Chapter 2
Polymeric Biomaterials

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2.1 Introduction

Recognition of the chemical nature of polymers began in the early 1920s, when Staudinger concluded from his research on starch, natural rubber and cellulose that these compounds consisted of giant chains of carbon atoms (plus oxygen atoms in the case of the polysaccharides) held together by covalent bonds. "They were truly macromolecules." This notion was met with disbelief and even ridiculed by many of his colleagues. Not until the 1930s, when linear polymers were synthesized, especially by W.H. Carothers in the Du Pont laboratories, did Staudinger's concept gain universal acceptance. The Nobel Prize in chemistry was finally given to him in 1953. Medical devices have been employing polymers in every aspect for many years. Typical examples are polyethylene and polyolefin bottles, polystyrene vials, rubber closures, plastic tubing for injection sets, flexible bag of plasticized polyvinyl chloride to hold blood and intravenous solutions. Barrels and plungers of hypodermic syringes are made of polypropylene. In addition to polymers used as excipients, some drugs themselves are polymers including insulin, heparin and its antagonist, protamine sulfate, the plasma extenders dextran, human serum albumin, and bulk laxative methylcellulose. Thus, it is seen that polymers are essential to all medical fields.

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2.2 Nomenclature

Generally, polymers are named by either common names or by the IUPAC naming system. The common name is given on the basis of starting monomer used for polymerization. According to this system, the polymer is named as a prefix "poly" before the name of monomer used written in brackets. For example, the name "poly(ethylene glycol)" is derived for the polymer prepared from ethylene glycol. Similarly, the name "poly(ethylene oxide)" is derived from the ring opening polymerization of ethylene oxide, although it has the same chemical structure of poly(ethylene glycol). According to the IUPAC system the polymers are named by writing the repeating units within bracket and "poly" as a prefix [1]. The common and IUPAC names of some polymers with their monomers used are listed in Table 2.1.

2.3 Biopolymer in Medical Applications

Biopolymers based on medical applications can be categorized into four groups, namely, inert, natural, bioactive, and biodegradable polymers. This classification does not clearly separate one group of polymers from the others. The first group that was introduced into the medical field is inert polymers, which are widely used. They suit very well with some applications that are aimed to last for a lifetime, such as breast implant polymer. When the concern over the load of non-biodegradable polymeric materials increases dramatically, the situation drives to the use of biodegradable instead. In particular, if the functions of the polymers are complete, they should be removed from the body in biomedical applications. Biomedical polymers in medicine and surgery are currently widely used and include intracorporeal, paracorporeal, and extracorporeal applications (inside, interfacing, or outside the body, respectively). Applications are given in Table 2.2.

The science and technology of polymers for biomedical applications has been dramatic for several years. Medical polymers must adhere to very rigid standard and must be non-toxic, non-carcinogenic, biocompatible, and in no way injurious to the biological environment. Artificial organs and prostheses constitute some of the most valuable remedies in present medical treatment. They have contributed immeasurably

Table 2.1 Common and IUPAC nomenclature of polymers

Monomer used	Common name	IUPAC name
Ethylene	Poly(ethylene)	Poly(methylene)
Vinyl acetate	Poly(vinyl acetate)	Poly(1-acetoxyethylene)
Styrene	Poly(styrene)	Poly(1-phenylethylene)
Vinyl chloride	Poly(vinyl chloride)	Poly(1-chloroethylene)
Formaldehyde	Poly(formaldehyde)	Poly(oxymethylene)
Ethylene glycol	Poly(ethylene glycol)	Poly(oxyethylene) etc.

Table 2.2 Biopolymer medical applications

Intra-corporeal (implanted) materials	Temporal devices	Surgical dressing, sutures, adhesives, polymeric intermedullary nails, polymer-fiber composite bone plates
	Semi-permanent devices	Tendons, reinforcing meshes, heart valves, joint reconstruction and bone cement, tubular devices, soft tissue replacement, interocular and contact lenses, drug delivery implants
	Complex devices	Artificial kidney/blood dialysis, artificial lungs/blood oxygenator, artificial pancreas/insulin delivery system, artificial heart
Para-corporeal or extra-corporeal materials		Catheters, blood bags, pharmaceutical containers, tubing, syringes, surgical instruments

Table 2.3 Medical applications of biomaterials in the United States (1983) [2, 3]

Applications	Type of application	Number per year
Permanent implantations	Heart valve	30,000
	Pacemakers	130,000*
	Vascular grafts	250,000*
	Hip prostheses	110,000
	Knees prostheses	65,000
	Shoulders and finger joints	50,000
	Retinal surgery	35,000
	Intraocular lenses	2,700,000*
	Breast prostheses	100,000
	Nose and chin prostheses	10,000
	Urinary incontinence	2500
	Hydrocephalus shunts	21,500
Intermediate applications	Contact lenses	30,000,000*
	Dental prostheses	15,000
	Renal dialyzers	16,000,000*
	Ventricular assists	>100,000*
Transient applications	Cardiopulmonary bypass	150,000
	Blood oxygenators	200,000
	Over–the-needle catheters	200,000,000*
	Therapeutic catheters	150,000
	Infusion catheters	300,000

*(2002)

to the welfare and health of the human race. Although the production of medical polymers is small compared with other industrial plastics, the number of individuals who benefit from these uses is large (Table 2.3).

Polymers penetrate virtually every aspect of medicine, although the science of polymeric biomaterials is much more recent than that of other high-molecular-weight polymers. A few polymers have been designed for medical use, e.g., hydrogels for soft contact lenses, poly(glycolic acid) for absorbable sutures, special ion exchange resin, semipermeable membranes; and more are likely to be created

Table 2.4 Medical uses of polymers

Polymer	Applications
Polyvinyl chloride	Extracorporeal devices; hemodialysis or hemoperfusion, blood tubing, cardiac catheters, blood bag and IV infusion set, endotracheal tubes surgical tapes, sheet oxygenator, artificial heart, blood pump, artificial limb
Ultrahigh MW polyethylene	Acetabulum in total hip prostheses, artificial knee prostheses
Polypropylene	Membrane oxygenator, finger joint prostheses, IV cannulae, unabsorbable sutures
Silicone rubber	Hydrocephalus shunts, catheters, membrane for oxygenator, artificial skin for burn dressing, plastic surgery implant, artificial heart, heart-assisted pump, drug release system, atrioventricular shunts, ear prostheses, facial prostheses, artificial heart valve, tendon, finger joint repair, tracheal prostheses, bladder prostheses, bladder patch, intestine patch, dura-mater prostheses, retinal detachment, impressing materials, heart pacemaker leads
Polycarbonates	Membrane for oxygenator, hemodialyzer, plasmapheresis membrane
Polyester	Vascular graft prostheses, fixation device for tissue, hernia repair, patches for heart, bladder, arteries, suture
Polytetrafluoroethylene	Vascular graft prostheses, heart patch, retinal detachment, femoral stems
Polyurethane	Artificial heart pump material, balloon, heart valve prostheses, wound dressing, vascular graft prostheses, coating for blood compatibility
Polymethyl methacrylates	Bone cement, artificial teeth, denture material, bone prostheses, cranial bone replacement, intraocular lenses, membrane for dialysis

(Table 2.4). Although production may be low in some cases, patient benefits are high enough to justify the industry's support of the high costs of research and development.

Most engineering progress through the centuries was dependent on the discovery and availability of new materials. In fact many modern technologies require materials with unusual combinations of mechanical properties, lightness, and ease of processing. For example, biomedical applications are increasingly searching for structural materials that have low density; are strong, stiff, abrasion, and impact resistant; and are not easily corroded. Table 2.5 gathers some characteristics of thermoplastic polymers used in medical applications.

2.4 Inert Polymers

Inert durable polymers (non-biodegradable) do not undergo any chemical change in vivo. Both hydrophobic and hydrophilic polymers may fit this category. Table 2.6 gives a list of the commonly used inert polymers.

Table 2.5 Characteristics of typical thermoplastic polymers [4]

Material	Tensile modulus (GPa)	Tensile strength (MPa)	Glass transition temperature (°C)	Melting point (°C)	Processing Temperature (°C)
Polypropylene	1.1–1.6	30–40	−10	165	200–240
Polyamides	3–3.3	80–90	47–57	225	240–270
Polyethyleneterephthalate	2.7–4	50–70	70	265	280–310
Polycarbonate	2.3–3	60–70	150	Amorphous	280–330
Polyglycolic acid	6.5	57	35	225	200–205
Polylactic acid	2.1	59–79	60	180	180–200
Polycaprolactam	0.3	19	−60	210–255	<300
Polyhydroxybutyrate	2.5–3.5	36–40	1	171	95
Polyorthoester	0.8–1.2	20–27	55–95	Amorphous	95
Polyanhydride	0.04	4	–	46–49	40–50

Table 2.6 Commonly used inert polymers

Inert polymers	Applications
Silicones	Pacifier, therapeutic devises, implants, adhesive in transdermal delivery
Polyacrylates	Bone and dental cement, intraocular lens
Polyethylene and related polymers	Load-bearing orthopedics, cardiovascular, surgical mesh, artificial blood vessels, and cochlear implants
Polyamides	Drug delivery, catheters, syringe
Polyurethanes	Drug delivery, tissue engineering, transdermal patch backing, blood pump, artificial heart, vascular grafts, foam in biomedical and industrial products
Polyesters	Drug delivery, transdermal patch packing
Polyethers	Coagulant, flocculent, swelling agent, plasticizers

2.4.1 Silicones

Silicones were one of the first polymers studied due to their excellent biocompatible and ease of fabrication into various medical devices. A number of medical products employing silicones have been commercialized including implants for contraceptives and ear replacement (Fig. 2.1). A class of polymers' considerable importance is based on a linear, cyclic, or cross-linked arrangement of alternating silicon and oxygen atoms, where the silicon is substituted with organic radicals or hydrogen. They are called polyorgano-polysiloxanes or simply "silicone" polymers.

The usual procedure for preparing silicone polymers is to hydrolyze single or combinations of R_3SiCl, R_2SiCl_2, $RSiCl_3$, and $SiCl_4$. The intermediates in the reaction are believed to be silanols which condense very rapidly with the elimination of water and formation of the Si-O-Si link (Scheme 2.1).

Linear silicones $[(CH_3)_3Si(OSi(CH_3)_2]_n–OSi(CH_3)_3$, where n is in the range of 10–20, are known as silicone oils. Cyclic silicones, formed in hydrolysis reactions

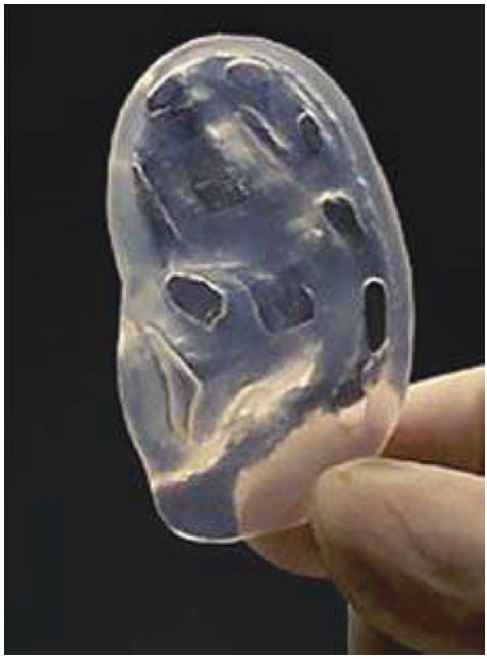
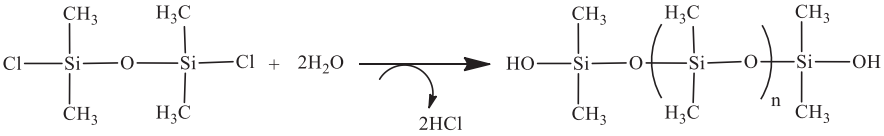


Fig. 2.1 Silicone ear replacement



Scheme 2.1 Preparation of polyorgano-polysiloxanes or silicone polymers

of the silane dihalides, especially $[(CH_3)_2SiO]_{3–4}$, are convertible to high-molecular-weight linear silicone elastomers. Various curing techniques are available for converting linear and cyclic materials to cross-linked elastomers and resins. Linear silicone polymers are conveniently prepared from a base-catalyzed ring opening polymerization of the cyclic tetramer or trimer.

Silicones have some unique chemical and physical properties. They are inert to cells and tissues and they are stable to heat and irradiation, which suggests that silicone-based products are sterilizable. It was these properties that inspired scientists and physicians to consider the use of silicones for medical applications [5]. Silicones are now used in many surgical and non-surgical procedures and their use extends to a variety of medical instruments.

Silicones have a specific gravity lower than water and are commonly used fluids in medical practice. The viscosity of oil is directly related to molecular weight but also the ability to slip past one another. Silicones are produced as oils and gels, gums and elastomers. The strength and elasticity of silicone elastomers is a function of polymer chain length, organic side groups and the degree of cross-linking. The

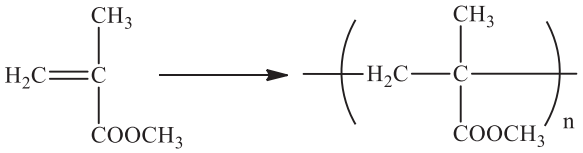
basic ingredients to make silicone elastomers clear and highly viscous are vinyl group substituents. Other radicals in the silicone rubber determine the physical properties of the resultant elastomer. The most common mechanism of cross-linking occurs by a radical attack on the pendant alkenyl groups from the silicon initiates by heat (heat vulcanization) or benzoyl peroxide. The reaction intermediates containing carbon free radicals then combine to form the carbon-carbon covalent cross-linking bond. In some cases, cross-linking-facilitated substitution of vinyl groups takes place because the double bond of this group is quite susceptible to free radical attack. In order to increase tensile strength, the pre-vulcanized silicone is usually mixed with fillers such as fumed silica, talc, and TiO_2. By changing the amount of filler added to a silicone rubber elastomer, one can change its degree of hardness.

The prototype of a silicone rubber sac filled with silicone gel was seen as a mammary prosthesis and was later marketed by Dow Corning after undergoing the first human trial. During 1960–1970, Dow Corning introduced many improvements to enhance the mammary prosthesis, which became a multimillion dollar product. Lately, silicone breast implants have been associated with complications such as capsular contracture, enlargement of lymph nodes, draining the implant area, and occasionally rupture of the silicone sac and bacterial contaminations [6]. The drying effects of silicone in the surrounding soft tissues enhance the scar formation, and this is another possible contributing factor to the formation of the capsule. Physical changes and alterations of the silicone implants as well as the use of wetting agent such as poly(vinyl pyrrolidone) have reduced the incidence of capsular contracture.

Polydimethylsiloxane is an inert polysiloxane and used as a drug delivery agent due to its biocompatibility of blood-contacting biomaterials. It has some ideal properties such as nontoxicity, elasticity, and durability, smother surface with transference, and good permeability of gas molecules such as oxygen and carbon dioxide; and thereby it has been used as wound dressing and contact lens applications after coating with collagen, fibronectin, or other bioadhessive materials because it itself has no adhesive property to tissue cells due to its hydrophobicity [7].

2.4.2 Polyacrylates

Polyacrylates may be safely bulk polymerized under mild conditions (Scheme 2.2). In this way it is possible to prepare a casting by in situ polymerization at 40 °C. The polymerization of acrylate esters can be carried out readily. The acrylate esters form glassy materials similar to the methacrylates but superior in light transmission. For

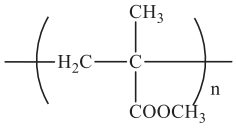
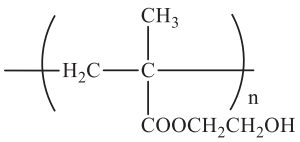
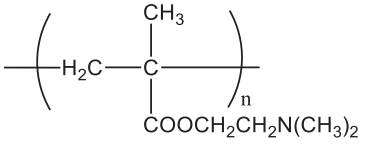
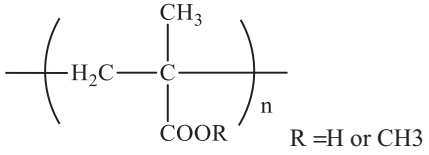


Scheme 2.2 Polyacrylate preparation using acrylates

this reason, methacrylate esters have achieved considerably greater popularity as clear plastic materials. The largest single factor in determining whether a polymerization is successful or not is the purity of the monomer used. It is absolutely essential that the material be pure. Polyacrylates have been used in different applications as summarized in Table 2.7. This group of polymers is widely used for intraocular lenses, bone cement, dentures, and middle ear prostheses. Polymethylmethacrylate (PMMA) is a standard implant material for intraocular lenses due to their bioinertness, nondegradability, UV light resistance, and transparency with a refractive index 1.5; as a result it is biocompatible with vascular tissues. Its smooth surface modified with heparin was used in intraocular lenses to reduce postoperative inflammation and corneal endothelial cell damage thereby improved biocompatibility compared to unmodified polymethylmethcrylate [8].

One of the most popular polymers in this group are cross-linked poly(2-hydroxyethyl methacrylate) (HEMA) hydrogels, invented in the 1950s by the Czech chemist Otto Wichterle. The permeability and hydrophilicity of these gels are

Table 2.7 Polyacrylates and their applications

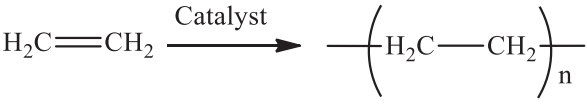
Structure	Applications
Poly(methyl methacrylate) 	Intraocular lenses, bone cement, dentures and middle ear prosthesis, orthopedic surgery
Poly(2-hydroxyethyl methacrylate) 	Soft contact lenses, cartilage, matrix in drug delivery system, burn treatment
Poly(2-(dimethylamino)ethyl methacrylate) 	Radical scavenging agent, drug delivery devices
Poly(methyl methacrylate)-*co*- (methacrylic acid)  R = H or CH3	Enteric coating in tablets, gel for encapsulation of biological materials, biofilm on medical implants

dependent on the cross-linking agent. Poly(HEMA) has been used for ophthalmic products including contact lenses as well as in many drug delivery systems. Macroporous poly(HEMA) gels have been prepared by freeze/thaw or particulate leaching techniques for cartilage replacement. Many different types of molecules and cells have been encapsulated into poly(HEMA) gels, and this approach has been reported to be successful for delivery of insulin and other proteins. Poly(HEMA) gels are not degradable in physiological conditions. Copolymers of MMA with methacrylic acid at a 1:1 ratio are insoluble at acid pH, but not at neutral pH. These copolymers are used as enteric coating of tablets that pass safely through the stomach and dissolve when the tablet reaches neutral pH in the small intestine. These group polymers such as methacryaltes (*N,N*-dimethylaminoethyl methacrylate) and methacrylamides (poly(*N*-isopropylacrylamide)) hydrogels and their microstructures are stimuli such as temperature, pH responsive polymers; and they are useful in drug delivery, tissue generation/repair, smart coatings, biosensing, and artificial muscles [9].

2.4.3 Polyethylene and Related Polymers

Low-density branched polyethylene was first prepared in 1933 (Scheme 2.3) by radical polymerization at high pressure and temperature (>200 °C) without a catalyst. Polyethylene made at high pressure with free radicals will vary in properties from a linear high-density to high-branched low-density material depending on polymerization variables. For the preparation of high-density polyethylene with a low degree of branching, a Ziegler Natta catalyst should be used. The product is usually obtained as a white powder which can be molded to clear, tough films or extruded to tough fibers. In medical applications, it has been used for disposable product such as tubing, shunts, syringes, or packaging materials. The combined polymeric matrix of high-density polyethylene (HDPE) with hydroxyapatite and aluminum particles was explored as load-bearing materials of teeth, bones, and joints. Similarly HDPE composites with acrylic acids and silanes to improve the mechanical properties were used in minor load-bearing bones such as cheek and ear drums [10]. Ultra-high-molecular-weight polyethylene (UHMWPE MW >2,000,000 Da) has been used as acetabular cups in hip and knee replacements by adding additives like vitamin E (Figs. 2.2 and 2.3) due to its high durability and resistance to abrasion.

Polypropylene may be polymerized over the catalyst (transition metallic halide). The polymers are generally high in molecular weight. In normal polymerization of a substituted olefin, a new asymmetric center is produced as each monomer unit is



Scheme 2.3 Polyethylene preparation using Ziegler Natta catalyst

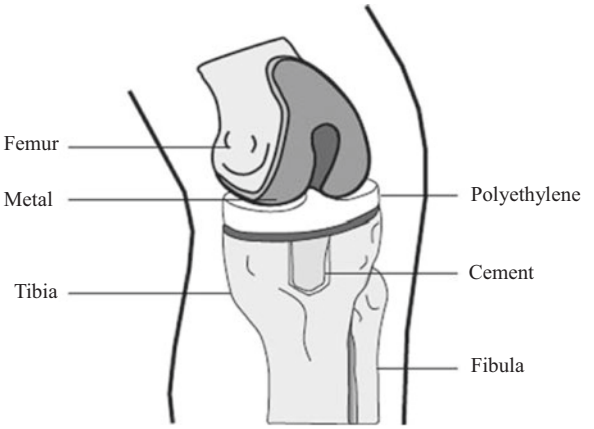


Fig. 2.2 Total knee replacement

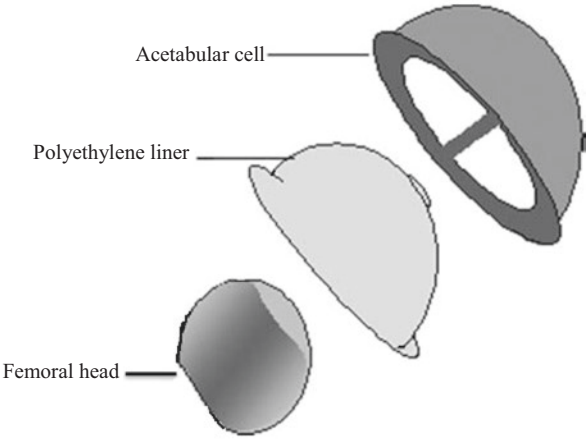
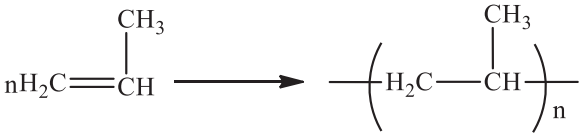


Fig. 2.3 Total hip replacement

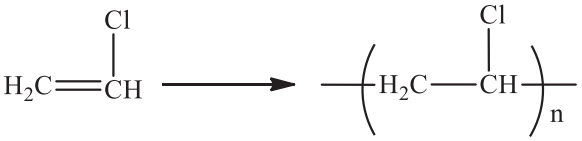
added, but there is no control of the configuration of each succeeding center (Scheme 2.4). The result is a completely random configuration of the chain. The stereo regularity permits the chains to crystallize; hence the properties of the polymers differ markedly from the random counterpart. Polypropylene showed high stiffness and strength with improved mechanical properties compared to polyethylene. Polypropylene fibers were used as drug delivery agents of tetracycline in teeth root canal treatment and high load-bearing bone materials [11, 12]. It is widely used as sutures catheters, collecting bags, prosthetic valve structures, plasmapheresis membrane, and packaging materials.

Polymerization of vinyl chloride was known to be a useful plastic material before World War I (Scheme 2.5). The polymerization is exothermic, and great quantities of heat have to be dissipated through the walls of the polymerization tank to the cooling medium in the jacket. In order to obtain better heat transfer once the polymerization begins, refrigerated brine is circulated in the cooling jacket at about

Scheme 2.4 Propylene polymerization over the transition metallic halide catalyst



Scheme 2.5 Polyvinyl chloride preparation



−20 °C. An accurate control of the temperature is necessary since the molecular weight is extremely sensitive to the variation in temperature. High-molecular-weight material is obtained with the internal temperature of 48–50 °C. The polymer is converted to dry powder by spraying onto a contoured rotating heated roller. The medical use of PVC is as tubing, plasmapheresis equipment, and blood bags.

2.4.3.1 Poly(Vinyl Alcohol)

Poly(vinyl alcohol) (PVA) is generally obtained from poly(vinyl acetate) by hydrolysis. The hydrophilicity and solubility of PVA can be controlled by the extent of hydrolysis. PVA forms hydrogels by chemical cross-linking with glutaraldehyde or epichlorohydrin. To avoid the toxicity and leaching of chemical cross-linkings, a repeated freeze/thawing method or electron beam has been applied to form PVA hydrogels. The gels formed by the repeated freeze/thawing method were reported to be stable at room temperature and highly elastic. These gels are not degradable in physiological situations and are therefore useful as long-term or permanent scaffolds. PVA hydrogels have been used in tissue engineering for regeneration of artificial cartilage and bone-like apatite formation. Graphite-polyvinyl alcohol composites form high porous hydrogels by freeze-thawing process, and particle leaching technique was used as a novel artificial cornea porous skirt [13].

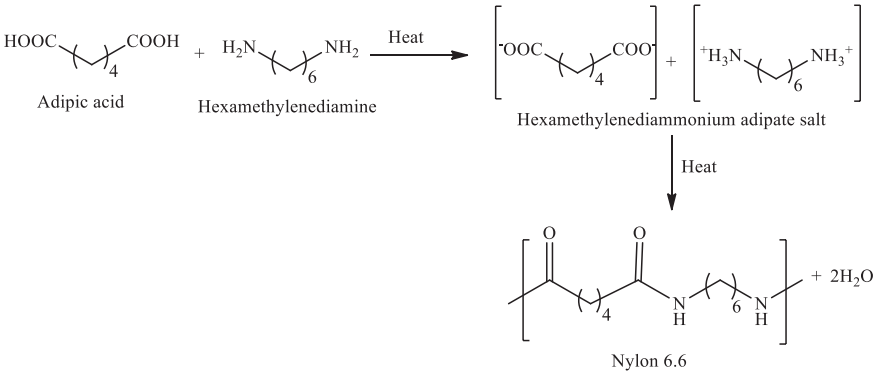
2.4.4 Polyamides

Polyamides are prepared from acids and amines. Regular high-molecular-weight polyamides such as polycaprolactam (Nylon 6) and Nylon 6.6 possess high mechanical strength, elasticity, and biocompatibility and resist enzymatic attacks. Adipic acid (6-carbon atom monomer) and hexamethylene diamine salts are prepared first and then the salts are heated at higher temperature to form Nylon 6.6 polyamide [14]. The polymerization reaction takes place at a higher temperature than the melting points of the reactants and the polymer (Scheme 2.6). In order to polymerize,

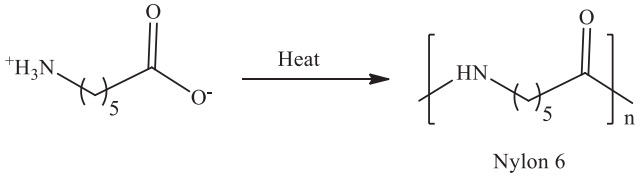
this mixture is brought to a temperature of 255–265 °C under nitrogen. Nylon 6 is prepared from the 6-carbon monomer, 6-amino hexanoic acid. Nylon 6 is a tough plug with melting point of about 215 °C. It may be fabricated into a tough film by pressing or extruding in the form of filament. Both film and filament may be stretched over a hot plate to give highly oriented crystalline products. These polymers have applications in surgical sutures and hemodialysis membranes.

2.4.5 Polyurethane and Polyurea

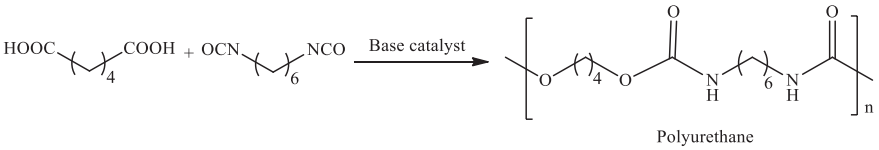
Polyurethanes are prepared by stepwise polymerization reaction, but without the elimination of byproducts such as water or hydrochloric acid [14]. The addition of diol (1,4-butanediol) to a diisocyanate (1,6-hexadiisocyanate) gives a polyurethane (Scheme 2.7). 68% of polyurethane production was utilized as flexible, semi-rigid, and rigid foams in the total polyurethane polymer production in worldwide; another 14% of polyurethane was used in coating applications; and remaining 18% polyurethane production was explored as cast elastomers, leathery polyurethanes, fibers, and films, thermoplastic elastomers, millable elastomers, adhesives, sealants, and plastics [15].



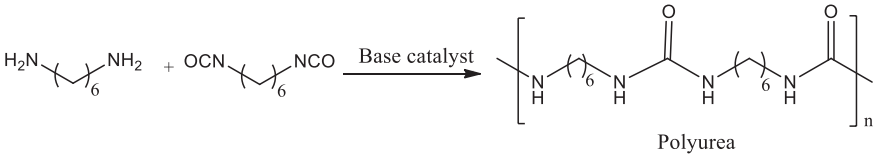
b. *Preparation of Nylon 6*:



Scheme 2.6 Polyamide preparation using acids and amines. (**a**) *Preparation of Nylon 6.6*: (**b**) *Preparation of Nylon 6*:



Scheme 2.7 Conjugation of carboxylic acids with isocyanates



Scheme 2.8 Conjugation of primary amines with isocyanates

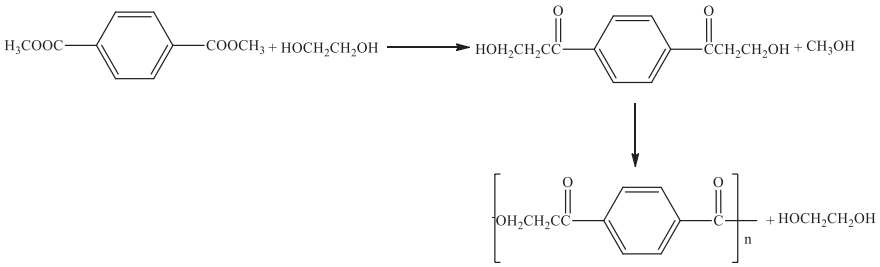
Similarly, polyurea is prepared from the reaction of a diamine such as hexamethylenediamine with a diisocyanate (Scheme 2.8). Several applications are found for this group of polymer such as catheters, pacemaker leads, tubing, intra-aortic balloons, wound dressing, artificial heart components, cardiac prosthetic valves (Fig. 2.4), device coatings, etc.

2.4.6 Polyesters

Poly(ethylene terephthalate) is a common polymer prepared by a melt polymerization, commercialized as Dacron®. The following polymerization process is applicable in general to any system in which monomers and polymers are thermally stable at temperatures above the polymer melting point and the glycol is sufficient volatile to permit the excess to be removed under vacuum. In this preparation there are two ester exchange reactions. The first forms monomer from excess glycol and dimethyl terephthalate, with elimination of methanol. The second eliminates glycol and forms the polymer (Scheme 2.9).

Dimethyl terephthalate and ethylene glycol at a 1:1 mole ratio heated at 200 °C in the presence of calcium acetate forms oligomers which at 300 °C gave poly(ethyleneterephthalate) and methanol as byproducts. This polymer is used in synthetic fibers, films bottles, vascular grafts, tissue patches, and shunts. PET has been used as sutures and vascular grafts like a sewing cuff around the heart valve to encourage tissue growth factors [16]. Knitted Dacron has been implanted after impregnating with albumin, collagen, and gelatin to make it more impermeable; otherwise blood has to be clotted before implantation [17]. PET-based films were fabricated with cationic biocompatible materials like polyethylene imine, Chitosan, etc.; and these films were used as antimicrobial medicinal applications of sterile packing, and sanitization. PET and polyethylene/propylene blending polymeric

Fig. 2.4 Artificial heart valve



Scheme 2.9 Poly(ethylene terephthalate) preparation by a melt polymerization

materials were used in shape-memory polymers and medicinal implants. PET-based artificial ligaments were prepared with significant abrasion, mechanical robustness, and biocompatible non-absorbable ligaments. PET-based stents and balloons were also reported. Medical electronic devices such as silver nanowires coated with transparent PET layer and electronically conductive PET/polyethylene composites were also prepared [18].

2.4.7 Polyethers

Poly(ethylene oxide) (PEO) and poly(ethylene glycol) (PEG) have the same polymer structure made of different monomers; one is made from ring opening of ethyleneoxide and one from the condensation of ethylene glycol, respectively. PEG has been approved by the FDA for several medical applications due to its biocompatibility and low toxicity. It has been extensively used as an excipient in pharmaceutical formulation for oral and injectable administration to stabilize proteins by chemical conjugation of PEG, surface modification of biomaterials, and induction of cell membrane fusion. PEG itself is very hydrophilic and can be synthesized by anionic or cationic polymerization of ethylene oxide. PEG gels can be prepared by UV polymerization of the precursor that consists of PEG with acrylate terminal at

each end in the presence of α-hydroxy acids. Star-shaped PEG has been cross-linked by irradiation to form hydrogels and modified with galactose moiety to enhance the interaction with liver cells. Various PEO-based polymers have been reported and utilized especially in drug delivery. One interesting copolymer is a triblock copolymer of PEO and poly(propylene oxide) (PPO) which is known under the trade name of Pluronics® or Poloxamers® and is available in various lengths and compositions. These polymers form thermally reversible gels without any permanent cross-links. Moreover, PEO-PPO-PEO triblock copolymers can be designed to form gels at body temperature. A few PEO-PPO-PEO copolymers are in clinical use as surfactants and solubilizers in injectable formulations.

2.5 Natural Biopolymer

Biomaterials are mainly from natural origin such as polysaccharides, collagens, fibrins, alginates, chitin and chitosan, etc. Such materials are often complex and difficult to characterize. Some of the biodegradable natural polymers are widely used in biomedical applications listed in Table 2.8 [19].

2.5.1 Collagen and Gelatins

Collagen is the most widely used tissue derived from natural polymer; and it is a main component of extracellular matrices of mammalian tissues including skin, bone, cartilage, tendon, and ligament. Only two types of collagens (type I and type III) in all those available collagens are abundantly available and used majorly. Type I is composed with α1 and α2 chains with a diameter about 50 nm, and type III is composed with 3α chains with a diameter of 30 to 150 nm. Collagen contains mainly three polypeptides with a left-handed helical pattern and every third repeating unit contains glycine, hydroxyproline, and proline. Due to their immunogenic response of native collagen, only reconstructive or purified collagen has been used in biomedical applications [19]. Physically formed collagen gels are thermally

Table 2.8 Biodegradable natural polymers for biomedical applications

Polymers	Applications
Starch	Foams, films, and bioactive food packing and coating materials
Cellulose	Bioactive food packing and coating materials
Collagen	Prosthetic heart valves, membranes, wound dressing, tissue engineering
Chitosan	Drug delivery, tissue engineering, surgical sutures, bone grafting, wound healing
Gelatin	Binding agent, tissue engineering, membranes

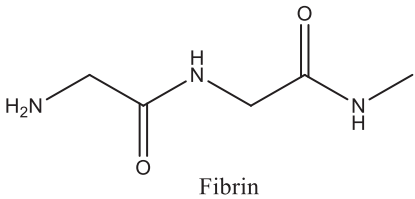
reversible and offer a limited range of mechanical properties. Chemical cross-linking of collagen using glutaraldehyde or diphenylphosphoryl azide can improve the physical properties. However, these gels are still short of physical strength and potentially immunogenic and can be expensive. Furthermore, there can be variations between batches. However, collagen meets many of the biological design parameters, as it is composed of specific combinations of amino acid sequences that are recognized by cells and degraded by enzymes secreted from cells (i.e., collagenase). Collagen has been used as a tissue culture scaffold or artificial skin due to the ready attachment of many different cell types and its cell-based degradation. The attachment of cells to collagen can be altered by chemical modification, including the incorporation of fibronectin, chondroitin sulfate, or low levels of hyaluronic acid into the collagen matrix. Collagen gels have been utilized for reconstruction of skin, blood vessel, and small intestine.

Gelatin is a derivative of collagen, formed by breaking the natural triple helix structure of collagen into single-strand molecules. There are two types of gelatin, A and B. Gelatin A is prepared by acidic treatment before thermal denaturation, while gelatin B is processed by alkaline treatment that leads to a high carboxylic content. Gelatin forms gel by changing the temperature of its solution. It has been used in many tissue engineering applications due to its compatibility and ease of gelation. Gelatin gels have also been used for the delivery of growth factors to promote vascularization of engineered new tissue. However, the weakness of the gels has been a problem and a number of chemical modifications have been investigated to improve the mechanical properties. Gelatin is used as hemostatic which produces hemostasis by accelerating the blood clotting process (Gelfoam®, Surgifoam®).

2.5.2 Fibrin

Fibrin is similar to natural collagen polymer and molecular weight is 360 kDa (Fig. 2.5). It contains three fibrinopeptides of A, B, and D and involved in the blood clotting process in the human body. It can form the linear fibrils with a diameter of 200 nm by enzymatic (thrombin) cleavages. Fibrin or fibrin glue has been used as a sealant and an adhesive in surgery as it plays an important role in natural wound healing. Fibrin gels can be produced from the patient's own blood and used as an autologous scaffold for tissue engineering. Bioseeds®-s is a commercially available wound healing product in the market, and it is a combination of keratinocytes pro-

Fig. 2.5 Structure of fibrin



Fibrin

duced by fibrin [20, 21]. No toxic degradation or inflammatory reactions are expected from this natural component of the body. Fibrin forms gels from enzymatic polymerization of the fibrinogen at room temperature in the presence of thrombin. An interesting feature of fibrin is the degradation and remodeling by cell-associated enzymatic activity during cell migration and wound healing.

Fibrin gels may promote cell migration, proliferation, and matrix synthesis through the incorporation of platelet-derived growth factors and transforming growth factor. Fibrin gels have also been used to engineer tissues with skeletal muscle cells, smooth muscle cells, chondrocytes, cells carrier, drug delivery, and active biomolecule transporter. However, fibrin gels are limited in mechanical strength and this prevents their use in certain applications. Fibrin was mixed with ceramic particles to get the porous scaffolds with favorable osteogenic properties for bone healing by providing enhanced mechanical and morphological cues used in angiogenesis, cell attachment, and proliferation as a favor compared to their ceramic individual. Fibrin is widely used in the 3D scaffolds development in tissue engineering for skin, liver, cardiac ocular, tendons, bone, cartilage and nervous systems [22, 23].

2.5.3 Polysaccharide Hydrogels

Cellulose composed of D-glucose units with β-(1 → 4) linkages (Fig. 2.6). Cellulose itself is fibrous hard material in wet state and major ingredient of wood and not soluble in water and their derivatives are soluble. Celluloses offer attractive drug delivery matrixes. Carboxy-methylcellulose (CMC) is one example of hydrogel in clinical use. It is prepared by swelling cellulose in sodium hydroxide solution, followed by reaction with monochloro acetic acid. The acid can react with hydroxyl on C2, C3, and C6 on each glucose unit to give a maximum degree of substitution. The presence of ionizable side groups disrupts the cellulose crystal structure, hence making CMC water soluble. The polymer forms high-viscosity solution. For example, CMC has been combined with hyaluronate to form hydrogel membranes used for the prevention of adhesion after intra-abdominal surgery. CMC also forms insoluble ionic complexes with cationic polymers such as chitosan, polyethyleneimine, and diethylaminoethyl dextran. Microbial cellulose obtained from bacterial species has been converted into micro- and nanofibers with high water retention capability and with high biocompatibility and gains attention in biomedical applications of

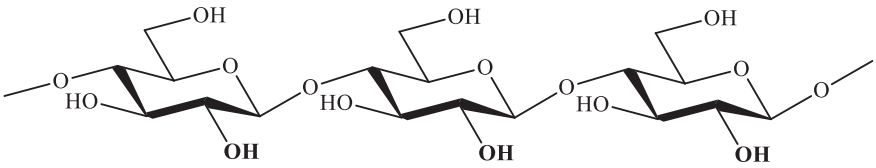
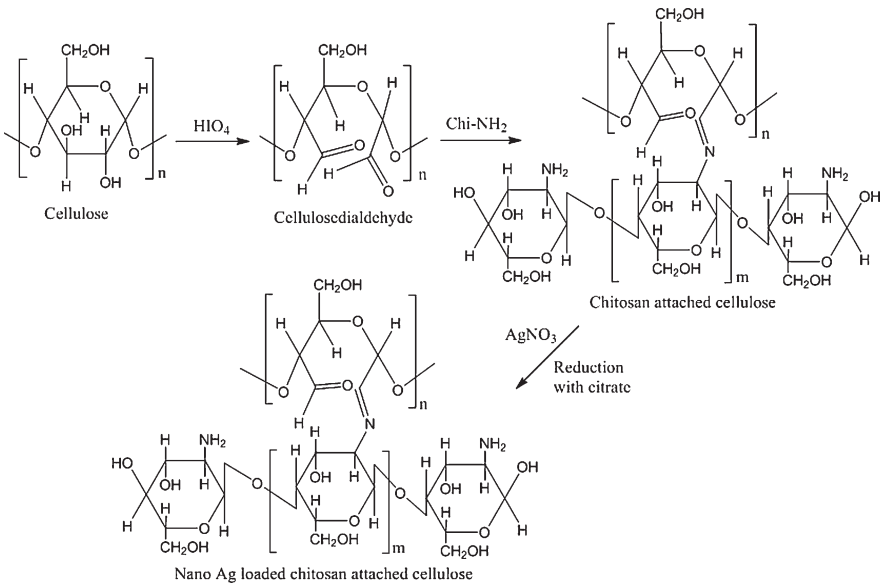


Fig. 2.6 Structure of cellulose

wound dressing and production of vascular conduits [24, 25]. Polyethyleneoxide and poly(*N,N*-dimethylamino)-ethyl methacrylate polymers were grafted on cellulose backbone to form the cationic cellulose polymers and also hydrophobically modified quaternized cellulose polymers were formed the self assembled micelles which are used in the delivery of water insoluble drugs [26].

2.5.3.1 Cotton Cellulose Fiber Composites

Cotton is a natural cellulosic fiber (90%) and swells in a high-humidity environment 7–8% and can hydrolyze or oxidize into hydro or oxycellulose. Most of the cotton fibers used in the textile industry and their cotton fiber-composites are used in biomedical applications. Chitosan-attached cotton fibers with Cu nanoparticles and alginate-attached cotton fibers with Ag nanoparticles are used as antibacterial agents against a number of microorganisms such as *E. coli.,* and can be prepared by grafting polymerization of cotton cellulose fibers with chitosan or alginates (Scheme 2.10) [27].



Scheme 2.10 Nanosilver-loaded chitosan-attached cotton cellulose fibers

2.5.4 Glycosaminoglycans

Glycosaminoglycans (GAGs) are linear hetero polysaccharides consisting of disaccharide units with the general structure of uronic-amino sugar (Figs. 2.7, 2.8, and 2.9). In their native form, several GAG chains are covalently linked to a central protein core and the protein-polysaccharide conjugates are termed proteoglycans.

There are six different types of GAGs – chondroitin sulfate, dermatan sulfate, keratan sulfate, heparin sulfate, heparin, and hyaluronic acid. Heparin and hyaluronate are interesting candidates for the development of implantable biomaterials. Heparin is being examined for tissue regeneration and wound healing. Many of current available hydrogels are based on synthetic non-biodegradable polymers. Hyaluronate has shown excellent potential for tissue engineering applications such as artificial skin, facial intradermal implant, and soft tissue augmentation. However, hyaluronate requires thorough purification to remove impurities and endotoxins that may potentially transmit diseases. In addition, hyaluronate gels possess low mechanical properties. Hydrogels synthesized from hyaluronic acids support the human embryonic stem cell growth in vitro because they co-regulate the gene expression, signaling, motility, adhesion, metastasis, proliferation, and morphogenesis of human embryonic stem cells in vivo [28].

Proteoglycons are formed complex biomaterials with proteins such as collagen, fibrin, and chitosan etc. and widely used Matrigel™ scaffold is the combination of GAGs and extracellular matrix proteins. Among those collagen forms biocompatible scaffold for tissue engineering applications with GAGs because collagen creates cell-friendly environments. The first commercially used tissue-engineered product is a collagen-GAG hybrid, an artificial skin scaffold, developed by Integra LifeSciences, New Jersey [29, 30].

2.5.5 Alginates

Alginic acids (Fig. 2.10) or alginates are isolated from several species of brown algae (e.g., *Macrocystis pyrifera*). Alginates are block copolymers of α-L-guluronic acid (G) and β-D-mannuronic acid (M) with average molecular weight of 200,000

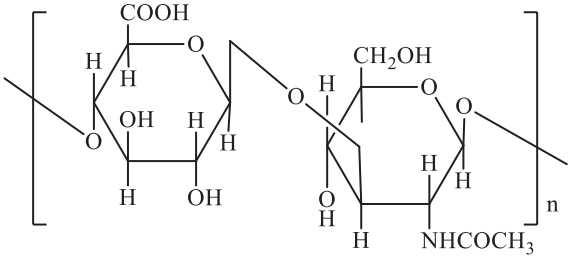


Fig. 2.7 Structure of hyaluronic acid

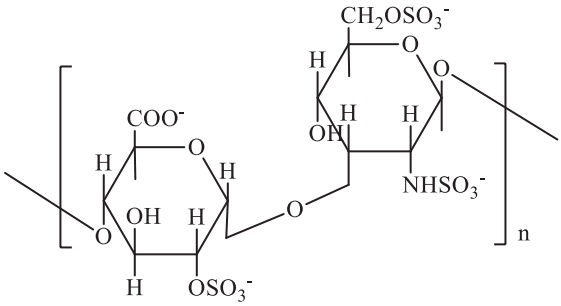


Fig. 2.8 Structure of heparin sulfate

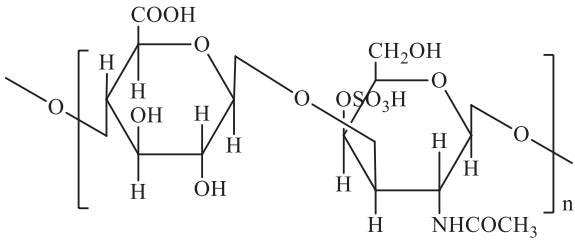


Fig. 2.9 Structure of chondroitin sulfate

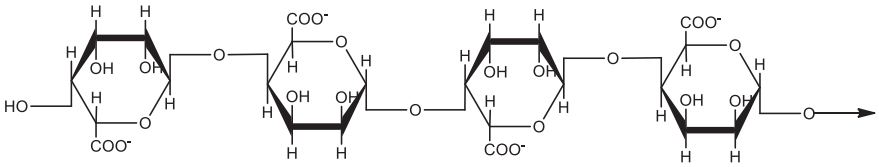


Fig. 2.10 Structure of alginic acid

to 500,000 (Fig. 2.11). G blocks are linked by α-(1 → 4) and M blocks are linked by β-(1 → 4) glycosidic bonds. Simple gelation will be obtained from adding divalent cation such as Ca^{2+} into a solution of alginates. Alginates have applications as an injectable cell delivery vehicle as well as wound dressing, dental impression, and immobilization matrix. Alginates are used as stabilizers in foods and also in low-calorie substitute foods. Alginate materials have been used in the tissue-engineered organs bioartificial pancreas, bone, vasculature, and liver. Alginate gel beads have also been prepared and used for transplantation of chondrocytes, hepatocytes, and islets of Langerhans.

Despite its advantage features, alginate itself may not be an ideal material because it degrades via a process involving loss of divalent ions into the surrounding medium and subsequent dissolution. This process is generally uncontrolled and unpredictable. Therefore, covalent cross-linking with various types of molecules has been attempted to control precisely the mechanical and swelling properties of alginate gels. In addition, molecular weights of many alginates are above the renal clearance threshold of the kidney. The limitation in tissue engineering of using algi-

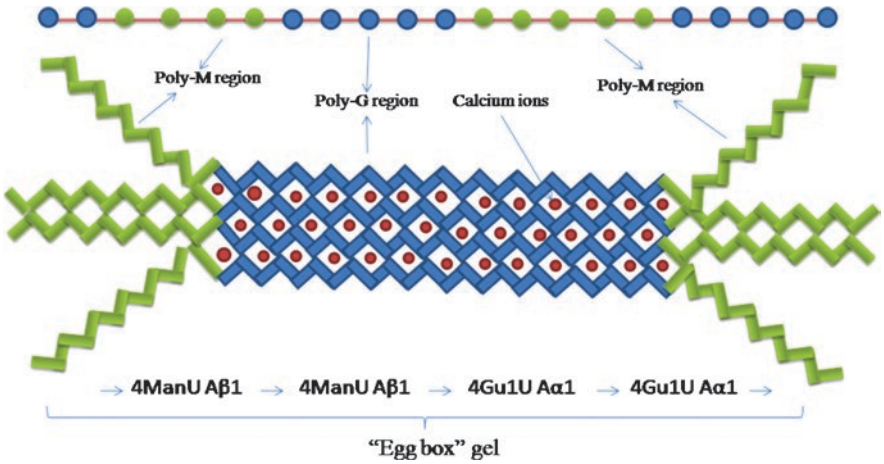


Fig. 2.11 Alginate gel. (Adapted from www.ifis.co.uk)

nate gels is the lack of cellular interaction. Alginate is known to discourage protein adsorption due to its hydrophilic character, and it is unable to interact with mammalian cells. Therefore, alginate has been modified with lectin, a carbohydrate-specific binding protein, to enhance ligand-specific binding properties.

2.5.6 Chitin and Chitosan

Chitosans are partially or fully deacetylated derivatives of chitin with alkaline solution (Fig. 2.12), the primary structural polymer in arthropod exoskeletons. Chitosans are the most promising polysaccharide biomaterials for the development of resorbable and biologically active implants. The primary source of chitin and chitosans is shells from crab, shrimp, and lobster. Shells are ground, demineralized with HCl, deproteinized with a protease or dilute NaOH, and then deacetylated with concentrated NaOH. Structurally, chitosans are very similar to cellulose, except for their amino or acetylamido substitute. The polymer is linear, consisting of β-(1 → 4) linked D-glucosamine units with a variable number of randomly located *N*-acetyl-glucosamine groups. The molecular weight of chitosan is in the range of 50,000–1,000,000. Commercially, available preparations carry 10–30% acetylamido residues.

Chitosan is crystalline and its degree of crystallinity depends on the degree of deacetylation (Fig. 2.13). Crystallinity is maximum when the polymer is fully acetylated with varying crystallinity at intermediate deacetylation. Chitosan is normally insoluble in aqueous solution above pH 7 but is readily soluble in dilute acid (pH < 5) where free amino groups are protonated.

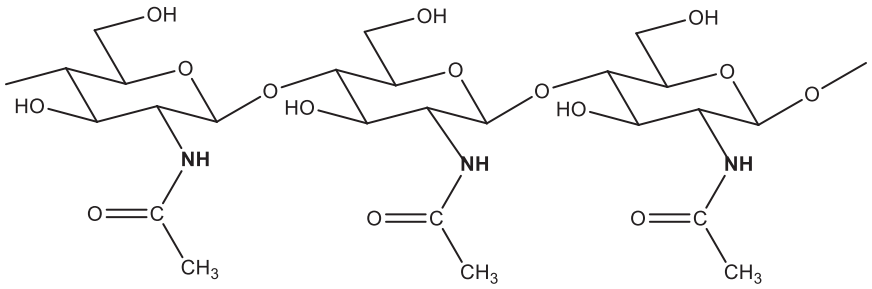


Fig. 2.12 Structure of chitin

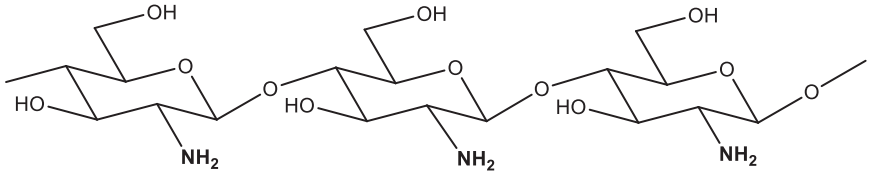


Fig. 2.13 Structure of chitosan

The high charge density of chitosan means that linear chains are of semi-rigid rod conformation. At pH higher than 5, amino groups are increasingly deprotonated and become available for hydrogen bonding, and at some critical pH, the chains in solutions develop enough H bonds to establish a gel network. Gelation pH depends on both the degree of deacetylation and average molecular weight. pH-dependent solubility of chitosan provides a convenient mechanism for its processing under mild conditions. Viscous solutions can be extruded into higher pH solutions or a nonsolvent such as methanol. Gelled fibers can be subsequently drawn and dried to form high-strength fibers. The polymer has been extensively studied for industrial application based on film and fiber formation. Numerous derivatives have been developed to alter biological functions of chitosan, including enhancement of cellular interactions for tissue-engineering approaches. Chitosan has been modified with sugar residues such as fructose or galactose for culture hepatocytes and with proteins such as collagen, gelatin, and albumin for neural tissue engineering. In addition, methylpyrrolidone derivatized chitosan has been reported to promote bone formation. Chitosan derivatives have been used in skin, cartilage, bone, and liver tissue-engineering applications. Chitosan is positively charged polymer, binds with the negatively charged bacterial cell membrane and inhibits the bacterial growth, and is therefore used as an antibacterial agent; and it has minimal immune rejection [31]. Chitosan has also been used as a dietary supplement and it reduces low-density cholesterol and consequently helps in losing weight [32].

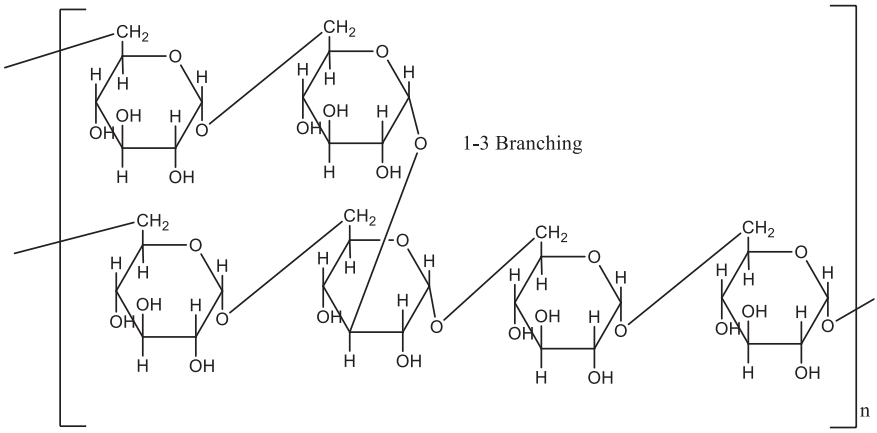


Fig. 2.14 Structure of dextran

2.5.7 Dextran

Dextran is a nontoxic biodegradable polymer and is widely used in many biomedical areas. It is primarily based on 1 → 6-α-D-glucopyranose and carries an average of three hydroxy groups per anhydroglucose unit (Fig. 2.14). Solution of dextran has been used as a surgical aid for reducing tissue adhesion. Derivatization of dextran with maleic anhydride gives the dextran-maleic acid half ester, followed by UV cross-linking and formation of dextran-maleic acid hydrogel. Swelling of dextran-maleic hydrogel increased with increasing the degree of maleic substitution over a wide range of pH. Dextrans have been used for drug conjugation, via reductive amination, to obtain large-molecular-weight drug derivatives for the purpose of altering drug distribution after intravenous injection and accumulation of the drug conjugates in cancer or in flamed tissues, where large molecules leak out from broken blood vessels. Also, conjugation of water-insoluble drugs to the water-soluble dextran provides a water-soluble derivative, which can be injected to a patient. Diethylaminoethyldextran and dextran-spermine are well-known examples of cationic natural polymers of dextran, and especially they are used as DNA/gene transfection agents [33].

2.6 Bioactive Polymers

Interest continued to grow in polymers which have inherent biological activities or are covalently bound with drugs. This part provides an introduction to the polymeric drug, polymeric-drug conjugates, and polymeric pro-drug and targeted polymeric-drug.

2.6.1 Polymeric Drugs

Many synthetic polymers are biologically inert while some exhibit wide ranges of biological activities. They can be categorized into four kinds of polymeric drugs: polycations, polyanions, polynucleotides/polypeptides, and polysaccharides.

2.6.1.1 Polycationic Polymers

These macromolecules have positive charges attached to the polymer chain or as a pendant to the chain. They are active against a number of bacteria or fungi. Recent reports indicate that polycationic polymers can enhance cellular antigen uptake and exhibit antitumor activities. Of the many polycations initially explored as non-viral vectors, polyethyleneimine (PEI) has been most widely studied. PEI promotes endosomal escape via the proton sponge mechanism; linear polymers of MW 22,000 are able to overcome the nuclear barrier and also yield the highest transfection efficiency. Recent promising results obtained using the PEI-polyplexes in vivo in AIDS and cancer are moving forward into clinical evaluation. PEI has the limitation of relatively high toxicity, and this could prove problematic for repeated systemic rather than local administration. PEI derivatives have been found to have a strong antimicrobial activity as well as anti-prion and viral activities. Dimethylamino ethyl methacrylate is another cationic polymer and used in protective coating applications as pH-dependent delivery systems to protect the pH-sensitive drugs. These coating polymers are used to cover the unpleasant odor and taste of the drug, and also to improve the storage stability of drug by protecting from environment moisture [34].

2.6.1.2 Polyanionic Polymers

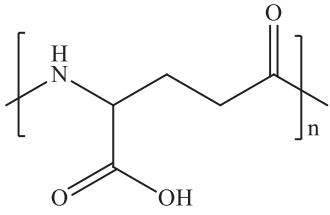
Polymers with negative charges exhibit various biological activities. They can enter biological functions by distribution throughout the host and behave like proteins, glycoprotein, and polynucleotides which modulate a number of biological responses related to the host defense mechanism. These are enhanced immune responses and activation of the reticuloendothelial system macrophages. Examples of polyanions are pentosane sulfate, dextran sulfate, poly(maleic acid) copolymers, and poly(vinyl amino acids). Generally anionic polymers having methacrylic acid functional group are used for drug delivery applications during pasting times because most of the healthy human stomach pH is 2 to 3 and methacrylic acid disassociates at higher pH (>5) and consequently drug can pass into intestine directly up to colon and releases drug slowly [34].

2.6.1.3 Polynucleotides/Polypeptides

Polynucleotides are potent interferon inducers. A mismatched double-stranded synthetic polyribonucleotide ampligen and double-stranded acids, polyadenylic-polyuridylic acid and polyinosinic-polycytidylic acids, have been studied for cancer therapy. Although these materials elicit excellent activity with rodents, therapeutic effects are dramatically decreased within primates. Gene therapy approach or gene delivery (DNA/RNA) from tissue scaffolds biomaterials or from biopolymeric conjugates can enhances the cell growth factors by producing therapeutic protein then leads to development of tissues or manipulate the surrounding tissues or block the formation of tissue. Polyglutamic acid (Fig. 2.15) is a homopolymer polypeptide of acidic monomer of glutamic acid. Polyglutamic acid is produced by the microbial fermentation method via γ-amide linkage, and it contains both L and D-glutamic acids. Poly(γ-glutamic acid) has protease resistance and has been used as a surgical adhesive, a hemostatic agent, drug delivery, and a tissue-engineering application [30, 35]. The polymer poly($_L$-lysine) has also been used in the delivery of nanoparticles siRNA and diagnostic applications of bioimage-enhancing agent by coupling with other chelating ions [36].

2.6.1.4 Polysaccharides

Sulfation of dextrin – a polysaccharide – routinely used for peritoneal dialysis in patients with end-stage renal failure at the 2 (or 6) position produces a polymer that blocks the infection of T cell lines by adapted strains of HIV-1. Dextrin-2-sulfate (MW 25,000 g/mol) given to patients intra-peritoneally daily for 28 days was well tolerated up to the maximal daily dose of 150 mg and in phase III clinical trials it reduced the replication of HIV-1 in patients with AIDS. Coincidentally, dextrin 2 (and6) sulfate inhibits morphological differentiation of endothelial cells into tubes; the reduced lesions are probably the result of anti-angiogenic effect. In gel form, dextrin sulfate is now approved for an intravaginal virucide.



Poly(glutamic acid)

Fig. 2.15 Structure of polyglutamic acid

2.6.1.5 Starch

Starch is composed of D-glucose units with α-(1 → 4) linkages (Fig. 2.16). Starch is derived from plant products which are renewable and sustainable materials and widely used in tissue-engineering applications. Starch contains linear (amylase, typically 20–35%) and branched (amylopectin) polymers with D-glucopyranoside repeating units and can be modified into many other biodegradable products by reacting with hydroxyl functionality of hexose. Acetylated starch forms structural nanofibers and films with good properties when compared to native starch which is more hydrophilic. Natural starch is not moldable and cannot plasticize, but granular starch is plasticized in the presence plasticizer of water, glycerol, or heat and shear. The melt-processable starch is called thermoplastic starch and depending on the plasticizer quantity used in the starch plastic materials are glassy to rubbery. Starch-based thermoplastics are often used in blended form with other hydrophobic thermoplastics to mask the moisture sensitivity, brittleness, and improved mechanical and dimensional stability. Thermoplastic starch was blended with polymers such as polyhydroxybutyrate-co-hydroxyvalerate (PHBV), polycaprolactone (PCL), polybutylene succinate (PBS), PVA, and PLA and used in the preparation of foams and films [37, 38].

2.6.2 Polymeric Drug Conjugates/Polymeric Protein Conjugates

The drug is covalently bonded to an appropriate polymer carrier. These large molecules diffuse more slowly and are adsorbed at pharmacological interfaces. Therefore, drug-polymer conjugates can prolong therapy. The major attributes of polymeric drug carriers are their depot effects, unique pharmacokinetics, and pharmacological efficacy. A model for polymeric drug-conjugates is shown in Fig. 2.17 [39].

It can be seen that four different groups are attached to the polymer backbone. One group is the drug, the second is a spacing group, the third is a transport system, and the last is the group that solubilizes the entire polymer system. The drug can be attached permanently by a stable bond or temporarily and removed by hydrolysis or

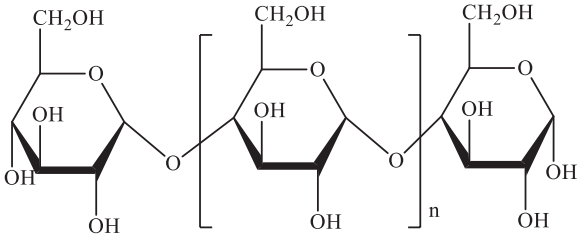


Fig. 2.16 Structure of starch

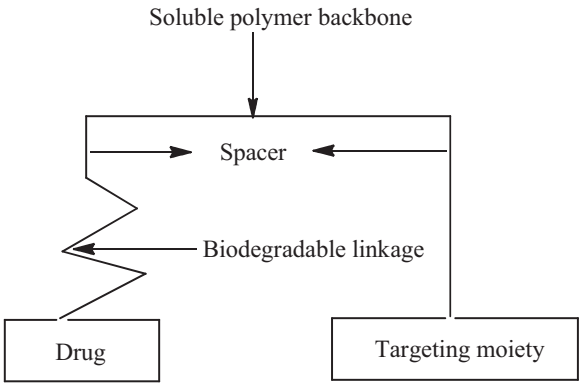


Fig. 2.17 Model for polymer drug carrier

enzymatic processes. The transport system can be made specific for tissue cells. Solubilizing groups are added to increase the hydrophilicity and solubility of the whole macromolecular system in aqueous system while non-polar groups enhance the hydrophobic character in lipid regions. The specificity of polymer is related to molecular size which alters the transport rate across compartmental barrier.

By controlling the weight of the polymer carrier of a polymer drug carrier, it is possible to regulate whether the drug passes through the blood membrane barrier or accumulates in some organs. The macromolecular transport theory of biopolymers through tissues has been successfully applied to the design, fabrication, and prediction of in vivo performance of polymeric drug conjugate systems.

Water-soluble and biodegradable polymers conjugated with drugs or proteins were used as polymeric-conjugates. Polyethylene glycol (PEG) and copolymer *N*-(2-hydroxypropyl)-methacrylamide (HPMA) with a molecular weight 30–40 kDa are used in polymeric conjugates preparation and not hydrolytically degradable. Poly(aminoacids) such as polyglutamic acid and aspartic acids derived with PEG were susceptible to enzymatic degradation but not hydrolytically acid-labile groups. Several polymeric conjugates were tried for cancer treatments including polyacetals which are pH-dependent release conjugates. Polyacetals conjugated with doxorubicin (antitumor) exhibited 1.4 times longer duration tumor targeting when compared to the PEG and HPMA-doxorubicin conjugates [40].

2.6.3 Polymeric Prodrugs

Polymeric prodrugs are designed to protect against rapid elimination or metabolism by adding a protective polymer to the therapeutic materials (Fig. 2.18). Therapeutic activity is usually lost with this attachment and reinstated with the removal of the protective group. The protective group is designed to be easily removed usually by hydrolysis. A drug which is active only after being cleaved from the polymer chain is called a prodrug. The drug is usually attached away from the main polymer chain

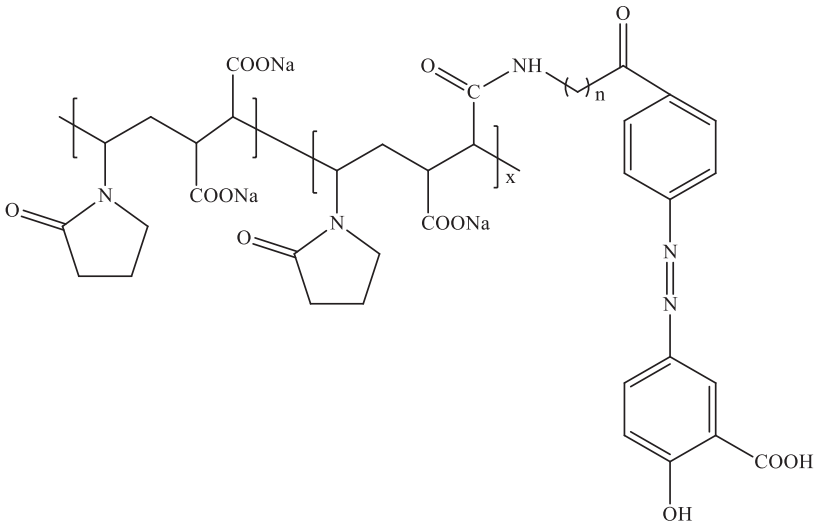


Fig. 2.18 Polymeric-prodrug containing 5-ASA conjugate covalently linked to poly(methyl vinyl ether/*co*-maleic anhydride) and poly(1-vinyl-2-pyrrolidone *co*-maleic anhydride)

and other pendant groups by means of a spacer moiety that allows for more efficient hydrolysis.

2.6.4 Targeted Polymeric Drug

Polymeric drug targeting to a specific site is an enormous advantage in drug delivery because only those sites involved are affected by the drug. Ideally, a targetable drug carrier is captured by the target cell to achieve optimum drug delivery while minimizing the exposure to the host. Most administered macromolecules are eliminated by the host before any significant cellular uptake takes place. If the macromolecules contain a moiety that is compatible with a receptor on a specific cell surface, then the molecule is attracted to the cell surface and the uptake is enhanced. This maximizes the opportunity for specific cell capture. This type of cell-specific targeting has been developed.

2.7 Biodegradable Synthetic Polymers

The term “biodegradable polymers” denotes water-insoluble polymers which, by means of a chemical reaction in the body, are converted slowly to water soluble materials. The polymer can have a side chain that undergoes hydrolysis in the body

to produce hydroxyl, carboxyl, or other hydrating groups. These groups make polymer fragments and degradation products water soluble. Another approach is to cross-link a water-soluble polymer with a hydrolysable crosslinking agent. Once cross-linked, the polymer is insoluble. When placed in the body, the cross-linking group is hydrolyzed or degraded to give a water-soluble polymer. Water-insoluble polymers which contain hydrolysable functional groups directly in the polymer chain are the most frequently used. As these groups in the chain are hydrolyzed, the polymer chain is slowly reduced to shorter chain segments which eventually become water soluble. The main advantage of the latter group of polymer is that polymer will have good mechanical properties. Table 2.9 lists examples of these biodegradable polymers with their biomedical applications.

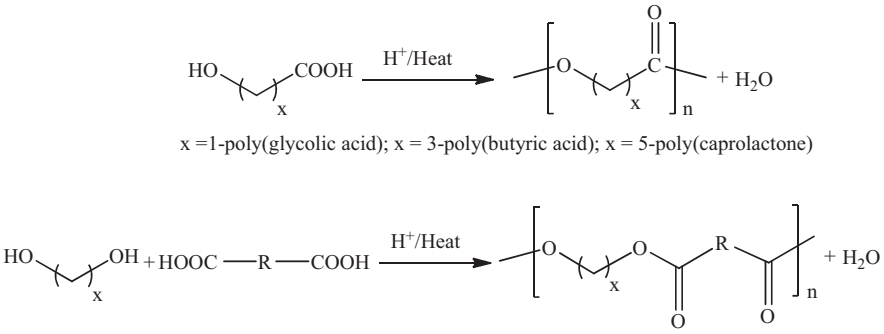
2.7.1 Polyesters

Polyesters are synthesized by condensation polymerization of dicarboxylic acids and diols, or hydroxy alkyl carboxylic acids. Examples for both polymerizations are aliphatic polyester based on monomers other than α-hydroxy-alkanoic acids which have been developed and evaluated (Scheme 2.11). These include the polyhydroxybutyrate and the polyhydroxyvalerate developed by ICI from a fermentation process and the polycaprolactone. Homopolymers in these series are hydrophobic and crystalline in structure, and therefore they have long degradation times in vivo (1–2 years). However, the use of copolymer in the case of polycaprolactone has led to materials with a shorter degradation time as a result of changes in the crystallinity and hydrophobicity of these polymers.

The ω-hydroxycaproic acid on condensation gave polycaprolactone. At every condensation reaction, the polymer chain grows but remains a ω-hydroxy carboxylic

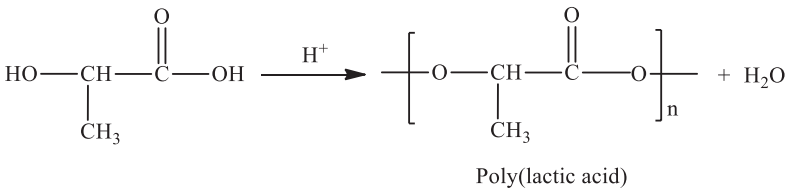
Table 2.9 Biodegradable synthetic polymers for biomedical applications

Polymers	Applications
Polylactic acid (PLA)	Sutures, bone plates, screws, scaffolds
Polyglycolic acid (PGA)	Sutures, bone plates, screws, scaffolds
Polylactic-co-glycolic acid (PLGA)	Tissue engineering, drug delivery, cartilage screws, sutures, wound dressing
Polyhydroxybutyrates (PHB)	Drug delivery, bone plates
Polycaprolactone (PCL)	Drug delivery, bone plates, fixators, tissue engineering
Polydioxanones (PD)	Sutures
Polyorthoesters	Drug delivery
Polycarbonates	Tissue engineering, fixators, and drug delivery
Polyanhydrides	Tissue engineering and drug delivery
Polyphosphate esters	Tissue engineering and drug delivery
Polyphosphazenes	Tissue engineering and vaccine adjuvant

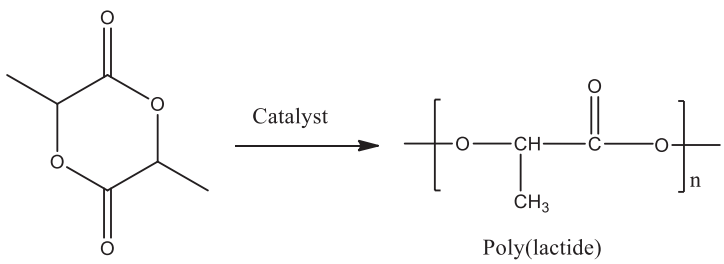


Scheme 2.11 Polyester preparation by condensation polymerization

1. Stepwise polymerization:



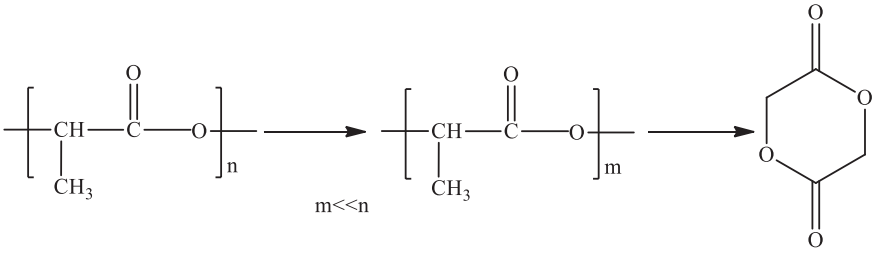
2. Ring-opening polymerization:



Scheme 2.13 Preparation of polylactide using different methods. 1. Stepwise polymerization; 2. Ring-opening polymerization

acid; hence it further reacts to form a longer polymer chain. For example, poly(lactic acid) (PLA) upon overheating converts into lactide (Scheme 2.12).

Polyesters can also be polymerized by stepwise polymerization and ring opening polymerization as shown in Scheme 2.13. One of the most versatile and widely used synthesized polymers is aliphatic polyesters prepared from lactic and glycolic acids. These polymers were first utilized as sutures and orthopedic plates and nails, and their biocompatibility and biodegradability are well known. Moreover, the commercial availability of these polymers and the accurate biodegradation rates has made



Scheme 2.12 Polylactide preparation by condensation polymerization

these biodegradable polymers the first choice of medical devices. The applications are also found in controlled release and tissue engineering.

PLA is available in four sterioisomers (L, D, DL, meso-lactic acids) and among those PLLA, PDLLA lactides are more promising biodegradable and PLLA is used in the bone fixators and tissue-engineering applications whereas PDLLA lactides are widely used in drug delivery applications. Polyglycolic acid (PGA) obtained from glycolic acid is more hydrophilic than PLA. PGA has a limitation in its applications because high biodegradation results high acidity to the surrounding tissues causes the inflammation. Poly(lactic-co-glycolic acid) (PLGA) is obtained by copolymerization of lactic and glycolic acids and is prepared to overcome those individual polymer disadvantages. PLGA is mostly used in tissue-engineering applications because it has high adhesive and cell proliferative properties and also controls delivery applications of drugs, vaccines, and peptides. The copolymer PLGA has an amorphous and less crystallinity and leads to faster degradation when compared to their homopolymers. Due to its advantage of biodegradation, it is widely used in tissue-engineering applications [19]. Polycaprolactone (PCL) is a semicrystalline powder which has slow degradation and therefore widely used in drug delivery systems. PCL-based electrospun nanofibers were highly soft porous scaffolds used in in vivo studies for the regeneration of bones and act as an extracellular matrix. Polydioxanones (PD) is also another polylactone obtained from p-dioxanone by ring opening polymerization which has ethers and esters units. PD can degrade into glycoxylate and further degrade into glycine. PDs are used in the preparation of monofilament sutures, drug delivery systems, and tissue-engineering applications and also used as screws and pins for the fixation of bones [30, 41, 42].

2.7.1.1 Polyhydroxyalkanoates as Coatings

A technologically developed biopolymer product which is called as the food packing or coating material as functionalities contain with added ingredients, is commercialized that provide a specific benefit for human health without loss of food functionalities [43]. The petrochemical-based synthetic plastics polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinylchloride (PVC), polyethylene terephthalate (PET), polyvinyl alcohol (PVA) and polycaprolactone (PCL) are among

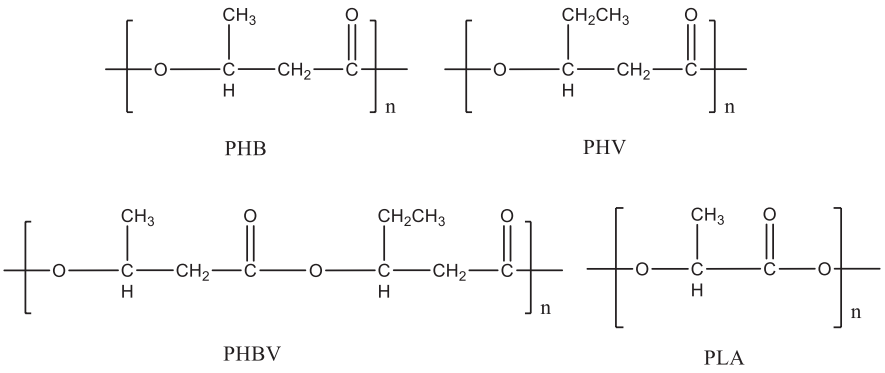
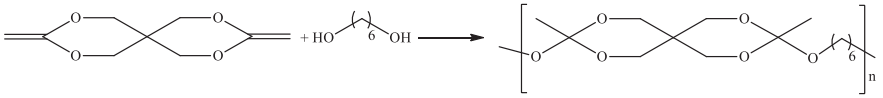


Fig. 2.19 Structures of polyhydroxyalkanoates



Scheme 2.14 Synthesis of polyorthoesters by condensation of diol and diketene acetals

the major synthetic polymers routinely utilized by the food packaging industry; the major drawback of synthetic plastics is that they are exceedingly uncontrollable to biodegradation. Starch-based polymers such as polyhdroxyalkanoates (PHA, Fig. 2.19), polyhydroxybutyrate (PHB), and polyhydroxy valerate (PHV), and a copolymer of polyhydroxybutyrate-covalerate (PHBV) and polylactic acid (PLA) are biopolymers that have excellent physical properties, exhibit excellent compatibility with other natural polymers, and, more importantly, are completely biodegradable in a variety of environments; and biobased packaging and insulation materials are now available commercially. PHAs are linear polymers and they are synthesized by microbial fermentation, and so they are excellent biocompatible and biodegradable thermoplastics. PHA has also been used in disposable items, such as diapers, feminine sanitation products, and so on. These alkanoates have also been used as implants and carriers for delayed release of drugs, insecticides, and herbicides [44, 45].

2.7.2 Poly(Ortho Esters)

Poly(ortho ester) (POE) can be synthesized by the reaction of ketene acetal and an alcohol, to form the orthoester bond (-O-COO-) between the polymer units (Scheme 2.14). For example, 3,9-bis(methylene) 2,4,8,10-tetraoxaspiro (5,5)-undecane on condensation with 1,6-hexanediol forms a poly(ortho ester) (Scheme 2.6). The reaction proceeds at room temperature using tetrahydrofuran as solvent and acid catalyst. The preparation of poly(ortho esters) from diol and diketene acetals is similar

to the preparation of polyurethanes from diol and diisocyanate (see previously). Both reactions proceed without the formation of a byproduct. Polyorthoesters contain hydrophobic units linked together along the polymer chain by functional groups susceptible to hydrolysis.

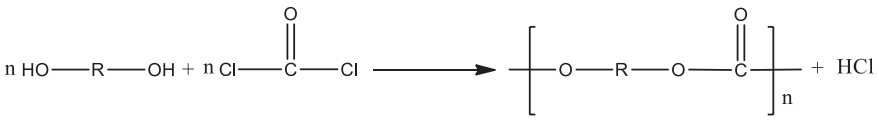
Exposure of the outer layer of polymer to water causes hydrolysis of the water labile linkages and subsequent degradation and loss of the outer layer of the polymer. As the outer layer is lost, another layer of polymer is exposed to water and the process continues such that polymers are slowly eroded from the surface. Such polymers are termed bioerodible and the rate of hydrolytic degradation at the surface of the polymer is much faster than the rate of water penetration into the polymer matrix. POE has geminal ether linkages and releases γ-hydroxy butyric acid in water and it causes auto catalytic effect. The erosion rates were reduced by adding lactic/glycolic acid segments in POE during copolymerization. POEs have been tested as carriers of drugs like insulin and antibiotics [46].

2.7.3 Polycarbonates

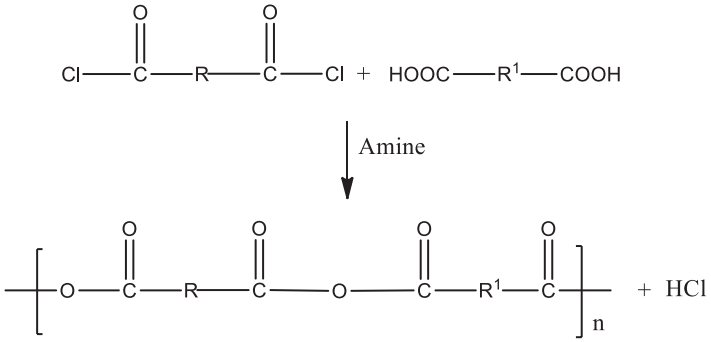
Biodegradable polycarbonates are synthesized by the condensation of an aliphatic diol with the derivatives of carbonic acid such as phosgene or biphenyl carbonate. Phosgene, on bubbling into a solution of a diol in pyridine at 20–35 °C, forms a polymer [47] which is isolated by precipitation in water or methanol (Scheme 2.15). These are linear polymers and hydrolytically stable nature but much faster degradation in the in vivo studies by enzymatic hydrolysis. These polycarbonates have been used as sutures and the bone fixation, drug delivery applications. Poly(trimethylene carbonate) is the most exploited polycarbonate with good flexibility and slow degradation kinetics. It is used in the preparation medical implants due to the poor mechanical strength of this polymer. Some other tyrosine-based polycarbonates and ethyl ester polycarbonates were used in tissue-engineering and bone fixation applications, respectively.

2.7.4 Polyanhydrides

Polyanhydrides are synthesized by stepwise polymerization from diacid monomers using a dehydrative agent, or melt condensation or from the reaction of a diacid chloride and a dicarboxylic acid by dehydrochlorination (Scheme 2.16). This hydro-



Scheme 2.15 Synthesis of polycarbonates using diols and phosgene

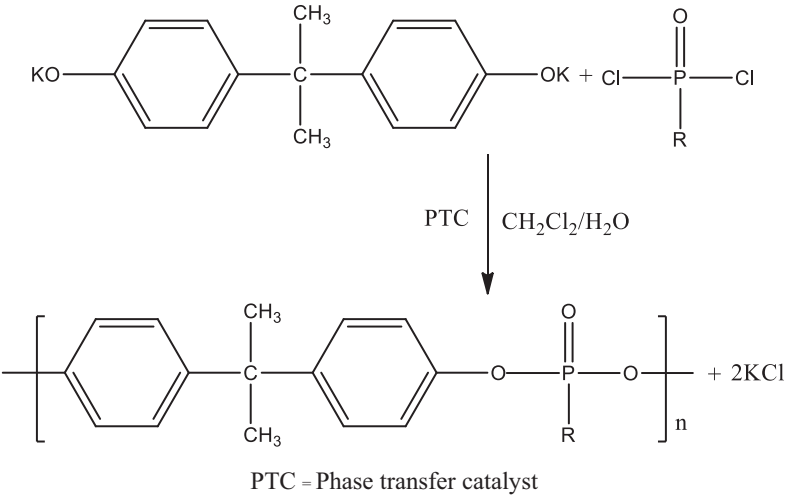


Scheme 2.16 Polyanhydride preparation by dehydrochlorination

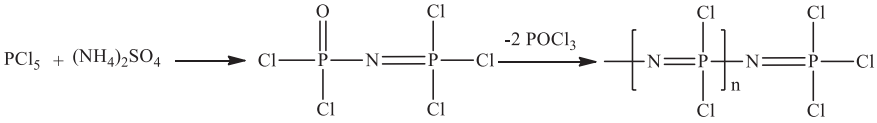
phobic monomer leads to a polymer with low water permeation. However, anhydride linkage is quite susceptible to hydrolysis and experiments have demonstrated that surface erosion of these polymers does occur. Mostly studied polyanhydrides are fatty acid–based polyanhydrides such as sebasic acid and erucic acid–based polyanhydrides having low melting points (~100 °C). These are more hydrophobic and soluble in organic solvents. Other types of polyanhydrides are aromatic polyanhydrides (1,3-bis-carboxy phenoxy propane–based polyanhydrides) which are crystalline and high melting points (>200 °C). Polyanhydrides have been used for controlled zero-order delivery of anticancer agents to the brain for treating brain tumors, which is now FDA approved [48]. Polyanhydrides are natively not used in tissue-engineering applications due to its low mechanical strength but modified polyanhydrides-co-amides were explored as scaffolds to tissue engineering and also methacrylated polyanhydrides as injectable materials highly cross-linked and improved mechanical strength were demonstrated for tissue-engineering applications. Polyanhydrides are exploited in the new area in biodegradable medical electronic sensors and delivery of vaccines [49].

2.7.5 Poly(Phosphate Ester)

Poly(phosphate ester) can be synthesized by the interfacial condensation of either ethyl or phenylphosphorodichloridates and various dialcohols under phase transfer conditions (Scheme 2.17). Polycondensation was found to be dependent on the catalyst concentration. Polyphosphate ester copolymers have been tested as drug carriers [50]. The degradation of polyphosphate esters leads to extractable phosphates, alcohols, and diols. These esters having the advantage of phosphorous are able to form the covalent linkage with drugs and other reagents or polymers as prodrugs or composite materials. These polyphosphate esters or its composite polymers can form the films, gels, micelles, and other microstructures which are useful in drug delivery and tissue-engineering applications.



Scheme 2.17 Polyphosphate ester preparation using phase transfer catalyst. PTC = Phase transfer catalyst



Scheme 2.18 Poly(phosphazene) preparation by condensation polymerization

2.7.6 Poly(Phosphazenes)

Poly(phosphazenes) are polymers consisting of an inorganic backbone of alternate nitrogen and phosphorus atoms linked by alternating single and double bonds. Different polymers can be prepared by nucleophilic displacement reactions. Poly[(dichloro)phosphazene] is prepared by condensation reaction. Monomeric phosphoranimine on condensation forms *N*-dichlorophosphoryl-P-trichloromonophosphazene [$Cl_2P(O)N{=}PCl_3$] with the elimination of phosphoryl trichloride $POCl_3$ (Scheme 2.18). Poly(phosphazenes) were also prepared by ring-opening polymerization methods. Different polyphosphazenes have been used as inert biomaterials for cardiovascular and dental applications. Bioerodible and water-soluble polyphosphazenes are also used for controlled drug delivery [50] in orthopedic applications as self-setting polyphosphazene bone cements and in regeneration of other tissues of nerve, vessel, and tendon. The advantage of phosphorous in this polyposhagene is able to form the covalent bond with hydrophobic groups and the resultant polyphosphagenes can be used in the tissue engineering applications also [51, 52].

The degradation of polyphosphazene can be controlled by changes in side-chain structure rather than the polymer backbone. A hydrophilic backbone as well as the structure versatility as a result of various substitutions offers possibilities in designing new classes of polyphosphazene gels. Various modifications of polyphosphazenes have been reported including poly(aryl/alkyl) phosphazenes, poly(amino acid-ester) phosphazenes, and methoxy-poly(ethylene glycol)-substituted polyphosphazenes with temperature-responsive features, and the biodegradability also increases by replacing the chlorine on phosphorus with these alkyl or aryl groups. Two types of hydrogels exist: non-ionic and ionic. Non-ionic polyphosphazene gels are based on water-soluble phosphazene containing glucosyl or glyceryl side groups. Ionic polyphosphazene hydrogels are formed with divalent ions. These polymers may be useful for skeletal tissue regeneration or encapsulation of hybridoma cells.

2.8 Characterization of Biomaterials

The understanding of the interactions which take place between a material surface and the compositions of the biological systems is an important requirement of biomaterial development (Table 2.10). The uppermost layers of a biomaterial which present certain chemical and physical properties have to be defined as it is a contact surface. Also, biological parameters such as adsorption of protein, cell growth, and blood compatibility need to be established. These properties are essential for biomaterials, although perhaps not required in industrial applications. This is necessary as living cells are very vulnerable to and readily killed by physical and chemical stimuli, for instance, by toxic substance invasion. Toxic compounds associated with polymers are listed in Table 2.11.

In general, we would expect the features shown in Table 2.12 to be influenced in determining the specific characteristics of biocompatibility that will be seen under different circumstances. It is important to note that it is not only the characteristics of the materials and device that control events but also host variables as we get older; repair processes are less efficient and the general state of health will influence defense mechanisms.

2.8.1 Chemical Properties on the Surfaces

The compositions of biomaterial surface can be measured by different methods such as attenuated total reflectance (ATR-IR), X-ray photoelectron spectroscopy (XPS), and secondary ion mass spectroscopy (SIMS) [56]. ATR-IR supplies the absorption spectra of functional groups with an informational depth of $0.1 - 10$ μm. XPS is a

Table 2.10 Minimum requirements for biomaterials [53]

Requirements	Examples
I. Non-toxicity	Non-pyrogenic, non-hemolytic, non-inflammatory (chronic), non-tumorigenic, non-allergic
II. Functionality	Organ and tissue replacement, tissue reconstruction, internal organ support, disposable medical devices, drug delivery
III. Sterilizability	Radiation, ethylene oxide gas, autoclave, dry heat
IV. Biocompatibility	Mechanical and interfacial

Table 2.11 Toxic compounds related to polymers

Components	Remarks
I. Monomers	Not polymerized, depolarized, oligomers
II. Initiators	Intact and decomposed
III. Catalysts	Cross-linking, curing, and other reactions
IV. Additives	Antioxidants, plasticizers, UV absorbents, lubricants, antistatic agents, dyes, pigments
V. Others	Byproducts, degradation products

Table 2.12 The features of biocompatibility [54]

Materials	Bulk chemistry
	Surface chemistry
	Surface roughness
	Surface energy
	Surface charges
	Chemical stability
	Chemistry of degradation products
	Physical characteristics of degradation products
Devices	Size
	Shape
	Elastic modulus/rigidity
Host	Species (animal study)
	Tissue type and location
	Age
	Sex
	General health status
	Pharmaceutical regimens
Systems	Operative technique
	Implant tissue attachment
	Infection

more sensitive surface analytical method which gives information not only about the type and amount of elements present but also their oxidation state and chemical surroundings. In SIMS, primary ions interact with the polymer surface and the mass spectra of the secondary ions are obtained which also give the chemical compositions of the outermost atomic layer (1 nm thickness).

2.8.2 Physical Properties of the Surfaces

Several methods are available to determine the physical parameters of polymer surfaces. Biomaterials penetrate liquids like blood or water present in soft tissue. It is known that the surface-free energy at the biomaterial/water interface is the driving force for the reorientation processes of the polar groups of the uppermost molecular layers of the polymer surface. The investigation of surface wettability by means of contact angle determination is of special interest in the characterization of a surface. Electrochemical properties are also physical surface parameters. The existing surface charge density, i.e., surface potential, has a strong influence on protein adsorption and blood compatibility. Table 2.13 shows surface analysis use in the characterization of biomaterials.

Table 2.13 Summary of surface analysis techniques in biomaterials [55]

Chemical compositions
Electron spectroscopy for chemical analysis
Auger electron spectroscopy
Ion scattering spectroscopy
Backscattering spectroscopy
Secondary ion on mass spectrometry
Surface extended X-ray absorption fine structure
Thermodynamic analysis
Wettability
Sorption-desorption
SEM
TEM
Scanning tunneling microscopy
Atomic force microscopy
Infrared spectroscopy
Electron energy loss spectroscopy
Thin-film X-ray diffraction
Electron diffraction
Low energy electron diffraction

2.8.3 Adsorbed and Immobilized Protein Determination

ELISA was employed to detect the adsorption of a protein at a biomaterial surface based on a specific reaction of antibodies with surface bound antigens [56]. The detection of binding capacity of antibodies is useful to establish the amount of adsorbed and immobilized fibronectin. When a large amount of adsorbed fibronectin exists at the polymer surface, enhanced growth of the cells, e.g., endothelial cells can be expected. Low fibrinogen adsorption may indicate good blood compatibility.

2.8.4 In Vitro Cell Growth

Cell culture permits the determination of cell growth–influencing factors and thereby the selection of cell toxic materials. In addition, it allows the investigation of tissue compatibility of biomaterials. In cell culture two cell types can be used: organ-specific cells and cells belonging to permanent cell lines which have lost their specificity. The evaluation is done by the measurement of cell density after a period of time.

2.8.5 Blood Compatibility

The contact of biomaterial surfaces with the blood provokes the activation of the intrinsic coagulation pathway at blood/biomaterial interface. The following coagulation parameters obtained after the contact are evaluated as compared with citrate plasma values: activated partial thromboplastin time (APTT), partial thromboplastin time (PTT), platelet adhesion, and leucocyte number. The most important parameters to characterize blood compatibility are thrombocyte adhesion and thrombocyte number. Materials which show strong platelet adhesion as a consequence of their contact with a foreign body or provoke a decrease in the number of blood platelets are considered as thrombogenic [57]. The decrease in the quantity of blood leukocytes after contact is a sign of cellular immune response of the biological system. When a biomaterial comes in contact with a living body, interactions occur between the foreign material and the living body, as shown in Table 2.14.

Table 2.14 Interactions between living systems and biomaterials

Interfacial biocompatibility	Non-stimulative	Short term	Complement non-activation
			Anti-thrombogenicity
			Tissue non-invasion
		Long term	Non-encapsulation
			Neointima formation
			Non-calcification
	Bioadhesive	Cell	Monolayer coverage
			Non-proliferative
			Teeth bonding
		Tissue	Proliferative
			Bone bonding
			Soft tissue adhesion

2.9 Fabrication Technology

Thermoplastic resins are fabricated in the molten state by extrusion into tubes, sheets, rods, films, and fibers and by molding into three-dimensional objects. Two processes are employed, namely extrusion and injection molding for fibers and films majorly. Preparations of artificial articles in three dimensions with different shapes such as heart, hip, finger, knee, kidney, and contact lenses, etc., are very important using molding techniques in the medical applications. Nano- and submicron-size fibers were also prepared by electrospinning technology extensively because of ease and economic benefit in lab- and industrial-scale processes. This technology also able to produce long and continuous with controlled morphological fibers for all types of polymers when compared to other technologies such as drawing, template synthesis, self-assembly, phase separation techniques, which are limited to lab scale, expensive, time consuming, and limit to some polymers only. Even spinning technology includes solution spinning, wet spinning, dry spinning, and melt spinning technology; and each technology has some advantages and limitations in time, scale, and economic ways [19, 58]. Many methods are there for the preparation of films and fibers using polymers and some of those important methods are discussed here.

2.9.1 Extrusion

A single screw extruder is a conveyer similar to a meat grinder. It consists of a screw, driven by a motor connected to its shaft through a gear reducer, rotating inside a cylindrical barrel. The rotating screw moves the resin pellets forward and generates by shear most of the heat required to melt pellets, as well as the hydrostatic pressure to force the molten plastic through the die (Fig. 2.20). The size of the extruder is described by the inside diameter of the barrel. The screw consists of

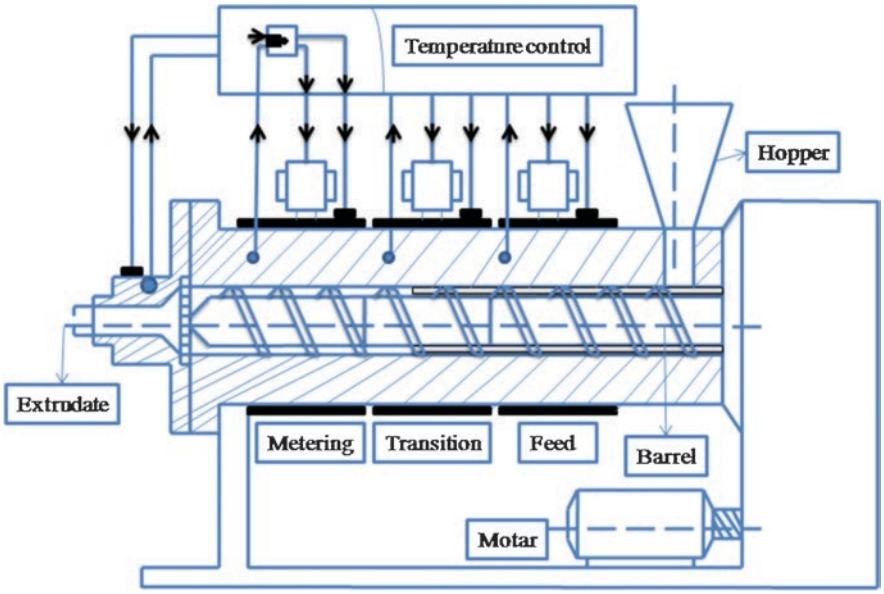


Fig. 2.20 Schematic drawing of a single screw extruder (adapted from www-rt.uni-aderborn.de/)

three zones, namely a feed section, a transition section, and a metering section. The screw usually has the same pitch or helical angle in the three sections. The process variables, temperature and speed of revolution, do not afford a range of conditions wide enough for the effective extrusion of different polymers. For example, polyamide shaves lower melt viscosities than polyethylene resins, while polyvinyl chloride resins degrade readily at high temperature. Therefore, different screws are available for a single extruder, having different lengths of the three zones and different compression ratios. Resin pellets, granules, or flakes are fed from the hopper into the feed section of the extruder, from where they were conveyed to the transition section. Here the pellets are compressed and melted. A large portion of the heat required to melt the resin is generated by viscous friction as the pellets are sheared between the rotating screw and the stationary wall of the barrel. Another portion of the heat is supplied externally through the barrel, usually by electric band heaters mounted on the barrel. As the resin advances through the transition zones, it is plasticized, melted, and mixed. By the time it reaches the metering section, it is a homogenous, very viscous liquid. The metering section of the screw has the shallowest channel depth. It pumps the melt through a screen-pack filter into the die cavity. The filter removes solid impurities and lumps of unmelted resin. If the extruded film is to have a uniform thickness, it is essential that the melt exits through the die slit at a constant flow rate, free of sudden surges. The metering section ensures a constant delivery rate. Flat film is extruded downward through a die with a long slit for an opening onto highly polished chilled rolls that are water cooled. From there, the sheet is rolled up on a windup roll. Tubular film is produced by

extruding the melt upward through an annular die around a mandrel (Fig. 2.21). As the tube is pulled upward, it is blown up to a bubble by air injected through the mandrel, stretched and biaxially oriented. The hot tubular film is cooled by air issuing through the holes of a hollow ring surrounding the tube near the point where it leaves the die, below the zone where it is inflated to a bubble. As the inflated, solidifying film moves upward, it is gradually deformed into the lay flat form by the action of guide rolls.

A pair of rubber-covered nip rolls collapses the film completely and thereby seals in the inflating air that expanded the molten film issuing from the die into a bubble. A windup roll then rolls the flattened film up, pulling it upward continuously away from the die.

Thermoplastic starch (TPS) was processed at 160–200 °C with a limited quantity of water (10–25%) and this molten plastic shows high viscosity by extrusion-cooking and is described as pseudo-plastic material. Extrusion technology has been applied for pasta processing from starch in the food industry [59]. Polymeric starch blends were prepared by reactive extrusion technique using polymers containing reactive functional groups such as acids, alcohols, nitriles, amines, amides, etc.,

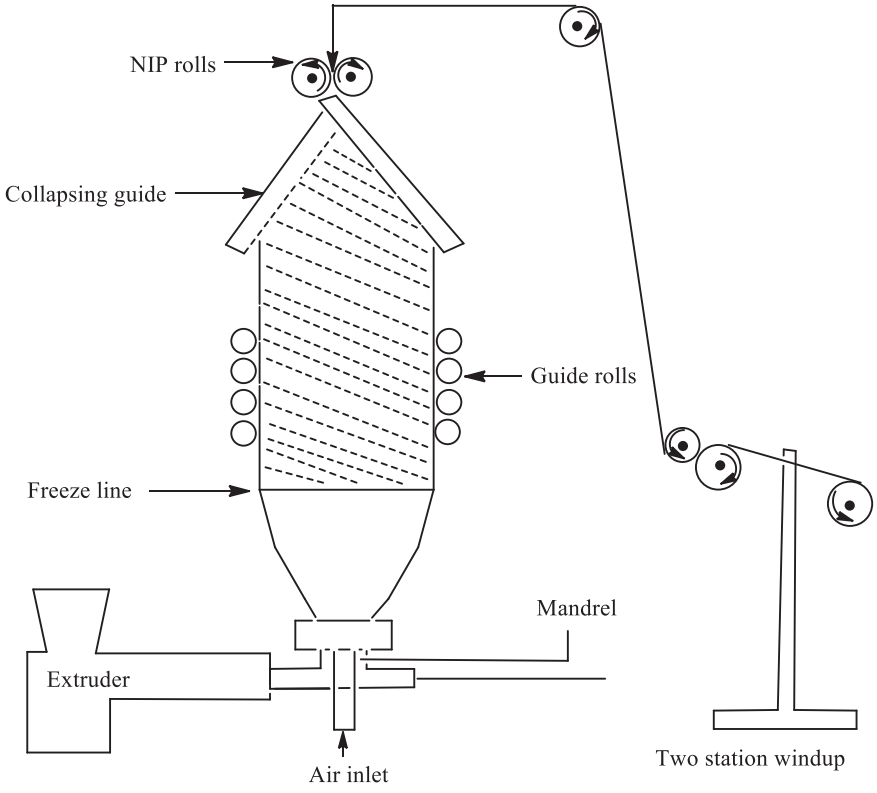


Fig. 2.21 Schematic drawing of tubular film extrusion

with hydroxyl groups of starch (TPS, >25–30%). In this reactive extrusion technique, all the traditional methods (polymerization process and extrusion) were combined into a single process of melting, blending, structuring, de-volatilization, and shaping and ready to use the form of the final product. Starch phosphate blends were prepared as potential hydrogelators for sustained release of metoprolol tartrate because of their nontoxicity and biodegradability [60–62].

Similar to starch, protein-based films and sheets were prepared using this extrusion technique for food applications. These films were also very sensitive to moisture and have brittleness. A mixture of soybean protein isolate and cellulose or starch was used to prepare microporous polymer membranes for biomedical applications using extrusion technique. All these blends exhibited higher tensile strength, elongation, and Young's modulus than the corresponding materials containing their individual. The intermolecular interactions of those components are attributed to the improvement of these properties mainly to the benefit of microphase separation [63]. Polyurethane-based scaffolds were prepared using extrusion technique as microfibers with a thickness of 20−60 μm with a pore diameter of 10–200 μm microporous (70%), and these scaffolds have been used for moderate albumin production (53.7 ± 5.6 ng/h/μg) by seeding the porcine hepatocytes [64]. Expanded polytetrafluoroethylene (PTFE) polymer (Gore-Tex®) was used as prosthetic vascular grafts clinically. These polymers are also used as patches for soft tissue regeneration applications of hernia repair and surgical sutures. These vascular grafts were prepared by extrusion technique as microporous materials having 30–100 μm diameter pores [65]. Polyglycolic acid (PGA) has been used to prepare a variety of sutures in the self-reinforcing technology and extrusion method. DEXON was the first resorbable synthetic suture approved by FDA in United States and commercially available biodegradable suture prepared with PGA polymer [66].

2.9.2 Injection Molding

Injection molding is a high-speed technique used for the production of both thermoplastic and thermosetting polymers and so useful for bulk production. Of the various processes, injection molding is the most widely used. The following three operations are carried out successively. The thermoplastic resin, in the form of pellets, is heated, melted, and pushed into the die cavity, which is filled with the melt. The molten plastic cools and solidifies in the mold while under pressure. Finally, the mold is opened and the part is ejected. Molds may have several cavities for the simultaneous molding of several parts. Two types of machines are used to melt and inject the resin into the mold, a plunger injection molding machine and a reciprocating screw injection molding machine. The plunger molding machine is fitted with a hydraulic arm that compresses the resin pellets at the same time that they are heated and melted. The molten resin is pushed through a nozzle into the mold cavities and cooled under pressure to below its melting or glass transition temperature. The

molten resin shrinks on cooling, the mold is opened, and the solidified plastic parts are ejected.

The second molding machine, equipped with a reciprocating screw, mixes and homogenizes the melting resin. The screw resembles that of the single-screw extruder depicted in Fig. 2.21, except that it is moved forward and backward in the barrel by a hydraulic mechanism. The resin is fed from a hopper into the barrel and is plasticized and melted by the rotating screw. The screw, then acting as a plunger, forces the melt into the mold cavities, where the plastic cools and solidifies. The molded plastic is then ejected from the mold cavities. The molten resin shrinks on cooling and solidifying because its density decreases with rising temperature. Amorphous plastics shrink far less on solidifying than semi-crystalline plastics owing to crystallization of the latter. Molds are filled under high pressure. By compressing the melt, more material is made to flow into the mold cavity, reducing the shrinkage on cooling. The average linear shrinkage of polystyrene on cooling from ~100 °C to room temperature ranges from 3.5% at atmospheric pressure to 1.4% at 10,000 PSI. The corresponding linear shrinkage of polyethylene is 7% and 5%, respectively. These values are higher because polyethylene is semi-crystalline whereas polystyrene is amorphous.

Nowadays fully automated reactive injection molding is a popular method and it has four interdependent components of feed storage tank, transmission of reactant stream, mixing chamber, and formation system. In this method, two monomers are injected together before entering into mold; a chemical reaction takes place in between the two monomers to form a new polymer. The newly formed polymer melts at low temperature and does not require high temperature and is therefore used extensively in human prosthetics preparation [58]. Using this technique, polyurethane foams, granules, and fibers are synthesized and; it has two conditions – high-pressure molding and low-pressure molding. In the high-pressure molding, mixing of liquid reactants (polyol, diisocyanates and other agents) occurs at heads with 5 to 20 MPa pressure with cross-linkage of reactants, and injected mold takes place at 0.1 to 3 MPa. In the low-pressure method the components are mixed with high-speed screw 1.5–20 thousand rpm/min and the mixing efficiency is adjusted by changing the distance between winding screw and chamber internal walls [67, 15]. Synthetic sutures were fabricated by injection molding technique using polyglycolic acid polymer for biomedical applications. Polyanhydrides were fabricated into thermal-sensitive fibers and films, which are used in drug delivery applications by this injection mold, and extrusion techniques and poly(anhydrides-co-imides) with improved mechanical properties were used in tissue-engineering applications [68].

2.9.3 Electrospinning

In recent times, electrospinning has been established as a successful technique for the preparation of the range of nano to submicron fibers. Electrospinning is an important process and gaining the attention in biomedical science to produce

continuous polymer nanofibers having high surface area and mimics the extracellular matrix by the action of an external high voltage electric field imposed on a polymer solution or melt [69]. These nanofibers can be used in a variety of applications such as scaffolds for tissue engineering, drug delivery devices, antimicrobial fibers, and encapsulation of antioxidants in the food science area [70–73]. The instrumental setup is shown in Fig. 2.22 containing syringe pump and syringe containing polymer solution, spinneret, and fiber collector attached with high-voltage power supply. The polymer solution in the needle is stretched by required high voltage supplied to the needle because the surface tension of that solution is altered due to electrostatic repulsions of solution and applied electric field or charge at needle. The activated polymer solution finally ejected from the sharp end point of the spinneret made by the Taylor is called "taylor cone." When the applied electric field surpasses the threshold energy of the viscoelasticity of polymer solution, the stretched polymer comes out from the talylor cone and forms the stable polymer jet. The stable polymer jet moves toward the fiber collector or counter electrode and simultaneously the solvent is also evaporated. While moving the stable jet elongated up to end of the electrostatic repulsive forces and become weak or unstable jet at initiating bends in the fiber and before reaching collector. The elongation or thinning of fiber resulting from the bending instability leads to the formation of uniform nanofibers [58]. The thickness of fiber and morphology can be changed by varying the properties, majorly the type of polymer, nature of solvent, applied voltage, distance engaged between tip of syringe, and the type of collector [74]. Different types of counter electrodes or collectors are used for different fibers, for example, rotating-type collector used for aligned nanofibers and static-type collector used for random nanofibers [19]. Semicrystalline fibers from the polymers such as polyethylene, polypropylene, polyester terephthalate can be produced by this electrospinning

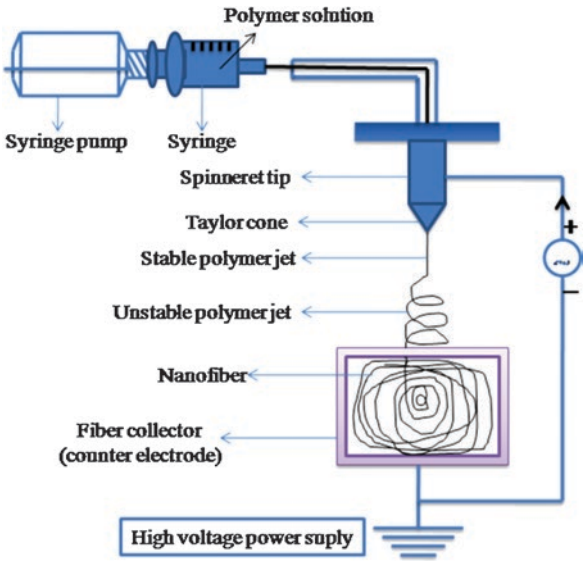


Fig. 2.22 Schematic drawing of electrospinning process of polymeric fibers

technique only because even in other spinning techniques (wet and dry spinning) cannot produce fibers of these polymers [58].

Different electrospun nanofibrous scaffolds were prepared by this electrospinning technique using biodegradable polymers. Native collagen type I polymer (8%) dissolved in an organic solvent hexafluoro-2-propanol at a high electric field of 25 kV was used for the preparation of nanofibers with a diameter of 100 ± 40 nm and useful in tissue-engineering applications [75]. Gelatin nanofibers with a range of 80–300 nm diameter were processed by this electrospinning using gelatin (7.5%) in trifluoroethanol at 10.5 kV and also gelatin meshes were prepared with gelatin fibers having consistent mechanical properties [76, 77]. Chitosan-based nanofibers with a large range of nanofibers (390–610 nm diameter) are also useful in biomedical applications and prepared by using 8% polymer dissolved in trifluoro acetic acid at an electric field of 15 kV [78]. Poly($_L$-lactic acid)-based nanofibrous scaffolds with a range of 150–500 nm diameter and a pore size of 100 nm were processed by this electrospinning using PLLA (2%) in dichloromethane and dimethyl-formamide solvent mixture in the ratio of 70:30 (v/v) at a high electric field of 12 kV and explored in neural tissue engineering applications [79]. Similar to PLLA, PGA and PLGA polymers were processed at a high electric field of 20–25 kV for the preparation of their nanofibrous highly porous scaffolds which are useful in tissue-engineering applications with an average diameter of 1.19 μm and 450 nm, respectively [80, 81]. Poly(caprolactone) polymer (10%) dissolved in hexafluoro-2-propanol electrospun nano to submicron fibers (440–1040 nm diameter) suitable for biomedical-engineering applications were synthesized by electrospinning technique [82]. All these nanofibers were used in the medical prosthetics such as vascular and breast prosthetics, implants in CNS systems and in drug delivery, dental restoration applications especially with 5% of Nylon 6 polymer, and also wound dressing and skin burn applications [19].

2.9.4 Calendering

Calendering is an important finishing process as shown in Fig. 2.23 to make films and sheets applied to textiles and plastics. In this method, plastic materials are passed in between several pairs of heated rollers to furnish a shiny surface. The heated plastic sheets are passed in between cool and finishing rollers continuously and then finally the sheets are wound up. Calendering process involved the heat and pressure to a fabric by passing it in between heated rollers results a flat, glossy, smooth surface and by increasing the heat and pressure the luster increases. The thickness of the sheets depends also on the altering speed of rollers along with the continuation of squeezing. The molten plastic material is a feed to the calendering rolls from a Banbury mixer or from a large extruder. During calendaring, rolls of extruded PVC are produced in this technique as well as other plastics. The extrusion process is economic compared to the calendering process in the preparation of films

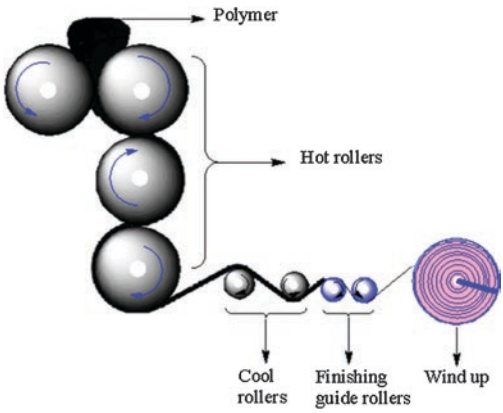


Fig. 2.23 Schematic drawing of calendering process

and sheets. However the calendaring process produces high-quality films and sheets compared to any other polymer process [83].

2.10 Future Trends in Biomedical Uses of Biopolymers

This chapter illustrates some of the polymer preparation methods, physicochemical properties, and their applications in medical sciences. This chapter was discussed in four divisions majorly: first part is about inert biopolymers, second part is natural biodegradable polymers, third part is synthetic biodegradable polymers, and fourth part is polymeric drug or protein conjugates. It continued the discussion about characterization, surface physicochemical properties of polymeric biomaterials, and their compatibility with cell and blood. It finally described the fabrication of fibers and films of the thermoplastic, thermosetting, and natural polymers by extrusion, injection mold, electrospinning, and calendering technologies. Instrument methods of extrusion, injection mold, electrospinning, and calendering technologies were described in detailed and the products of the polymers exploited using these technologies in the biomedical applications were also discussed.

In the past, medical sciences used polymers in much smaller amounts than other industries such as textile, packaging, and tire industries. Therefore, the manufactures of plastics and elastomers found no economic incentive to tailor-make polymers for the special needs of the industry, or to seek clearance from the FDA for the application of existing polymers. An example of the latter situation is methyl cyanoacrylate, which has been used in industrial glue for many years. It has been employed successfully to repair incisions or tears in a variety of tissues and organs.

Presently, medical scientists, commercial laboratories, and some pharmaceutical companies design, prepare, manufacture, and process or fabricate their own polymers in accordance with their specialized requirement. In addition to sutures, implants of plastics and elastomers in human bodies are widely used for repair or

replacement of tissues, organs, or parts of organs. Some of the problems encountered with implants are degeneration of adjoining tissues and formation of blood clots and thrombi on the surfaces of implant synthetic polymers, enlargement of implants through sorption of lipids or moisture, which constitutes a problem with precision parts and corrosion, and weakening of implants due to the interaction with enzymes or other physiologic compounds and/or mechanical stresses. A skin substitute to cover burns has recently been introduced. It is a composite made of an outer layer of silicone elastomer to protect the wound from infection and dehydration, bonded to a porous bottom layer that is adhesive and biodegradable consisting of cross-linked collagen combined with glycosaminoglycan. After the skin has grown back underneath this composite film, the bottom layer is biodegraded and the elastomeric top layer sloughed off. Considerable research is in progress to achieve the biocompatibility of synthetic polymers through surface modification to prevent blood clotting and to search for strong and more durable polymers.

In earlier days, inert polymers were selected for the production of implantable materials to attain the bioinertness, and mechanical and structural compatibility and majority of the materials are limited to in vitro studies. In the present generation, the trend was shifted to polymers used as implantable devices which are also active to molecular, cellular, and mechanical cues along with biocompatibility. In recent days, a variety of synthetic and natural biodegradable polymeric materials are available in the commercial market for regenerative or tissue-engineering applications and most of the polymeric biomaterials (collagen and polyesters) are subjected to in vivo studies as long-term prosthesis before coming to clinical uses. Many advanced processing technologies are available now for the synthesis of polymeric materials to reduce the gap between the biocompatibility and immunogenicity of polymeric material. Different novel co-polymeric materials by physical blending or chemical reactions using advanced processing technologies to achieve the proper biocompatibility and biodegradable properties could be allowed to serve widely in the renovation of tissues or organs of biomedical field in future.

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