identified that a second soft segment of intermediate polarity, a polyether polyol, could be used as a "compatibilizer" to facilitate the formation of high molecular weight polymers with polydimethyl siloxane (PDMS) and methylene diphenylene isocyanate (MDI) [73]. One example of PDMS-based polyether urethane, Elast-Eon 2A (E2A), synthesized utilizing 20% poly (hexamethylene oxide) PHMO/80% PDMS for the soft segments and MDI/butanediol (BDO) for the hard segments, has been shown to be significantly more biostable through improved resistance to oxidation and hydrolysis over polyether- and polycarbonate-based PUs through a number of in vitro and in vivo studies [75–77].

In a study by Simmons et al. [76], Elast-Eon 2A (E2A) was tested for biostability in vivo along with commercial control polyether- and polycarbonate-based polyurethanes; Pellethane 2363-80A, Pellethane 2363-55D, and Bionate 55D for periods ranging from 3 to 24 months. All samples were explanted and examined using scanning electron microscopy (SEM), attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), and X-ray photoelectron spectroscopy (XPS) to investigate surface morphological changes. Gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and tensile testing provided bulk characteristics. These results revealed the flexible silicone polyurethane E2A provided significantly better biostability than the control material having similar

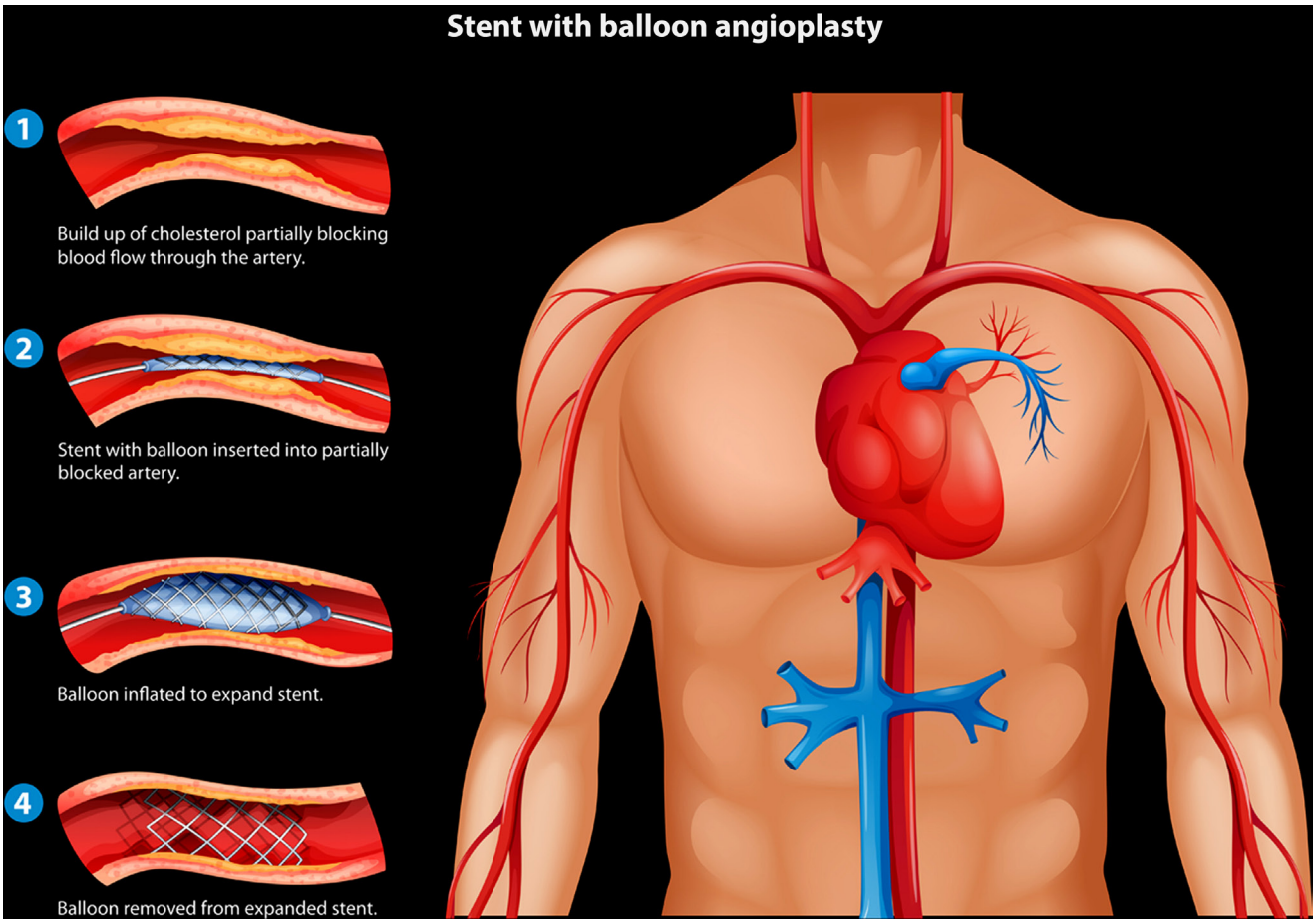


Figure 28 Balloon angioplasty with stent placement.

durometer (softness), Pellethane 80A, and equal or superior biostability to both of the higher durometer negative control polyurethanes, Pellethane 55D, and Bionate 55D.

A comprehensive assessment of cardiac lead insulation for over 5 years of human implantation was recently reported [78]. This study employed microscopy imaging, molecular weight determination, FTIR spectroscopic analysis, and tubing tensile properties to evaluate the performance of polyether-based polyurethanes of varying hardness and E2A. The conclusion shows that the robustness of the siloxane based E2A is on par, if not superior, to the performance in vivo of the harder formulation (55D) in polyether-based TPU.

The fluoropolymers, PTFE and expanded PTFE (ETFE) have certain advantageous properties such as high biostability and good abrasion properties [39]; however, these materials have a high degree of stiffness and therefore are limited in use in inner layers of insulation. They are used as a thin coating on conductor strands; this inner insulating layer can prevent electrical communication between conductor strands and can also protect them from interacting with an adjacent outer layer of polyurethane, thereby reducing MIO.

7 Cardiac Artery Disease Treatment Applications

The treatment for coronary artery disease (CAD) can be either opening up of the blood vessels or providing an alternative pathway for the blood to reach the heart. The technique of balloon angioplasty is usually used wherein a balloon is inflated within a vessel to compress the plaque against arterial walls to open up the vessel and increase flow. Frequently balloon angioplasty is followed with the placement of a stent (Fig. 28). Stents are metal scaffolds that give support to the blood vessel (Fig. 29). Stents can be infused with drugs that elute over time; these drugs help in the healing process of the vessel by preventing restenosis. Another approach in the treatment of CAD is the provision of an alternative pathway for

Figure 29 Stent.

the blood; this bypass can be using a vein from the patient's body (saphenous) or a synthetic graft. The bypass creates new pathways for blood by circumventing the blockage site (Fig. 30).

7.1 Balloon Angioplasty

The technique of balloon angioplasty is referred to as percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI). Improving technology and catheter-based techniques have broadened the spectrum of lesions that are amenable to PTCA [79]. The increasing use of vascular stents in the treatment of thrombotic lesions has further increased the number of applications for balloon angioplasty.

In angioplasty, the inflation of a tiny balloon is used to widen an artery that has been narrowed by plaque formation (Fig. 31). A wire is threaded through the artery past the site of the blockage, a catheter is then guided to the plaque. The location of a catheter in relation to the plaque is constantly monitored through fluoroscopy using radiopaque markers on the catheter at each end of the balloon [80]. When the balloon is at the exact position, it is inflated with saline forced through a syringe and exerting high pressure on the balloon. The inflation compresses the plaque against the walls of the artery thereby widening the artery and enabling normal blood flow to the muscle. When the balloon is inflated, the proximal and the distal ends inflate first, and the middle section or the body of the balloon forms a waist [80]. The middle portion of the balloon is usually located at the segment of most severe blockage of the vessel. For retraction, a vacuum is pulled through the balloon to collapse it and the catheter is then withdrawn.

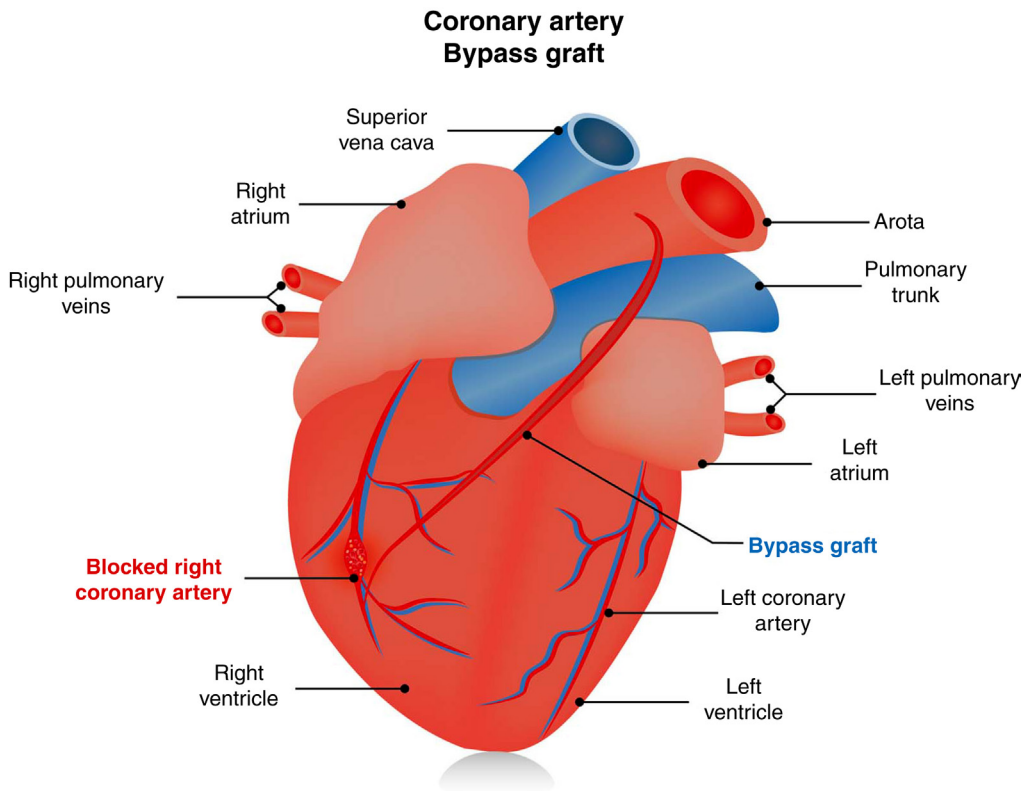


Figure 30 Coronary artery bypass graft.

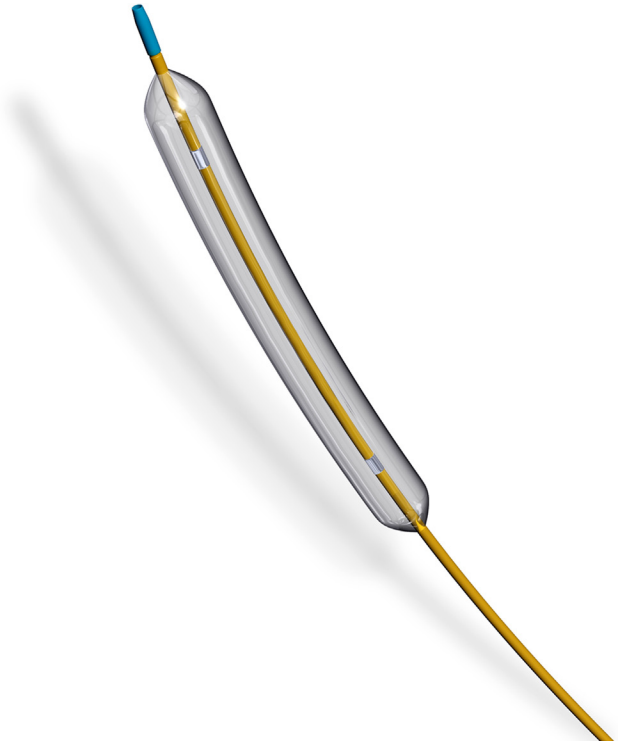


Figure 31 Balloon catheter.

Angioplasty balloons are made by a process combining extrusion and blow molding. The material, from which balloon is to be manufactured, is first extruded as a tube. The extruded tube is preform that is used in the blow molding process. The preform is inserted into mold; this mold corresponds with the shape and dimensions of the required balloon, one end of the tube is welded shut whereas the other end is connected to a supply of compressed air [80,81]. The tube in the mold is heated to a deformable temperature and compressed air at a high pressure inflates the tubular profile converting it to a thin walled balloon. The formed balloon is then tightly wrapped around a catheter shaft and is glued or heat bonded to the shaft. The angioplasty catheter is usually bi-lumen with one lumen permitting the catheter to glide over the guidewire and the other for the passage of the saline to inflate the balloon. Various balloon diameters are available ranging from 1.5 mm to over 2 cm [81], the selection of the balloon dimensions and type depend on a number of factors. These factors include the location of the lesion, the type of the lesion, the blood vessel, and the requirement of a stent placement. In general, angioplasty catheters must pass over a 0.035 inch guidewire, catheters typically range from 3F to 7F and balloon sizes ranging from 3 mm to 2 cm [81]. Burst pressures range from 8 to 15 atm with pressures greater than 15 atm used for heavily calcified, recalcitrant lesions.

The key requirements for an angioplasty balloon are strength and flexibility. Nylons, PET, polyurethanes, and polyolefins (HDPE) are most often used in the manufacture of balloon catheters. One material property that is important in the application of balloons is compliance. Balloon compliance is the term used to describe the degree to which balloon's diameter changes as a function of pressure. A low-compliance balloon might expand only 5–10% when inflated to the rated pressure while a high-compliance balloon might stretch 18–30%. For angioplasty, it is especially important that the balloon does not continue to expand and damage the artery after it has effectively dilated the artery and cleared the blockage. PET and nylons are favored in angioplasty operations due to their low compliance properties. PET can be blow molded to very thin walls and precise shapes allowing balloons made from PET to be of a low profile. Balloons made from nylons tend to be softer than ones made from PET and have a lower tensile strength therefore requiring a greater wall thickness. This means that nylon balloons have a larger profile; however, their softness makes them easier to collapse and withdraw [80].

Another important property for balloon materials is its burst pressure. Burst pressure of the tube is the ability of the expanding balloon to withstand the exerted pressure inside the tube. As seen earlier, the burst pressure is given by

$$P = \frac{T(d_o^2 - d_i^2)}{d_i^2\left(1 + \frac{d_o^2}{d_i^2}\right)} \tag{16}$$

where T is the ultimate tensile strength of the catheter, d_o is the outer diameter of the catheter, d_i is the inner diameter of the catheter, and P is the burst pressure of the catheter.

Clearly, the burst pressure is directly related to the material tensile strength, the wall thickness of the balloon, and the outer diameter of the balloon. Materials with high ultimate tensile strength are ideal for the expansion operation. Increasing the wall thickness and increasing the outer diameter can also result in an increase in the overall burst pressure; however, these dimensions are limited by the application. We have also seen that larger diameter catheters can result in stiffer shafts with increasing potential of causing damages to the blood vessels.

One of the ways to counter the issue of burst strength versus overall stiffness is to split the catheter into sections. In angioplasty routines, only select lumens are pressurized; one approach has been to line specific lumens with high tensile strength materials [81]. The rest of the lumen and the catheter can remain to be constructed with a more flexible material. In this approach, the burst pressure of the specific lumen is increased but the overall flexibility of the catheter is retained.

7.2 Stents

Angioplasty is very often accompanied with the placement of a coronary stent device. Stents are used frequently after angioplasty as the vessels can collapse after ballooning and thus the stents act as a scaffolding structure. A stent is a small, expandable, metallic mesh structure shaped in a tubular form (Fig. 29). The metal typically used is nickel–titanium alloy and the alloy is known as nitinol. Stents can be balloon expandable or self-expandable. In balloon expandable stents, the metallic stent is mounted onto tiny balloons and expanded inside the artery to restore blood flow. In self-expanding stents, the metallic stent is compressed into the catheter and expanded at the point of the lesion [82].

In general, a successful stent design needs to have the following characteristics:

- Low profile—ability to be crimped on the catheter
- Good expansion and shape memory characteristics—the stent should undergo sufficient expansion and conform to the vessel wall;
- Mechanical strength—once implanted, the stent should be able to withstand the radial forces
- Flexibility—navigation through the vasculature
- Adequate radiopacity—to assist physicians in the accurate placement of the device
- Magnetic resonance imaging (MRI) compatibility
- Biocompatibility—the material needs to be blood compatible and not encourage thrombosis

The physical design of a wire mesh structure made from the nitinol alloy has been the most successful of stent designs [82,83]. Nitinol is typically made from 55% nickel and 45% titanium. Nitinol has very good mechanical properties and has excellent shape memory characteristics. Hence it is frequently used to fabricate self-expanding stents. Self-expanding stents have a smaller diameter at room temperature and expand to a preset diameter at body temperature. There are four basic stent designs, the bare metal stent (BMS), the coated metallic stent, drug eluting stent (DES), and the bioresorbable stent [83]. There tend to be questions and concerns about the interaction of the stent surface and the arterial surroundings. The biocompatibility of the surface of stents is frequently improved using coatings. These coatings could be metallic treatments such as galvanization or sputtering, metallic depositions, or polymeric coatings.

One significant issue with stents is the potential for re-occlusion of the artery or restenosis. After stent placement a smooth thick layer of tissue can develop inside the artery. This layer is known as the neointima, and this neointimal growth can actually reocclude the artery leading to restenosis. This restenosis will need reintervention. To prevent this neointimal layer developing and the resultant restenosis, several approaches have been tried [82–86]. One of the more successful attempts has been the use of DESs with drugs such as heparin, paclitaxel, and sirolimus. These drugs slowly release and are antiproliferative agents that prevent scar tissue formation, the scar tissue that forms as a result of the injury caused by the deployment of the stent. By the prevention of the scar tissue, DES can reduce the incidence of restenosis. DES has been seen as effective treatment against the formation of the scar tissue as the drug release is spread out over a period of time and is targeted precisely at the point of injury. Polymeric coatings are frequently used as a carrier for drugs in DES [83,86]. The polymer may be used as a coating for DES where the coating is absorbed as the drug is released over a matter of months. Both biostable and biodegradable polymers have been used as coatings for DESs. For drug release in a biostable polymer, simple diffusion controls the release profile. The rate of release is also controlled by the hydrophobicity or hydrophilicity of the drug-polymer combination. In drug release with a biodegradable polymer, the rate of degradation of the polymer in the artery controls the rate of release of the drug into the injury site. Variants and copolymers of polylactic acid (PLA) and polyglycolic acid (PGA) are used in biodegradable coatings whereas a triblock copolymeric formulation of poly(styrene-b-isobutylene-b-styrene) also known as SIBS is used in biostable coatings [83,86].

Restenosis is observed in spite of using measures such as using drug eluting coatings on stents, late

stage thrombosis continues to be seen with DES [87]. The exact mechanism and the reasons for the occurrence of this thrombosis are still being studied and as yet unknown. A stent that treats the lesion and supports the artery healing process over the short term and then disappears by completely being absorbed into the body over the long term can address the issue of late stage thrombosis effectively. A bioresorbable stent is therefore an attractive prospect. A stent composed of a bioabsorbable polymer as the lone stent material is starting to be used. Although the concept of bioabsorbable stents has created interest for more than a couple of decades, there have been challenges in creating a stent with sufficient radial strength for an appropriate duration, that can be a drug delivery vehicle, and where degradation does not generate an unacceptable inflammatory response. A stent made out of PLA, capable of drug elution and marketed by Abbott Vascular has been approved for clinical use [87,88]. In the absorption process, the bonds between the repeat units of the lactide chain are hydrolyzed and are metabolized to carbon dioxide and water. The absorption process happens by bulk erosion; this ensures that the absorption is not surface dominated but occurs throughout the mass of the implant. This bulk absorption process allows the stent strut to retain its shape until the later stages of absorption. The use of these stents has shown positive outcomes from the first applications. Trials with a stent made from a bioabsorbable metal, stents made from magnesium and different polymeric biodegradable formulations are under investigation [89].

7.3 Vascular Grafts

In cases of severe CAD, where angioplasty and stent placement is not adequate, bypass surgery and the use of vascular grafts is indicated. With a graft the obstruction to the flow of blood through an artery due to an occlusion or plaque formation is bypassed in the surgery. The blockage to blood flow could be in one of the main arteries supplying blood to the heart or it could be in the peripheral region.

The graft used can be the person's own vein, another person's vein, or a polymeric tube made from expanded PTFE (ePTFE) or thermoplastic polyester (Dacron) [90]. In general, the person's own blood vessel, autogenous vessels, is considered the gold standard in these surgeries; however, in many cases these autogenous vessels may be unavailable due to intrinsic vascular disease or because the vessel has been used in previous procedures. In such situations, synthetic grafts have been used. Synthetic grafts are suitable for large caliber (> 4 mm) graft sizes and their success in smaller graft sizes has been limited [90].

Among the autogenous vessels, the greater saphenous vein in the thigh is the most commonly utilized for both peripheral and coronary vascular applications. The saphenous vein provides the standard by which the efficacy of all other materials utilized for bypass vascular procedures are compared. Much of the effort in the development of synthetic vascular grafts has focused on thrombogenic resistance, porosity, and the mechanical characteristics of candidate materials. All these properties can affect the long-term patency of the graft and the development of a stable neoinitima. Additional features that are highly desirable in a small synthetic graft include durability, resistance to infection, and immediate availability [90,91]. The main materials tried out in the application of a vascular graft have been ePTFE, Dacron (PET), and polyurethane [90–93]. Larger bore grafts (>7 mm diameter) have done well and are regularly used; however, synthetic grafts smaller than 7 mm have been associated with various issues of abnormal cell growth, intimal hyperplasia, compliance mismatch, thrombosis, and restenosis. These have been documented in various publications [90,93,94]. The texture of the internal and external surfaces is also important. The porosity of vascular graft significantly affects the patency and long-term healing of the implanted graft. The porosity directly affects the growth of endothelial cells onto the graft. The growth of endothelial cells on the inner surface of vascular grafts is desirable as endothelium maintains the fluidity of the blood through the graft; ingrowth of cellular material also reduces the likelihood of infection. The porosity is also important on the tissue contacting the outer surface of the graft. Thus the fabrication method used to manufacture the graft becomes important. The compliance of the material also is believed to be a critical factor in the success of synthetic grafts. The compliance of the material is the strain or elongation response to an applied stress and, as described earlier, is the reciprocal of the Young's modulus. Hence, it is an intrinsic property of the material. Ideally, the compliance of a material for a synthetic graft should match the compliance of the vessel wall as closely as possible. A mismatch of mechanical properties may lead to turbulent blood flow, which may reach levels that result in thrombus formation or destruction of formed blood elements. This mismatch can frequently occur

at the junction between the natural artery and the graft known anastomosis [93,95,96].

PTFE grafts are formed by the extrusion of PTFE tubes. These tubes are extruded to an exact diameter and are later placed over metallic fixtures and stretched yielding an expanded version of the tube and hence ePTFE (Fig. 30). These tubes have a microporous structure which allows natural tissue ingrowth and cell endothelization once implanted in the vascular system. This contributes to long-term healing and patency of the graft [94,96]. Grafts formed of ePTFE have a fibrous structure which is defined by interspaced nodes interconnected by elongated fibrils. The spaces between the node surfaces that are spanned by the fibrils are defined as the internodal distance (IND). A graft having a large IND enhances tissue ingrowth and cell endothelization as the graft is inherently more porous.

In PET or Dacron grafts, the porosity is obtained through the use of knitting and weaving techniques utilizing a Dacron yarn. The level of porosity can be controlled by control of the textile manufacturing technique. The porosity is crucial for the ingrowth of tissue into the graft and successful integration of the implant. Dacron grafts are often crimped longitudinally to increase flexibility, elasticity, and kink resistance [96]. However, these properties are lost soon after implantation, as a consequence of tissue ingrowth (Fig. 32).

In comparison between the grafts, there have not been any differences noted between the two materials (ePTFE and Dacron) in terms of efficacy of use or long-term survival rates [94,95].

Polyurethanes have been an attractive material for vascular grafts, primarily because of its high elasticity. The high elasticity would allow for the greater compliance that limits the other materials in the smaller diameter grafts. However, it is observed that the elasticity of the polyurethane material tends to decrease after implantation, this loss of elasticity and the lower biostability as compared with the other materials are the two big factors that limits their use in the field of grafts [95,97].

8 Aortic Aneurysm

The formation of an aneurysm is the result of the thinning of a blood vessel and the rupture that can subsequently occur, this rupture can frequently result in fatal consequences. Ruptures are believed to occur when the wall tissue strength is exceeded by the mechanical stress acting on the aneurysm wall. This tension can be calculated using the Laplace law for wall tension [98]:

$$F = \frac{P.R}{d} \tag{17}$$

where F is the force of tension on the vessel wall, P is the mean arterial blood pressure, R is the blood vessel radius, and d is the arterial wall thickness.

As the wall tension increases, the risk of vessel rupture increases and it can be seen from Eq. (17) that risk of vessel rupture increases with a decrease in the thickness of the arterial wall (Figs. 33 and 34).

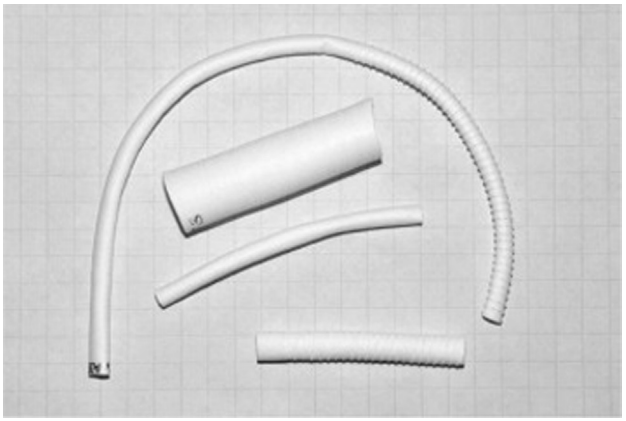


Figure 32 ePTFE vascular graft of different diameters. *Courtesy: Elsevier Publications; R. Guidoin, M.W. King, L. Wang, Z. Zhang, R. Guzman, G. Marinov, Y. Douville, 15 – Vascular prostheses for open surgery, Biotextiles As Medical Implants (2013) 434–484 [96].*

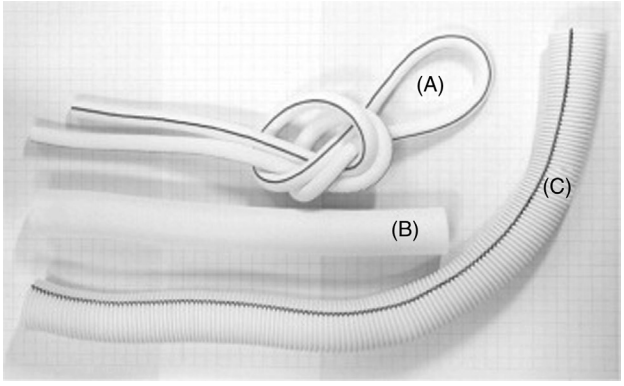


Figure 33 PET vascular graft with different diameters (A) femoro-popliteal arteries, (B) abdominal aorta, (C) thoracic aorta. *Courtesy: Elsevier Publications; R. Guidoin, M.W. King, L. Wang, Z. Zhang, R. Guzman, G. Marinov, Y. Douville 15 – Vascular prostheses for open surgery, Biotextiles As Medical Implants (2013) 434–484 [96].*

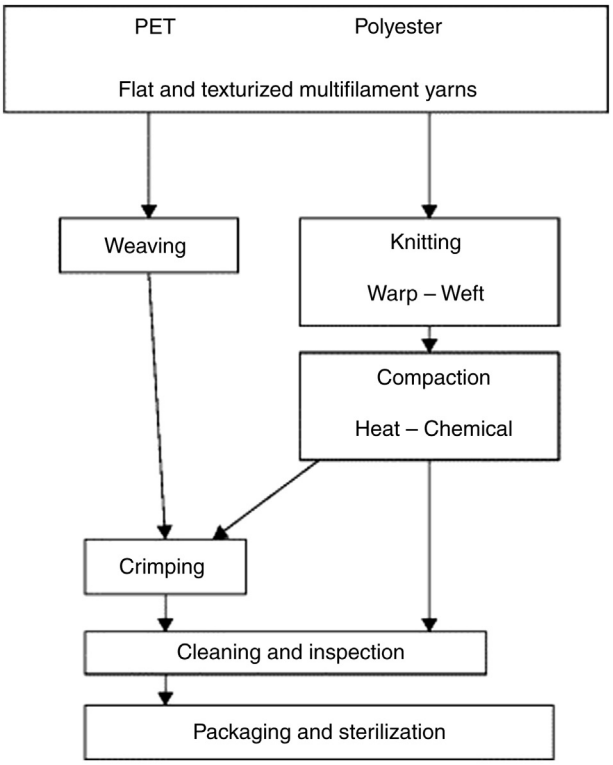


Figure 34 Sequence of steps for the manufacture of PET vascular grafts. *Courtesy: Elsevier Publications; R. Guidoin, M.W. King, L. Wang, Z. Zhang, R. Guzman, G. Marinov, Y. Douville 15 – Vascular prostheses for open surgery, Biotextiles As Medical Implants (2013) 434–484 [96].*

The treatment for aneurysm is commonly done using a stent graft [99,100]. A stent graft is a plastic tube that is reinforced with a metallic wire mesh. The tube is also known as the graft that is supported by the rigid structure of the metal sometimes referred to as the skeleton. This is placed at a point of aneurysm in the artery and is designed to seal tightly just above and below the aneurysm. The stent graft is stronger than the aneurysm and the weakened artery therefore allows blood flow in that section of the artery without it pressing on the weak spot. This placement significantly reduces the chances of a burst aneurysm and associated heavy internal bleeding. In most cases, stent grafts are put in position using an endovascular technique and fixed either with balloon expandable stents or are self-expanding. Stent grafts have been widely used since the early 1990s. Stent grafts are used to treat both abdominal aortic aneurysms (AAA) and thoracic aortic aneurysms (TAA).

Stent graft use became commonplace as the endovascular surgery to repair aneurysms (EVAR) was introduced and proven successful since the early 1990s. As mentioned earlier, stent grafts are composed of nitinol stents sewn onto a plastic tube. Radio opaque markers are placed at different points within the stent graft device to facilitate correct placement inside the artery. The stent graft is usually oversized approximately 10–25% of the size of the artery to form a tight seal with the artery (Fig. 35) [98].

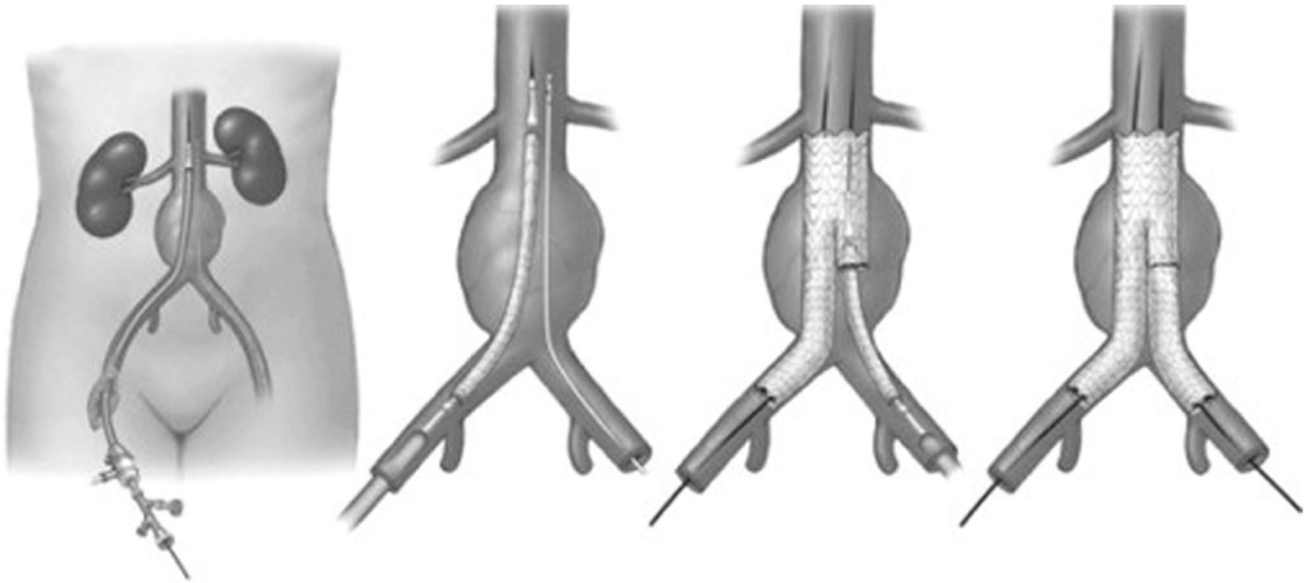


Figure 35 Typical endovascular stent graft deployment for AAA. *Courtesy: Elsevier Publications; G. Marinov, R. Guidoin, L.W. Tse, A.A. Ruthrauff, T. Yao, M.W. King 21 – Endovascular prostheses for aortic aneurysms: a new era for vascular surgery, Biotextiles As Medical Implants (2013) 640–675 [98].*

The manufacturing technique involves the accurate placement of the components in relation to each other and often this is a labor intensive and operator dependent, manual technique. The nature of the manufacturing process can result in variations in the performance of the device either in the accurate placement or in the functioning of the device. Manufacturing companies are working to smoothen out these variations [101]

Plastics used in this device are either thermoplastic polyester (PET) or ePTFE [98,102]. Dimensional stability, robustness, sterilizability, and biostability are the most important attributes of a graft material. Porosity, to a certain extent, is also an important aspect of the graft. Porosity is important to enable a degree of tissue ingrowth. Similar to the construction of a vascular graft, in PET, porosity is induced by the use of a polyester fabric. The fabric can be either woven or knitted.

9 Vascular Closure Devices and Sutures

With millions of cardiac procedures occurring annually, effective closure techniques are an important aspect of the entire procedure. The closure techniques in cardiac surgery can be in the form of a suture or a plug to repair the punctured blood vessel [103,104]. Sutures are used to hold tissues together after surgery. Application generally involves using a needle with an attached length of thread or suture [105]. Surgical knots are used to secure the sutures. The sutures themselves can be made from a variety of materials. The materials can be natural or synthetic, absorbable or permanent. Synthetic absorbable sutures are made with biodegradable polymers such as polyglycolides, polylactic acid, and polydioxanone [106]. Cardiac surgery generally utilizes permanent sutures; these sutures are characterized by a permanent retention of mechanical strength especially important in the case of a stressful internal environment such as the heart. Constant pressure and movement around the heart implies that absorbable sutures might not be adequate. With the dissolution of the biodegradable material in an absorbable suture, the balance between disappearance of the suture and the healing of the tissue may not be adequate enough for the pressures as experienced in the heart. Nonabsorbable sutures can be composed of polymers such as polypropylene, polyester, or nylons. These sutures are in the form of a monofilament ranging from a diameter of 0.01 mm up to 0.5 mm [106].

Seldinger technique for vascular intervention has been in regular use for vascular intervention for more than the past 50 years. The intervention could be for therapeutic or diagnostic purposes. After most catheter-based procedures, the vascular access site needs

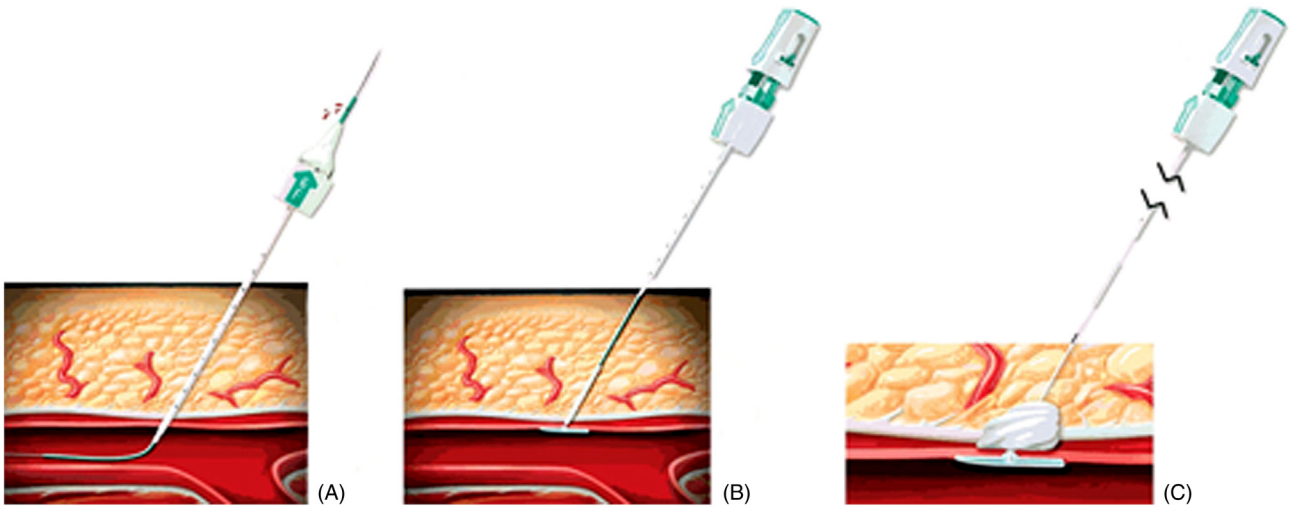


Figure 36 Deployment of Angio-Seal®, a VCD from St. Jude Medical. *Courtesy: Elsevier Publications; L.Q. Hon, A. Ganeshan, S.M. Thomas, D. Warakaulle, J. Jagdish, R. Uberoi, An overview of vascular closure devices: what every radiologist should know, Eur. J. Radiol. 73 (1) (2010) 181–190 [106].*

to be properly closed to achieve right hemostasis for the blood vessel to start its healing process and the patient to have a short recovery process. Manual compression, which involves the mechanical compression over a period of time, is often limited by the need to interrupt anticoagulation, prolonged bed rest, patient discomfort, and time demands for healthcare providers. The introduction of VCD in the 1990s provided an alternative to manual compression. VCDs can shorten the procedure, speed up recovery times and significantly improve patient comfort. The main requirements of any VCD include ease in device location, use and application, successful hemostasis of the punctured vessel, a short time to patient ambulation, and low rates of complications.

Currently available VCDs fall into three major classes [106]:

- Devices using a bioresorbable plug,
- Devices using clips
- Devices that perform suture closure at the arterial access site

The role of VCD and their comparison to manual compression has been studied and reported in various references [103–106].

VCDs use different mechanisms [107] to plug the punctured vessel. The devices that rely on the use of a bioresorbable matrix to achieve hemostasis use either natural tissue or a synthetic biodegradable polymer as the plug. The natural tissue used as a plug is usually bovine collagen. Primary vascular hemostasis after arterial puncture is facilitated by blood contact with the exposed arterial wall smooth muscle cells and collagen. This in turn causes platelets adherence, activation and aggregation resulting in clot formation. Bovine collagen used in these devices augments hemostasis by increasing the availability of collagen at the arterial wall defect. Devices that use a biodegradable polymer as the plug rely on different bioresorbable formulations such as polyethylene glycol, PGA, and caprolactone, etc [103]. A couple of examples are shown in Figs. 36 and 37.

Closure devices utilizing clips for closure use metal based extra-luminal devices that remain in situ post deployment. The suture-based closure devices use a biostable suture material such as polypropylene in a monofilament form (Fig. 38).

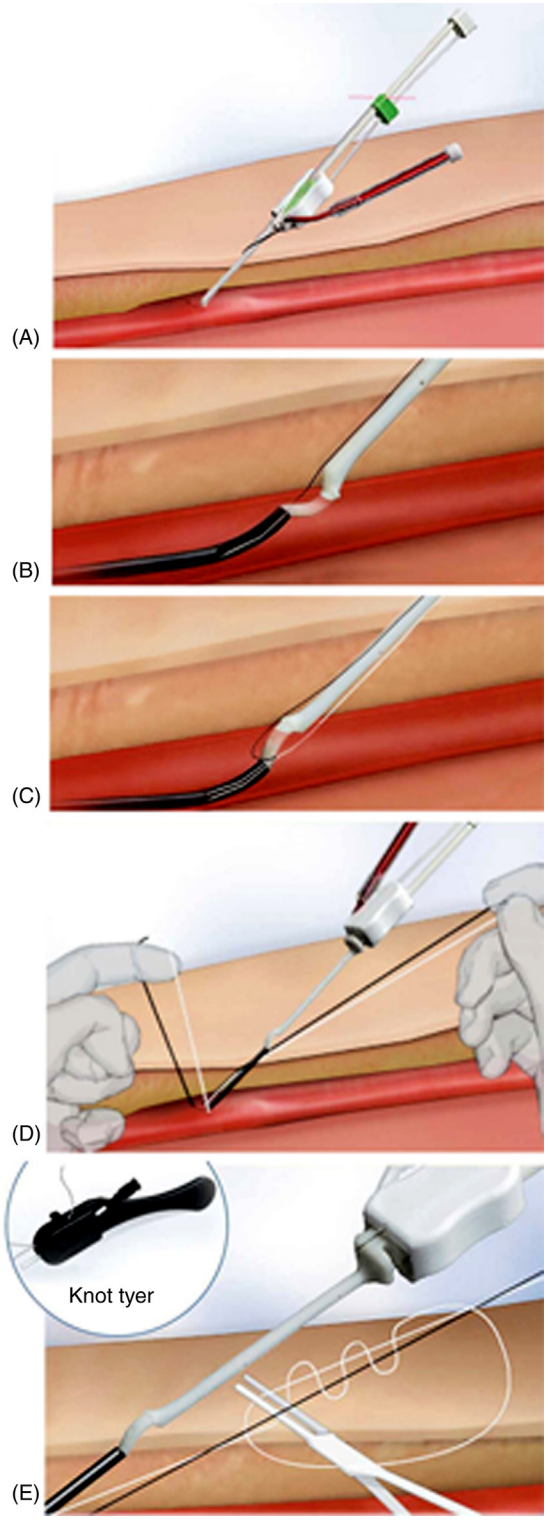


Figure 37 Deployment of VCD VasoSea®l Elite. *Courtesy: Elsevier Publications; L.Q. Hon, A. Ganeshan, S.M. Thomas, D. Warakaulle, J. Jagdish, R. Uberoi, An overview of vascular closure devices: What every radiologist should know, Eur. J. Radiol. 73 (1) (2010) 181–190 [106].*

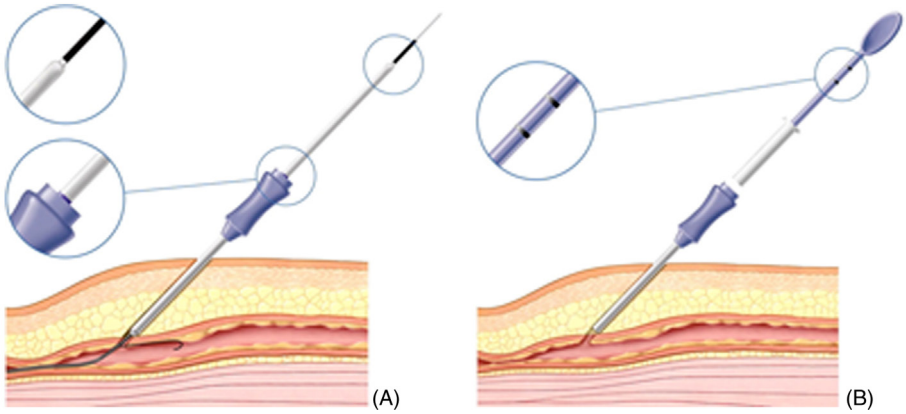


Figure 38 Suture based VCD, X-site. *Courtesy: Elsevier Publications; L.Q. Hon, A. Ganeshan, S.M. Thomas, D. Warakaulle, J. Jagdish, R. Uberoi, An overview of vascular closure devices: what every radiologist should know, Eur. J. Radiol. 73 (1) (2010) 181–190 [106].*

References

[1] Bccresearch.com., Cardiac Medical Devices to Reach $67.5 Billion in 2019; Emerging Markets Hold Highest Growth Promise (2016) Available from: http://www.bccresearch.com/pressroom/hlc/cardiac-medical-devices-to-reach-$67.5-billion-in-2019

[2] Marketsandmarkets.com., Cardiac Monitoring Market by Product & End-Users—2020 | MarketsandMarkets (2016) Available from: http://www.marketsandmarkets.com/Market-Reports/cardiac-monitoring-advanced-technologies-and-global-market-55.html

[3] Allied Market Research, 3. World Catheter Markets, Opportunities and Forecasts (2014), 2013–2020.

[4] Grandview Research, CA, USA, Catheters Market Analysis By Product (Cardiovascular, Urology, Intravenous, Neurovascular And Specialty Catheters) And Segment Forecasts To 2020 (2015).

[5] Marketsandmarkets.com., Prosthetic Heart Valve Market worth 4.80 Billion USD by 2020 (2014) Available from: http://www.marketsandmarkets.com/PressReleases/prosthetic-heart-valve.asp

[6] Smithersapex.com., Coronary Heart Disease Medical Devices News | Smithers Apex (2015) Available from: http://www.smithersapex.com/news/2015/february/coronary-artery-disease-to-drive-$22-5-billion-mar

[7] PR Newswire (2014) Available from: http://www.prnewswire.com/news-releases/aortic-stent-grafts-market-worth-19-billion-by-2020-282151891.html

[8] Abbott.com., Abbott | Global Healthcare & Research (2016) Available from: http://www.abbott.com/

[9] Biotronik (2016) Available from: https://www.biotronik.com/

[10] Bostonscientific.com., Products | Boston Scientific (2016) Available from: http://www.bostonscientific.com/

[11] Cookmedical.com., Products | Cook Medical (2016) Available from: https://www.cookmedical.com/products/

[12] Edwards.com., Edwards Lifesciences—the leader in heart valves & hemodynamic monitoring (2016) Available from: http://www.edwards.com/

[13] Goremedical.com., Gore Medical Products (2016) Available from: https://www.goremedical.com/

[14] Biosensewebster.com., Biosense Webster Inc. (2016) Available from: https://www.biosensewebster.com/products/

[15] Medtronic.com (2016) Available from: http://www.medtronic.com/

[16] Livanova.sorin.com., Sorin (2015) Available from: http://www.livanova.sorin.com/home.action

[17] Sjm.com., St. Jude Medical (2016) Available from: https://sjm.com/

[18] R. Mueller, T. Sanborn, The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions, Am. Heart J. 129 (1) (1995) 146–172.

[19] R. Dalley, Flow rate variance of commonly used IV units, J. Am. College Emerg. Phys. 2 (5) (1973) 341–342.
[20] S. Barcelona, F. Vilich, C. Coté, A comparison of flow rates and warming capabilities of the level 1 and rapid infusion system with various-size intravenous catheters, Anesth. Analg. 97 (2) (2003) 358–363.
[21] E. Ozcan Cetin, M. Cetin, U. Canpolat, E. Kalender, S. Topaloglu, D. Aras, S. Aydogdu, The forgotten variable of shear stress in mitral annular calcification: whole blood viscosity, Med. Princ. Pract. 24 (5) (2015) 444–450.
[22] O.K. Baskurt, H.J. Meiselman, Blood Rheology and Hemodynamics, Semin. Thromb. Hemost. 29 (5) (2003) 435–450.
[23] R. Roth, Design Considerations in Small-Diameter Medical Tubing | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2001) Mddionline.com. Available from: http://www.mddionline.com/article/design-considerations-small-diameter-medical-tubing A. Ugural, S. Fenster, Advanced strength and applied elasticity, Prentice Hall, Upper Saddle River, NJ, 1995.
[24] J. Hartford, New Extrusion Techniques Advance Catheter Design | MDDI Medical Device and Diagnostic Industry News Products and Suppliers, (2013) Mddionline.com. Available from: http://www.mddionline.com/article/new-extrusion-techniques-advance-catheter-design
[25] M. Saab, Applications of High-Pressure Balloons in the Medical Device Industry | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2000) Available from: http://www.mddionline.com/article/applications-high-pressure-balloons-medical-device-industry
[26] S. Leonard, Extrusion Process Bumps Catheter Design to the Next Level | Qmed (2001) Qmed.com. Available from: http://www.qmed.com/mpmn/article/extrusion-process-bumps-catheter-design-next-level
[27] Mddionline.com., Radiopaque Polymer Formulations for Medical Devices | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2000) Available from: http://www.mddionline.com/article/radiopaque-polymer-formulations-medical-devices
[28] D. Entrikin, J. Leipsic, J. Carr, Optimization of radiation dose reduction in cardiac computed tomographic angiography, Cardiol. Rev. 19 (4) (2011) 163–176.
[29] J. Rasor, The Science of Friction (2009) Medical Device Network. Available from: http://www.medicaldevice-network.com/features/feature52481/
[30] DuPont, Method of coating surface with transparent film and product resulting therefrom (1956) US2768909 A.
[31] J. Simon, What's next for hydrophilic coatings? (2009) Medicaldesign.com. Available from: http://medicaldesign.com/materials/whats-next-hydrophilic-coatings
[32] G. Jin, M. Wang, D. Zhao, H. Tian, Y. Jin, Design and experiments of extrusion die for polypropylene five-lumen micro tube, J. Mater. Process. Technol. 214 (1) (2014) 50–59.
[33] Mddionline.com., Medical Tubing: Dimensions Aren't Everything | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2006) Available from: http://www.mddionline.com/article/medical-tubing-dimensions-aren%E2%80%99t-everything
[34] B. Lischefski, B. Maicke, A Processor's Advice on How to Get Moisture Testing Right: Plastics Technology (2013) Ptonline.com. Available from: http://www.ptonline.com/articles/a-processors-advice-on-how-to-get-moisture-testing-right
[35] N. Rao, Design Formulas for Plastics Engineers, Hanser Publishers, Munich, (1991).
[36] COMPUPLAST®—Extrusion Specialists. Compuplast.com. Available from: http://www.compuplast.com/
[37] J. Meijer, Laser beam machining (LBM), state of the art and new opportunities, J. Mater. Process. Technol. 149 (1-3) (2004) 2–17.
[38] Medicaldesign.com., The Basics Of Silicone Tubing (2007) Available from: http://medicaldesign.com/materials/basics-silicone-tubing
[39] M. Maitz, Applications of synthetic polymers in clinical medicine, Biosurf. Biotribol. 1 (3) (2015) 161–176.
[40] K. McLaughlin, B. Jones, R. Mactier, C. Porteus, Long-term vascular access for hemodialysis using silicon duallumen catheters with guidewire replacement of catheters for technique salvage, Am. J. Kid. Dis. 29 (4) (1997) 553–559.

[41] M. Knehtl, R. Ekart, S. Bevc, M. Horvat, R. Hojs, Exit-site infection and acute peritonitis due to peritoneal dialysis catheter rupture, Perit. Dial. Int. 35 (3) (2015) 362–363.
[42] L. Pruitt, J. Furmanski, Polymeric biomaterials for load-bearing medical devices, JOM 61 (9) (2009) 14–20.
[43] Access Technologies, Catheter Tubing Specifications (n.d) Available from: http://www.norfolkaccess.com/pdf/Catheter%20Materials%20Comparison%20Chart.pdf
[44] S. Wald, C. Coté, Procedures for vascular access, in: C.J. Cote, J. Lerman, B. Anderson (Eds.), A Practice of Anesthesia for Infants and Children,, Elsevier Inc, Boston, 2009, pp. 1049–1064.
[45] M. Silva, C. Cheng, Guidewires, catheters, and sheaths, in: W.S. Moore, S.S. Ahn (Eds.), Endovascular Surgery, first ed., Elsevier/Saunders, Philadelphia, 2011, pp. 59–69.
[46] M. Helmus, C. Cunanan, Mechanical and bioprosthetic heart valves, in: M. Lysaght, T.J. Webster (Eds.), Biomaterials for Artificial Organs, Woodhead Publishing Limited, Cambridge, 2011, pp. 113–162.
[47] H. Mohammadi, K. Mequanint, Prosthetic aortic heart valves: modeling and design, Med. Eng. Phys. 33 (2) (2011) 131–147.
[48] D. Bezuidenhout, D. Williams, P. Zilla, Polymeric heart valves for surgical implantation, catheter-based technologies and heart assist devices, Biomaterials 36 (2015) 6–25.
[49] Y. Kuan, L. Dasi, A. Yoganathan, H. Leo, Recent advances in polymeric heart valves research, Int. J. Biomater. Res. Eng. 1 (1) (2011) 1–17.
[50] G. Grunkemeier, Artificial heart valves, Annu. Rev. Med. 41 (1) (1990) 251–263.
[51] F. Schoen, R. Levy, Tissue heart valves: current challenges and future research perspectives, J. Biomed. Mater. Res. 47 (4) (1999) 439–465.
[52] H. Herrmann, Transcatheter aortic valve implantation: past, present, and future, Circulation 1 (3) (2008) 159–160.
[53] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, In vitro oxidation of high polydimethylsiloxane content biomedical polyurethanes: correlation with the microstructure, J. Biomed. Mater. Res. A 87A (2) (2008) 546–556.
[54] A. Kumar, P. Khanwilkar, Long-term implantable ventricular assist devices (VADs) and total artificial hearts (TAHs), in: P. Ducheyne (Ed.), Comprehensive Biomaterials, Elsevier Ltd., Boston, 2011, pp. 389–402.
[55] M. Slepian, Y. Alemu, J.G. Soares, R. Smith, S. Einav, D. Bluestein, The Syncardia™ total artificial heart: in vivo, in vitro, and computational modeling studies, J. Biomech. 46 (2) (2013) 266–275.
[56] J. Copeland, R. Smith, R. Bose, P. Tsau, P. Nolan, M. Slepian, Risk factor analysis for bridge to transplantation with the CardioWest total artificial heart, Ann. Thorac. Surg. 85 (5) (2008) 1639–1644.
[57] D. Ufukerbulut, I. Lazoglu, Biomaterials for improving the blood and tissue compatibility of total artificial hearts (TAH) and ventricular assist devices (VAD), in: M. Lysaght, T.J. Webster (Eds.), Biomaterials for Artificial Organs, Woodhead Publishing Limited, Cambridge, 2011, pp. 207–235.
[58] R. Gordon, B. Quagliarello, F. Lowy, Ventricular assist device-related infections, Lancet Infect. Dis. 6 (7) (2006) 426–437.
[59] W. Holman, B. Rayburn, D. McGiffin, B. Foley, R. Benza, R. Bourge, L. Pinderski, J. Kirklin, Infection in ventricular assist devices: prevention and treatment, Ann. Thorac. Surg. 75 (6) (2003) S48–S57.
[60] L. Marcuccilli, J. Casida, R. Peters, Modification of self-concept in patients with a left-ventricular assist device: an initial exploration, J. Clin. Nurs. 22 (17-18) (2013) 2456–2464.
[61] R. Latchamsetty, F. Morady, Catheter ablation of atrial fibrillation, Heart Fail. Clin. 12 (2) (2016) 223–233.
[62] L. Rosenfeld, Temporary permanent or permanent temporary pacing?, Pacing Clin. Electrophysiol. 34 (6) (2011) 670–671.
[63] H. Haqqani, L. Epstein, J. Cooper, Engineering and construction of pacemaker and ICD leads, Clinical Cardiac Pacing Defibrillation and Resynchronization Therapy, Elsevier Inc., Philadelphia, (2011) pp. 127–143.
[64] R. Mehra, S. Furman, Comparison of cathodal, anodal, and bipolar strength-interval curves with temporary and permanent pacing electrodes, Heart 41 (4) (1979) 468–476.
[65] H. Mond, D. Hunt, J. Vohra, J. Sloman, Cardiac pacing: memories of a bygone era, Pacing Clin. Electrophysiol. 31 (9) (2008) 1192–1201.
[66] L. Liem, Implantable Cardioverter-Defibrillator, Springer Netherlands, Dordrecht, (2001).

[67] R. Pickett, G. Crossley, Pacemaker, Defibrillator, and Lead Codes and Headers, Clinical Cardiac Pacing Defibrillation and Resynchronization Therapy, Elsevier Inc., Philadelphia, (2011) pp. 195–199.
[68] Materials and coatings for medical devices, ASM International, Materials Park, Ohio, 2009.
[69] N.M.K. Lamba, K.A. Woodhouse, S.L. Cooper, M.D. Lelah, Polyurethanes in Biomedical Applications, CRC, Boca Raton, (1998).
[70] M. Szycher, Biostability of polyurethane elastomers: a critical review, J. Biomater. Appl. 3 (2) (1988) 297–402.
[71] Kenneth S., Coury A., Urbanski P., Autooxidative degradation of implanted polyurethane devices, J. Biomater. Appl. 1 (1987) 411–448.
[72] M.J. Wiggins, B. Wilkoff, J.M. Anderson, A. Hiltner, Biodegradation of polyether polyurethane inner insulation in bipolar pacemaker leads, J. Biomed. Mater. Res. 58 (3) (2001) 302–307.
[73] P.A. Gunatillake, D.J. Martin, G.F. Meijs, S.J. McCarthy, R. Adhikari, Designing biostable polyurethane elastomers for biomedical implants, Austral. J. Chem. 56 (6) (2003) 545–557.
[74] K. Stokes, R. McVenes, J.M. Anderson, Polyurethane elastomer biostability, J. Biomater. Appl. 9 (1995) 321.
[75] R. Hernandez, J. Weksler, A. Padsalgikar, J. Runt, In vitro oxidation of high polydimethylsiloxane content biomedical polyurethanes: correlation with the microstructure, J. Biomed. Mater. Res. A 87 (2) (2008) 546–556.
[76] A. Simmons, J. Hyvarinen, A. Odell Ross, J. Martin Darren, et al. Long-term in vivo biostability of poly(dimethylsiloxane)/poly(hexamethylene oxide) mixed macrodiol-based polyurethane elastomers, Biomaterials 25 (20) (2004) 4887–4900.
[77] T. Choi, J. Weksler, A. Padsalgikar, R. Hernéndez, J. Runt, Polydimethylsiloxane-based polyurethanes: phase-separated morphology and in vitro oxidative biostability, Austral. J. Chem. 62 (8) (2009) 794.
[78] A. Padsalgikar, E. Cosgriff-Hernandez, G. Gallagher, T. Touchet, C. Iacob, L. Mellin, A. Norlin-Weissenrieder, J. Runt, Limitations of predicting in vivo biostability of multiphase polyurethane elastomers using temperature-accelerated degradation testing, J. Biomed. Mater. Res. B 103 (1) (2014) 159–168.
[79] V. Krepel, G. van Andel, W. van Erp, P. Breslau, Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results, Radiology 156 (2) (1985) 325–328.
[80] N. Singh, P. Schneider, Balloon angioplasty catheters, in: W.S. Moore, S.S. Ahn (Eds.), Endovascular Surgery, first ed., Elsevier/Saunders, Philadelphia, 2011, pp. 71–80.
[81] R. Decker, Balloon catheters present unique design challenges (2009) Medicaldesign.com. Available from: http://medicaldesign.com/materials/balloon-catheters-present-unique-design-challenges
[82] A. Michaels, Angioplasty versus bypass surgery for coronary artery disease, Circulation 106 (23) (2002) 187e–190.
[83] S. Garg, M. Magro, P. Serruys, Drug-eluting stents, in: P. Ducheyne (Ed.), Comprehensive Biomaterials, Elsevier Ltd., Boston, 2011, pp. 427–448.
[84] A. Kastrati, J. Mehilli, J. Pache, C. Kaiser, M. Valgimigli, H. Kelbæk, M. Menichelli, M. Sabaté, M. Suttorp, D. Baumgart, M. Seyfarth, M. Pfisterer, A. Schömig, Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents, New Engl. J. Med. 356 (10) (2007) 1030–1039.
[85] H. Takebayashi, Y. Kobayashi, G. Mintz, S. Carlier, K. Fujii, T. Yasuda, I. Moussa, R. Mehran, G. Dangas, M. Collins, E. Kreps, A. Lansky, G. Stone, M. Leon, J. Moses, Intravascular ultrasound assessment of lesions with target vessel failure after sirolimus-eluting stent implantation, Am. J. Cardiol. 95 (4) (2005) 498–502.
[86] J. Ormiston, P. Serruys, E. Regar, D. Dudek, L. Thuesen, M. Webster, Y. Onuma, H. Garcia-Garcia, R. McGreevy, S. Veldhof, A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial, Lancet 371 (9616) (2008) 899–907.
[87] A. Guildford, M. Santin, G. Phillips, Cardiovascular stents, in: T. Gourlay, R. Black (Eds.), Biomaterials and Devices for the Circulatory System, first ed., Woodhead Publishing, 2010, pp. 173–216.
[88] E. Christiansen, The absorb trial: evaluation of the absorb Everolimus eluting bioresorbable vascular scaffold in the treatment of patients with de novo native coronary artery

lesions: 4 year clinical results of cohort B, J. Am. College Cardiol. 63 (12) (2014) A1706.
[89] C. Wiltz, Polymer vs. Metal: The Battle of Bioresorbable Stents | MDDI Medical Device and Diagnostic Industry News Products and Suppliers (2013) Mddionline.com. Available from: http://www.mddionline.com/article/polymer-vs-metal-battle-bioresorbable-stents
[90] A. Ucuzian, H. Greisler, Vascular grafts, in: P. Ducheyne (Ed.), Comprehensive Biomaterials, Elsevier Ltd., Boston, 2011, pp. 449–467.
[91] N. Lamba, K. Woodhouse, S. Cooper, M. Lelah, Polyurethanes in Biomedical Applications, CRC Press, Boca Raton, (1998).
[92] P. Klinkert, P. van Dijk, P. Breslau, Polytetrafluoroethylene femorotibial bypass grafting: 5-year patency and limb salvage, Ann. Vasc. Surg. 17 (5) (2003) 486–491.
[93] W. Johnson, K. Lee, A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for femoral-popliteal above-knee revascularization: a prospective randomized Department of Veterans Affairs cooperative study, J. Vasc. Surg. 32 (2) (2000) 268–277.
[94] S. Ravi, E. Chaikof, Biomaterials for vascular tissue engineering, Regen. Med. 5 (1) (2010) 107–120.
[95] F. Montini-Ballarin, G. Abraham, P. Caracciolo, Mechanical behavior of polyurethane-based small-diameter vascular grafts, in: S.L. Cooper, J. Guan (Eds.), Advances in Polyurethane Biomaterials, Elsevier Ltd., 2016, pp. 451–477.
[96] R. Guidoin, M. King, L. Wang, Z. Zhang, R. Guzman, G. Marinov, Y. Douville, Vascular prostheses for open surgery, in: M.W. King, B.S. Gupta, R. Guidoin (Eds.), Biotextiles As Medical Implants, Woodhead Publishing Limited, Philadelphia, 2013, pp. 434–484.
[97] M. Kapadia, D. Popowich, M. Kibbe, Modified prosthetic vascular conduits, Circulation 117 (14) (2008) 1873–1882.
[98] G. Marinov, R. Guidoin, L. Tse, A. Ruthrauff, T. Yao, M. King, Endovascular prostheses for aortic aneurysms: a new era for vascular surgery, in: M.W. King, B.S. Gupta, R. Guidoin (Eds.), Biotextiles As Medical Implants, Woodhead Publishing Limited, Philadelphia, 2013, pp. 640–675.
[99] D. Drury, J. Michaels, L. Jones, L. Ayiku, Systematic review of recent evidence for the safety and efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysm, Br. J. Surg. 92 (8) (2005) 937–946.
[100] C. Bicknell, J. Powell, Aortic disease: thoracic endovascular aortic repair, Heart 101 (8) (2015) 586–591.
[101] Vascutek.com (2016) Anaconda™ AAA Stent Graft System—Vascutek, a Terumo Company. Available from: http://www.vascutek.com/vascutek/products/item/anaconda-aaa-stent-graft-system
[102] L. Buchanan, S. Stavropoulos, J. Resnick, J. Solomon, Endovascular repair of aortic disease: a venture capital perspective, Semin. Intervent. Radiol. 26 (01) (2009) 056–066.
[103] E. Courtiss, The effectiveness and mechanism of collagen-induced topical hemostasis, Plast. Reconstruct. Surg. 58 (2) (1976) 256.
[104] C. Schmelter, A. Liebl, N. Poullos, V. Ruppert, D. Vorwerk, Suitability of exoseal vascular closure device for antegrade femoral artery puncture site closure, Cardiovasc. Intervent. Radiol. 36 (3) (2012) 659–668.
[105] E. Hoffer, R. Bloch, Percutaneous arterial closure devices, J. Vasc. Intervent. Radiol. 14 (7) (2003) 865–885.
[106] L. Hon, A. Ganeshan, S. Thomas, D. Warakaulle, J. Jagdish, R. Uberoi, An overview of vascular closure devices: what every radiologist should know, Eur. J. Radiol. 73 (1) (2010) 181–190.
[107] A. Chen, Review of femoral artery vascular closure devices, Br. J. Cardiac Nurs. 8 (8) (2013) 375–381.

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