20 Pharmaceutical Polymers

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Know the basic concepts of polymers, definitions, and descriptive terms.
2. Understand the principles of polymer synthesis.
3. Distinguish the basic principles of homogeneous and dispersion polymerizations.
4. Understand the thermal, physical, and mechanical properties of polymers in general.
5. Explain the glass transition temperature and factors affecting the T_g.
6. Understand how polymer molecular weight affects its properties.
7. Know what types of polymers are generally used in the pharmaceutical area.
8. Explain why polymers are used in drug delivery applications.

Introduction

Synthetic and natural-based polymers have found their way into the pharmaceutical and biomedical industries and their applications are growing at a fast pace. Understanding the role of polymers as ingredients in drug products is important for a pharmacist or pharmaceutical scientist who deals with drug products on a routine basis. Having a basic understanding of polymers will give you the opportunity to not only familiarize yourself with the function of drug products but also possibly develop new formulations or better delivery systems. This chapter will provide the basis for understanding pharmaceutical polymers. The basic concepts of polymer chemistry, polymer properties, types of polymers, polymers in pharmaceutical and biomedical industries, and reviews of some polymeric products in novel drug delivery systems and technologies will be covered.

History of Polymers

Polymers have a wide-ranging impact on modern society. Polymers are more commonly referred to as “plastics” since people are more familiar with plastic products that they encounter around the house than any other type of polymeric product. Plastics have the ability to be molded, cast, extruded, drawn, thermoformed, or laminated into a final product such as plastic parts, films, and filaments. The first semisynthetic polymer ever made was guncotton (cellulose nitrate) by Christian F. Schönbein in 1845. The manufacturing process for this polymer was changed over the years due to its poor solubility, processability, and explosivity resulting in a variety of polymers such as Parkesine, celluloid (plasticized cellulose nitrate), cellulose acetate (cellulose treated with acetic acid), and hydrolyzed cellulose acetate soluble in acetone. In 1872, Bakelite, a strong and durable synthetic polymer based on phenol and formaldehyde, was invented. Polycondensation-based polymeric products such as Bakelite and those based on phenoxy, epoxy, acrylic, and ketone resins were used as cheap substitutes for many parts in the auto and electronic industries. Other synthetic polymers were invented later including polyethylene (1933), poly (vinyl chloride) (1933), polystyrene (1933), polyamide (1935), Teflon (1938), and synthetic rubbers (1942). Polyethylene was used to make radar equipment for airplanes. The British air force used polyethylene to insulate electrical parts of the radars in their airplanes. Synthetic rubber, which could be made in approximately 1 hr as compared to 7 years for natural rubbers, was used to make tires and other military supplies. Teflon was used in atomic bombs to separate the hot isotopes of uranium. Nylon was used to make parachutes, replacing silk, which had to be imported from Japan.

The plastics revolution advanced technologies in the 20th century and opened new fields of application in the pharmaceutical and biomedical sectors. In recent years, polymers have been used to develop devices for controlling drug delivery or for replacing failing natural organs. In oral delivery, polymers are used as coatings, binders, taste maskers, protective agents, drug carriers, and release controlling agents. Targeted delivery to the lower part of the gastrointestinal tract (e.g., in the colon) was made possible by using polymers that protect drugs during their passage through the harsh environment of the stomach. Transdermal patches use polymers as backings, adhesives, or drug carriers in matrix or membrane products (these are described later in the book). Controlled delivery of proteins and peptides

has been made possible using biodegradable polymers. In many drug products you may find at least one polymer that enhances product performance. The key difference between early polymers and pharmaceutical polymers is biocompatibility.

Polymers in General[1,2,3,4,5]

The word “polymer” means “many parts.” A polymer is a large molecule made up of many small repeating units. In the

early days of polymer synthesis, little was known about the chemical structures of polymers. Herman Staudinger, who received the Nobel Prize in Chemistry in 1953, coined the term “macromolecule” in 1922 and used it in reference to polymers. The difference between the two is that polymers are made of repeating units, whereas the term macromolecule refers to any large molecule, not necessarily just those made of repeating units. So, polymers are considered to be a subset of macromolecules.

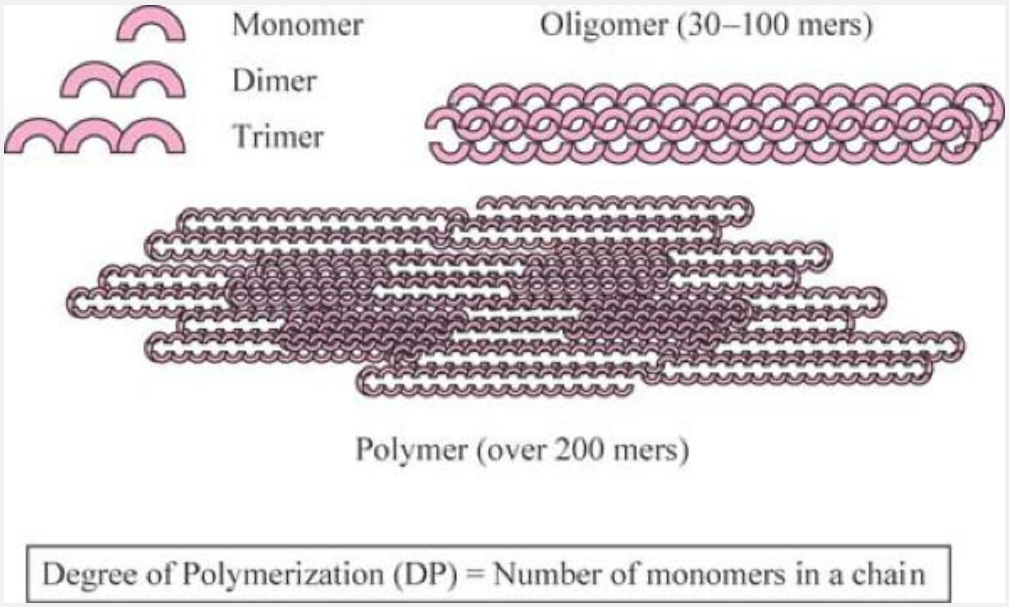


Fig. 20-1. Polymer anatomy.

A *monomer* is a small molecule that combines with other molecules of the same or different types to form a polymer. Since drawing a complete structure of a polymer is almost impossible, the structure of a polymer is displayed by showing the repeating unit (the monomer residue) and an “*n*” number that shows how many monomers are participating in the reaction. From the structural prospective, monomers are generally classified as olefinic (containing double bond) and functional (containing reactive functional groups) for which different polymerization methods are utilized. If two, three, four, or five monomers are attached to each other, the product is known as a dimer, trimer, tetramer, or pentamer, respectively. An *oligomer* contains from 30 to 100 monomeric units. Products containing more than 200 monomers are simply called a polymer (Fig. 20-1). From a thermodynamic perspective, polymers cannot exist in the gaseous state because of their high molecular weight. They exist only as liquids or high solid materials.

Example 20-1
Molecular Weight

A polyethylene with molecular weight of 100,000 g/mol is made of almost 3570 monomer units (—CH_2CH_2—) with the molecular weight of 28 g/mol.

Since polymers originate from oil, they are generally cheap materials. Unlike other materials such as metals or ceramics, polymers are large molecular weight materials and their molecular weight can be adjusted for a given application. For example, silicone polymers are supplied as vacuum grease (low molecular weight) and as durable implants (very high molecular weight). By changing the molecular weight, the physical and mechanical properties of the polymer can be tailor-made. This can be achieved by changing the structure of the monomer building blocks or by blending them with other polymers. Blending is a process intended to achieve superior properties that are unattainable from a single polymer. For example, polystyrene is not resistant against impact, so a polystyrene cup can be easily smashed into pieces if compressed between your fingers. However, polystyrene blended with polybutadiene is an impact resistant product. Alternatively, monomers of styrene and butadiene can be copolymerized to make a new copolymer of styrene–butadiene.

Polymer Synthesis

To make polymers, monomers have to interact with each other. Let us consider a simple scenario in which just one monomer type is going to be polymerized. The structure of the monomer molecule will tell us how we should polymerize it. A monomer may be unsaturated; in other words it may contain a double bond of *σ*(sigma) and π (pi) between a pair of electrons. The π bond generally requires low energy to break; therefore, polymerization starts at this site by the addition of a free radical on the monomer. On the other hand, if a monomer does not contain a double bond but possesses functional groups such as hydroxyl, carboxyl, or amines, they can interact via condensation. These two types of polymerization processes are described in the next two sections.

Addition Polymerization

Free-radical polymerization is also known as chain or addition polymerization. As the name implies, a radical-generating ingredient induces an initiator triggering polymerization. The initiator is an unstable molecule that is cleaved into two radical-carrying species under the action of heat, light, chemical, or high-energy irradiation. Each initiating radical has the ability to attack the double bond of a monomer. In this way, the radical is transferred to the monomer and a monomer radical is produced. This step in polymerization is called*initiation*. The monomer radical is also able to attack another monomer and then another monomer, and so on and so forth. This step is called *propagation* by which a *macroradical* is formed. Macroradicals prepared in this way can undergo another reaction with another macroradical or with another inert compound (e.g., an impurity in the reaction) which terminates the macroradical. Figure 20-2 shows the free-radical polymerization of styrene, a monomer, to polystyrene. Monomers such as acrylic acid, acrylamide, acrylic salts (such as sodium acrylate), and acrylic esters (methyl acrylate) contain double bonds and they can be polymerized via addition reactions.

Condensation Polymerization

In condensation polymerization, also called step polymerization, two or more monomers carrying different reactive

functional groups interact with each other as shown in Figure 20-3. For example, a monomer containing a reactive hydrogen from the amine residue can react with another monomer containing a reactive hydroxyl group (a residue of carboxyl group) to generate a new functional group (amide) and water as a side product. If a monomer containing the reactive hydrogen reacts with a monomer containing reactive chlorine, the side product will be hydrochloric acid. Since each monomer is bifunctional (in other words, it contains two reactive hydrogens or two reactive chlorines), the reaction product can grow by reacting with another monomer generating a macromonomer. Nylon is prepared via condensation polymerization of a diamine and diacid chloride. The diamine and diacid chloride are dissolved in water and tetrachloroethylene, respectively. Since the two solutions do not mix with each other, they form two immiscible separate layers, with tetrachloroethylene at the bottom. At the interface of the two solutions, the two monomers interact and form the polymer. The polymers can then be gently removed from the interface as fiber. There are no radicals involved in this polymerization reaction.

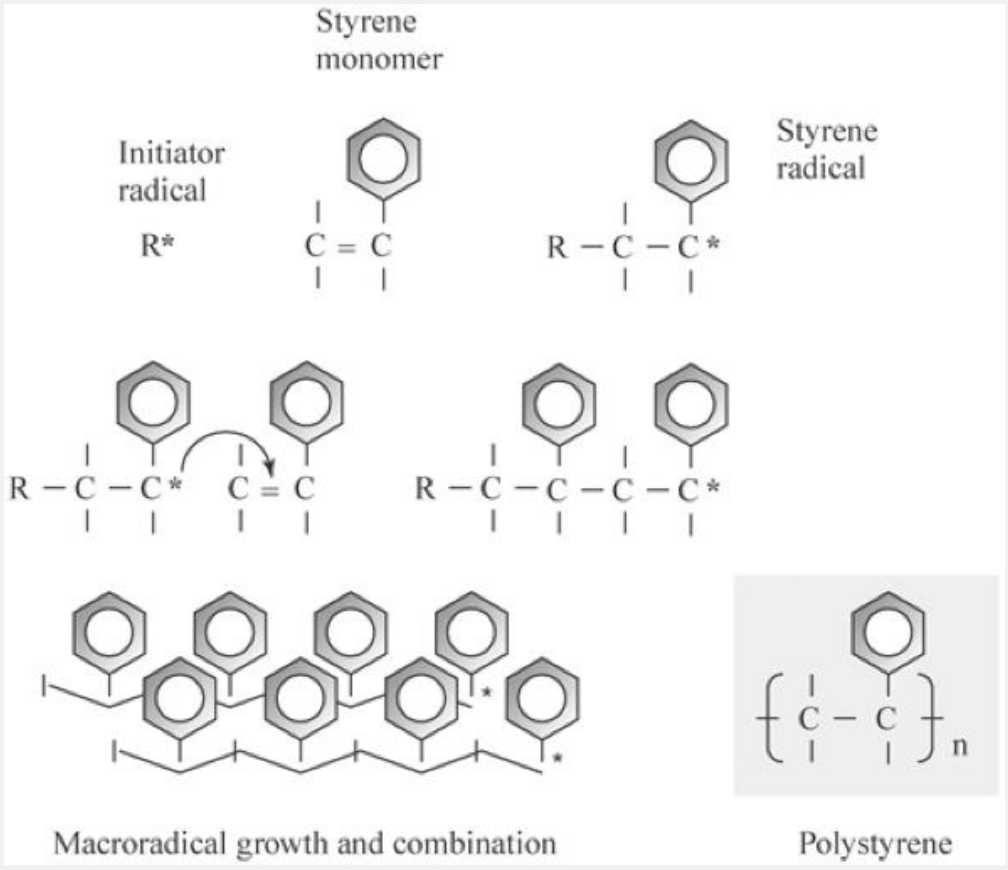


Fig. 20-2. Addition or free-radical polymerization of styrene.

Free-radical polymerization is an addition reaction that is characterized by fast growth of macroradicals. There is a high chance that high–molecular-weight chains are formed at the beginning of the reaction. On the other hand, condensation polymerization is a stepwise reaction in which smaller species are initially formed first and then combined to make higher-molecular-weight species. This reaction tends to be slow generally lasting for several hours. Figure 20-4 shows the concept.

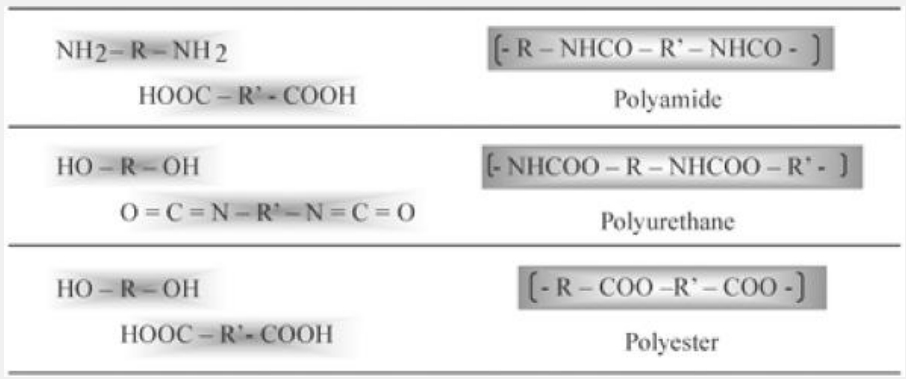


Fig. 20-3. Examples of condensation polymerization.

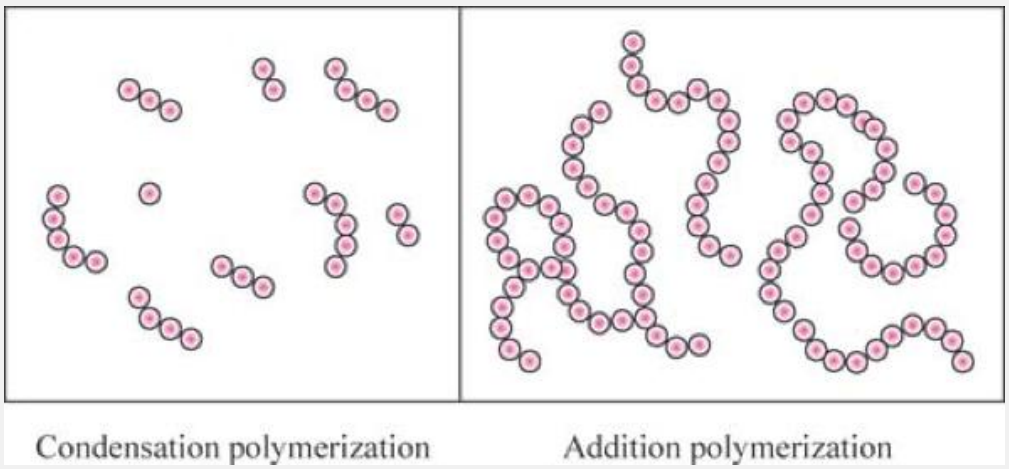


Fig. 20-4. Condensation versus addition polymerizations.

Polymerization Methods

Now, the question is how can polymers be made from monomers? Reactions may be carried out in homogeneous or heterogeneous systems. The former includes bulk and solution polymerizations, whereas the latter includes any dispersed system such as suspensions, emulsions, and their reverse phase counterparts; in other words, inverse suspensions and inverse emulsions.

Homogeneous Polymerization

Bulk polymerization occurs when no other materials except the monomer and initiator are used. If the monomer is water-soluble, a linear water-soluble polymer is theoretically prepared. With oil-soluble monomers, the polymer will be linear and soluble in oil. Surprisingly, sometimes when an olefinic water-soluble monomer is polymerized in bulk, a water-swellable polymer is prepared. This is due to excessive exothermic heat resulting in hydrogen abstraction from the polymer backbone, which promotes cross-linking reactions at the defective site. The cross-linked polymer obtained without using any chemical cross-linker is called a popcorn polymer and the reaction is called “popcorn polymerization.” Crospovidone, a superdisintegrant in solid dose formulations, is a cross-linked polymer of vinyl pyrrolidone which is produced by popcorn polymerization.

In certain circumstances when the monomer is very temperature sensitive, a popcorn polymer can be obtained even without using an initiator. The monomer acrylic acid is glacial with a melting point around 13°C. If the monomer was stored at freezing temperature, the polymerization stabilizer will be unevenly distributed between the liquid and thawing phases. This results in poor protection of the monomer and sudden polymerization that generates tremendous amounts of heat.

To solve the problems associated with exothermic heat in bulk polymerization, polymerization can alternatively be conducted in solution. Depending on the monomer solubility, water or organic solvents can be used as diluents or solvents. Again, a water-soluble or an oil-soluble polymer is obtained if monomers are water-soluble or oil-soluble, respectively. The solvent or diluent molecules reside in between the monomer molecules and they reduce the amount of interaction between the two neighboring monomers. In this way, less amounts of heat are generated in a given period of time and a

less exothermic but controllable reaction is conducted. Polymers prepared accordingly are generally soluble in their corresponding solvents, but they are swellable if a cross-linker is used during their polymerization. The cross-linker can be water-soluble or oil-soluble. Swellability of a polymer can be modified by the simultaneous use of water-soluble and oil-soluble cross-linkers.

Dispersion Polymerization

Dispersion polymerization occurs in suspensions, emulsions, inverse suspensions, and inverse emulsions. In dispersion polymerization, two incompatible phases of water and oil are dispersed into each other. One phase is known as the minor (dispersed) phase and the other as the major (continuous) phase. The active material (monomer) can be water-soluble or oil-soluble. To conduct polymerization in a dispersed system, the monomer (in the dispersed phase) is dispersed into the continuous phase using a surface-active agent. The surfactant is chosen on the basis of the nature of the continuous phase. Generally, a successful dispersion polymerization requires that the surfactant be soluble in the continuous phase. Therefore, if the continuous phase is water, the surfactant should have more hydrophilic groups. On the other hand, if the continuous phase is oil, a more hydrophobic (lipophilic) surfactant would be selected. Generally, two basic factors control the nature of the dispersion system. These are surfactant concentration and the surface tension of the system (nature of the dispersed phase) as shown in Figure 20-5. Dispersed systems were discussed in earlier chapters. The surfactant concentration determines the size of the polymer particles. The system will be a suspension or inverse suspension with particle sizes around 0.2 to 0.8 mm below the critical micelle concentration. Above the critical micelle concentration, 10 to 100 μm particles are formed. Nanosize particles can be made if a sufficient amount of surfactant is used. Nanoemulsion or inverse nanoemulsion systems are rarely used in the pharmaceutical industry because of the amount of surfactant required to stabilize the system. Surfactants represent undesirable impurities that affect drug stability and formulation acceptability. Water-insoluble polymers based on acrylic or methacrylic esters are prepared via suspension or emulsion polymerization. Eudragit L30D is a copolymer of methacrylic acid and ethyl acrylate which is manufactured using an emulsion technique. Eudragit NE30D is also a copolymer of ethyl acrylate and methyl methacrylate which can be manufactured in an emulsion system. On the other hand, water-soluble polymers based on acrylic or methacrylic salts as well as acrylamide can be prepared using inverse suspension or inverse emulsion systems. Emulsion systems that use water as a continuous phase are known as latex. Table 20-1 summarizes important polymerization methods that are potentially used to prepare pharmaceutical polymers.

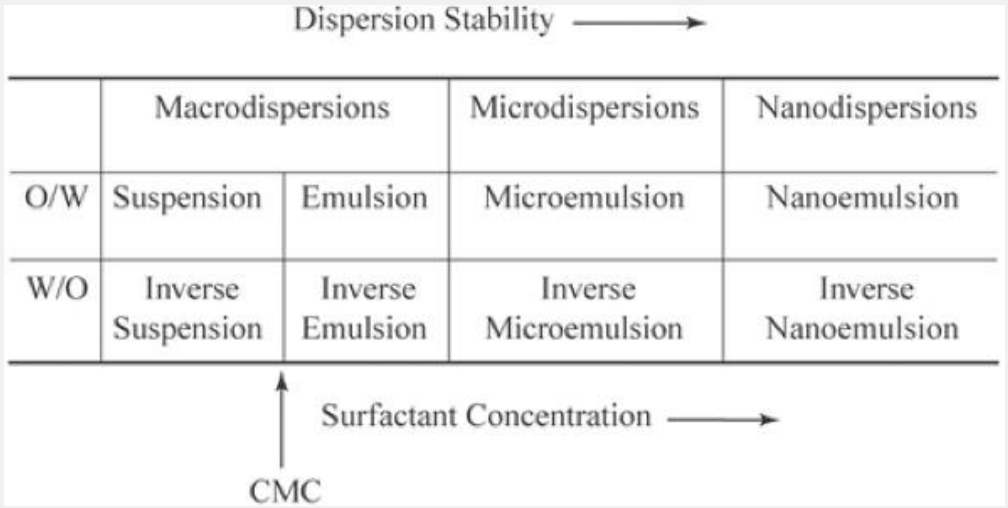


Fig. 20-5. Dispersion systems.

Copolymers and Polymer Blends

If one polymer system cannot address the needs of a particular application, its properties need to be modified. For this reason, polymer systems can be physically blended or chemically reacted. With the former, a two-phase system generally exists, whereas with the latter a monophase system exists. This can clearly be seen in a differential scanning calorimeter by monitoring the glass transition temperature (T_g) of the individual polymers. With polymer blends, two T_g values are observed while one single T_g is detected for copolymers. Thermal analysis is discussed in detail in Chapter 2.

Copolymerization refers to a polymerization reaction in which more than one type of monomer is involved. Generally, copolymerization includes two types of monomers. If one monomer is involved, the process is called polymerization and the product is a *homopolymer*. For example, polyethylene is a homopolymer since it is made of just one type of monomer. Depending on their structure, monomers display different reactivities during the polymerization reaction. If the reactivities of two monomers are similar, there will be no preference for which monomer is added next, so the polymer that is formed is called a *random copolymer*. When one monomer is preferentially added to another monomer, the monomers are added to each other alternatively and the polymer product is called an *alternate copolymer*. Sometimes, monomers preferentially add onto themselves and a *block copolymer* is formed. This happens when one monomer has a very high reactivity toward itself. Once more reactive monomers have participated in the reaction, the macroradical of the first monomer will attack the second monomer with the lower activity, and the second monomer will then grow as a block. Pluronic surfactants (EO-PO-EO terpolymers) are

composed of block units of ethylene oxide and propylene oxides attached to each other. The major difference between graft copolymer and the other copolymer types is the nature of their building blocks. Other copolymer types are made of two or more monomer types, while a monomer and a polymer are generally used to make graft copolymers. For example, the physical chemical properties of carboxymethyl cellulose (CMC) can be changed by grafting various monomers such as acrylic acid, acrylamide, and acrylonitrile onto the cellulose backbone. Although not very common, a terpolymer will be obtained when three monomers participate in the polymerization reaction. Different types of copolymer products are shown in Figure 20-6.

Table 20-1 Polymerization Methods

	Bulk	Solution	Suspension	Inverse Suspension	Emulsion	Inverse Emulsion	Pseudo latex
Monomer	WS or OS	WS or OS	OS	WS	OS	WS	
Initiator	WS or OS	WS or OS	Generally OS	Generally WS	Generally OS	Generally WS	

Cross-linker *	WS or OS	WS or OS	Generally OS	Generally WS	Generally OS	Generally WS	
Water		If WS monomer is used	CP	DP	CP	DP	CP
Organic solvent		If OS monomer is used	DP	CP	DP	CP	DP
Surfactant			WS;C_{surf}	OS; C_{surf}	WS;C_{surf}	OS; C_{surf}	WS
			<CMC; high	<CMC; low	>CMC; high	>CMC; low	
			HLB	HLB	HLB	HLB	
Polymer							OS†

*Cross-linker is added if a swellable polymer is desired.

†Polymer is soluble in organic solvents, but the latex itself is water dispersible.
Key: WS = water-soluble; OS = organic-soluble; DP = dispersed phase; CP = continuous phase; CMC = critical micelle concentration; HLB = hydrophilic lipophilic balance; C_{surf} = surfactant concentration.

Example 20-2
Pharmaceutical Polymers

In pharmaceutical solid oral dosage forms, the Eudragit polymers are used for sustained release, drug protection, and taste-masking applications. These polymers are made of acrylic esters (methyl methacrylate, ethyl acrylate). Their solubility, swellability, and pH dependent properties have been modified by incorporating anionic and cationic monomers such as methacrylic acid and dimethylaminoethyl acrylate.

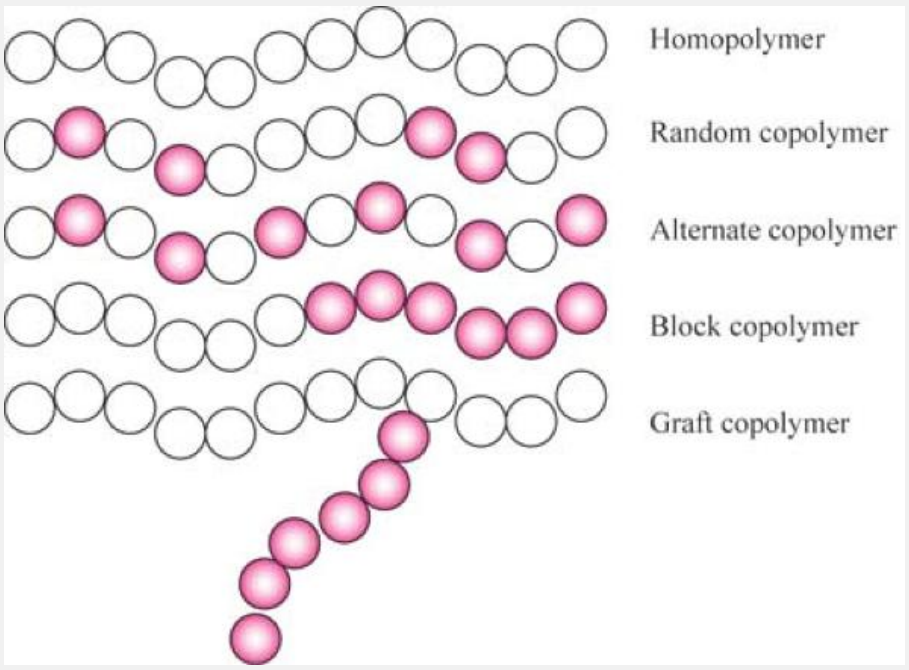


Fig. 20-6. Polymers made of two or more monomer units.

From a commercial standpoint, polymer properties can be simply changed by mixing or blending one or two polymer systems. Polymer blends are simply made by physical blending of two different polymers in molten or in solution state. The blend is either solidified at lower temperature if prepared by melting or recovered at higher temperature if prepared in solution. Some thermoplastic polymers are not resistant to sudden stresses. Once impacted, the craze (microcrack) and macrocracks will grow very quickly within their structure and the polymer will simply and suddenly break apart. These polymers have rigid structures with high T_g values. Adding a low T_g polymer (in other words, a flexible polymer) such as rubber particles improves the impact resistance of these polymers by preventing the cracks from growing.

Interpenetrating Polymer Networks

Interpenetrating polymer networks (IPNs) are also composed of two or more polymer systems but they are not a simple physical blend. Semi-IPNs or semi-interpenetrating polymer networks are prepared by dissolving a polymer into a solution of another monomer. An initiator as well as a cross-linker is added into the solution and the monomer is polymerized and cross-linked in the presence of the dissolved polymer. The result will be a structure in which one cross-linked polymer interpenetrates into a non–cross-linked polymer system. With fully interpenetrated structures, two different monomers and their corresponding cross-linkers are polymerized and cross-linked simultaneously. This results in a doubly cross-linked

polymer system that interpenetrates into one another. Alternatively, conducting the cross-linking reaction on a semi-interpenetrated product can form a full-IPN structure. The non–cross-linked phase of the

semi-IPN product will be further cross-linked with a chemical cross-linker or via physical complexation.[6,7]

Example 20-3

IPN Polymer Structure

Elastic superporous hydrogels have been developed for oral gastric retention of the drugs with a narrow absorption window. These hydrogels are prepared using a two-step process. First, a semi-IPN structure is prepared by polymerizing and cross-linking a synthetic monomer (such as acrylamide) in the presence of a water-soluble polymer (e.g., alginate). Although the cross-linked acrylamide polymer is not soluble in water, the alginate component is. In the second step, the prepared semi-IPN is further treated with cations (such as calcium) to provide insolubility to the alginate component via ion-complexation. This results in a full IPN structure with a balanced swelling and mechanical properties.

Topology and Isomerism

The topology of a polymer describes whether the polymer structure is linear, branched, or cross-linked. Topology can affect polymer properties in its solid or solution states. With a linear polymer, the polymer chains are not chemically attached to each other, instead weaker intermolecular forces hold the polymer chains together. A linear polymer can show dual behavior. Chains in a linear polymer can freely move, which offers the polymer a low melting temperature. On the other hand, linear chains have a higher chance of approaching each other in their solid state, which increases their crystallinity and melting temperature. The same holds true for branched polymers in which short or long side groups are attached to the backbone of the polymer. Branched polymer chains move with difficulty because of the steric hindrance induced by the side groups but they presumably possess weaker intermolecular forces, which apparently help them move freely. With cross-linked polymers, the chains are chemically linked and will be restricted from moving to a sensible extent depending on the level of cross-linking. Very highly cross-linked polymers are very rigid structures that degrade at high temperatures before their chains start to move.

In solution, a branched polymer might display a better solvent permeability compared to its linear counterpart due to its side groups. Gum Arabic is a highly branched polymer with very high solubility in water. If a linear polymer is cross-linked, its solubility will be sacrificed at the expense of swellability. Therefore, a cross-linked polymer can swell in a solvent to an extent that is inversely related to the amount of cross-linker. Figure 20-7 summarizes and correlates polymer topology to its solution and melt properties.

Isomerism can be classified as structural isomerism (Fig. 20-8a), sequence isomerism (Fig. 20-8b), and stereoisomerism (Fig. 20-8c). Gutta Percha natural rubber (*trans*-polyisoprene) and its synthetic counterpart (*cis*-polyisoprene) are similar in structure but their *trans* and *cis* nature results in a medium-crystal and amorphous behavior, respectively. This important feature can be accounted for in terms of the position of a methyl group. The *cis* and*trans* isomers of a same polymer display different T_g and T_m values, for example, polyisoprene (T_g of -70°C versus -50°C; T_m of 39°C versus 80°C), polybutadiene (T_g of -102°C versus -50°C; T_m of 12°C versus 142°C).1 With sequence isomerism, monomers with pendant groups can attach to each other in head-to-tail, head-to-head, or tail-to-tail conformation. Stereoisomerism applies to polymers with chiral centers, which results in three different configurations—isotactic (pendant groups located on one side), syndiotactic (pendant groups located alternatively on both sides), and atactic (pendant groups located randomly on both sides) configurations.

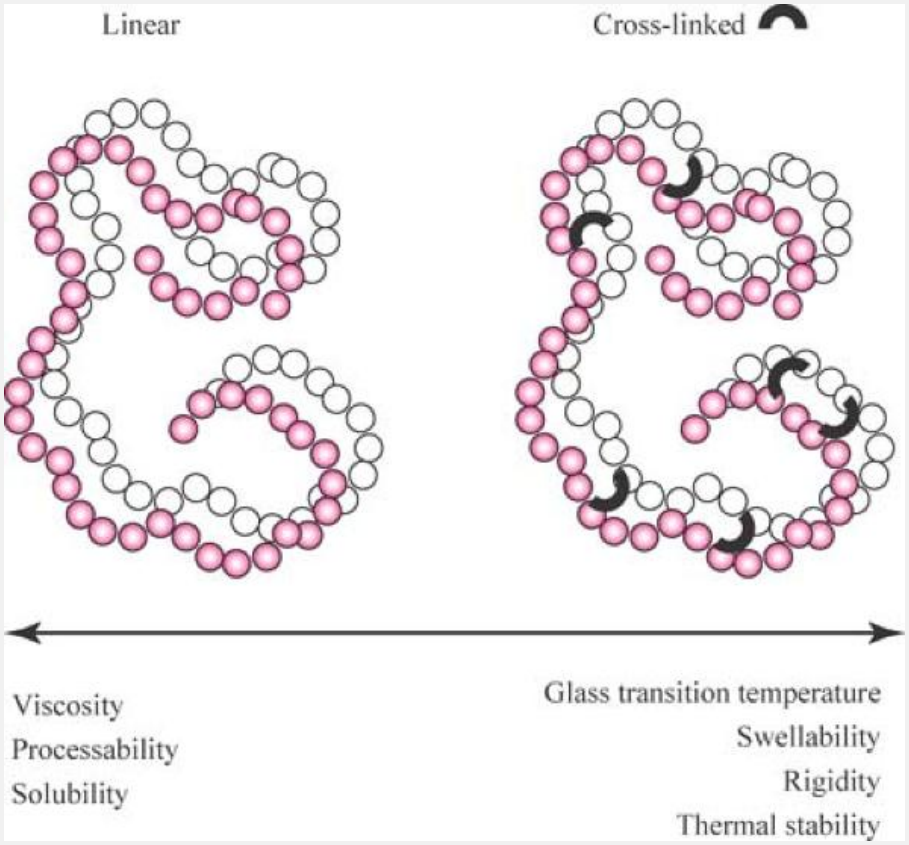


Fig. 20-7. Polymer topology and properties.

Example 20-4
Stereoisomerism
The isotactic and atactic polypropylenes display glass transition temperatures of 100°C and -20°C, respectively. While the isotactic one is used for special packaging purposes, the atactic one is commonly used as a cheap excipient in general adhesive formulations.

Thermoplastic and Thermoset Polymers

Polymers with a linear or branched structure generally behave as thermoplastics. Thermoplastic polymers can undergo melting, which is potentially useful in processes such as compression molding, injection molding, and thermoforming. In other words, a polymer that is originally a solid can flow upon application of heat. The process of thermomelting and

solidification can be repeated indefinitely with thermoplastic polymers. Examples include polystyrene, polyethylene, and poly (vinyl chloride). On the other hand, thermosetting polymers are cross-linked polymers, which are formed upon combined application of a cross-linker and heat or combined application of heat and reaction of internal functional groups. In some cross-linking reactions such as in curing rubbers, the reaction is assisted by simultaneous application of heat and pressure. Therefore, these polymers assume a different status than thermoplastic polymers as their flow behavior is temperature independent. Once a thermoset polymer is formed, it does not soften upon heating and decomposes with further application of heat. Since there is no reversible melting and solidifying in thermoset polymers, this feature is very useful when a thermoresistant polymer is desirable. Processing of polymers is generally favored by increasing temperature. A more processable polymer is one that

requires a lower temperature to move its chains. A cross-linked polymer loses its processability as chain movement is hindered with the addition of cross-linker. On the other hand, linear and branched polymers gain more freedom to move as temperature increases.

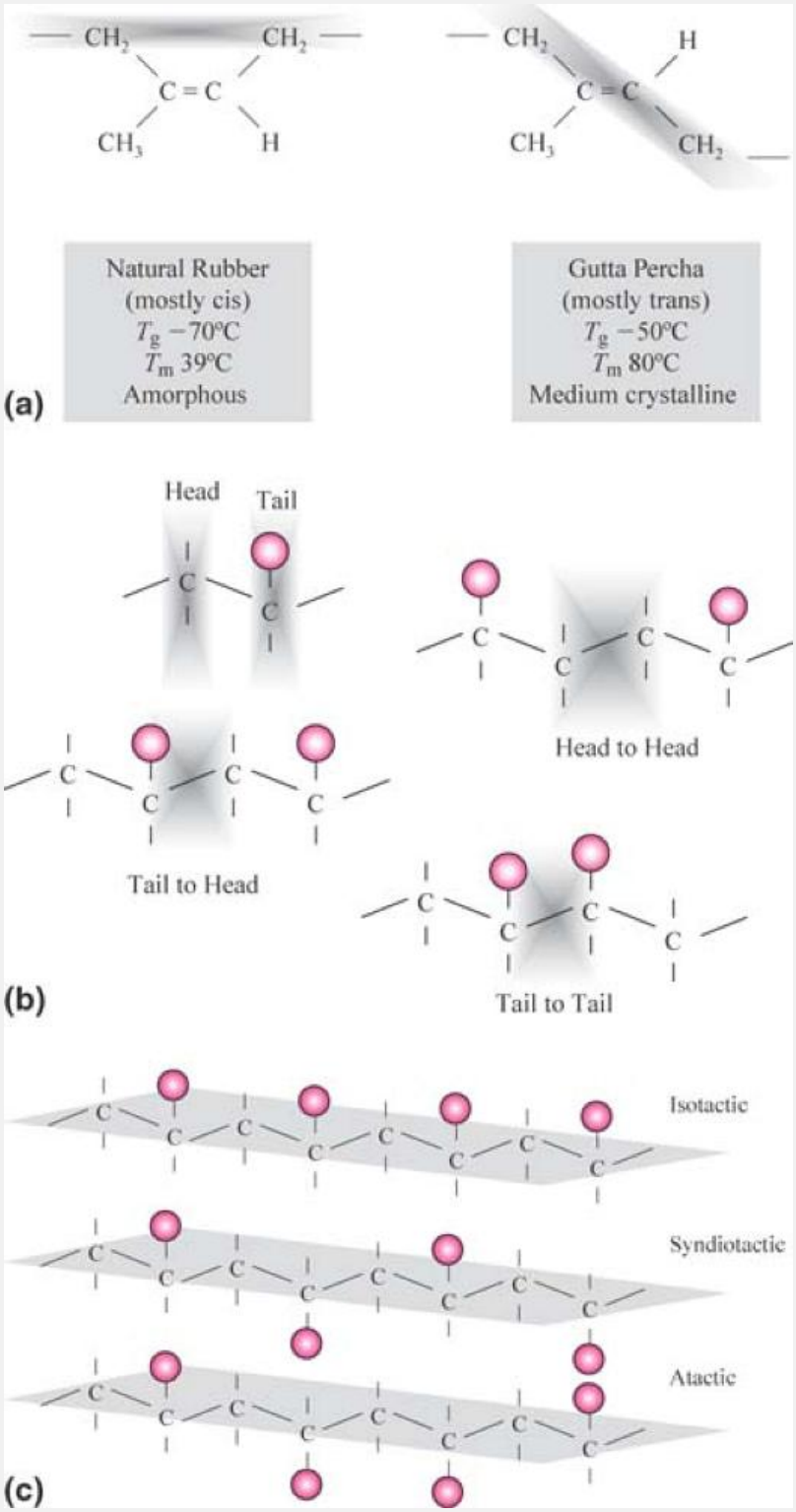


Fig. 20-8. (*a*) Structural isomerism; (*b*) sequence isomerism; and (*c*) stereoisomerism.

Key Concept

Cross-Linking

A ladder is composed of two long legs and multiple short pieces that are used to connect them. When a ladder is used, you do not want its legs to move or even worse, to separate from each other. A ladder with more connection points on the two legs is more secure and more stable than a ladder with less. One cannot climb on a ladder without a connector. In polymer terms, cross-linked polymers are long linear chains (ladder legs) that are cross-linked using a functional or an olefin cross-linker (ladder legs connector). Cross-linked polymers are also intended for applications where a certain amount of load is applied. Examples of this are tires (made of cross-linked rubbers) and hydrogels (made of cross-linked hydrophilic polymers) that are expected to function and to survive under the service load of mechanical and swelling pressure, respectively. When you drive your car, the last thing you want is to have your tire melt away.

For a polymer in its solution state, solubility in a solvent is also an entropy-favored process. In other words, a linear or branched polymer generally dissolves in an appropriate solvent. Addition of cross-links to their structure will hinder chain movement and reduce their solubility in that solvent. This is why cross-linked polymers swell when they are placed in a compatible solvent.

Polymer Properties

Crystalline and Amorphous Polymers

Polymers display different thermal, physical, and mechanical properties depending on their structure, molecular weight, linearity, intra- and intermolecular interactions. If the structure is linear, polymer chains can pack together in regular arrays. For example, polypropylene chains fit together in a way that intermolecular attractions stabilize the chains into a regular lattice or crystalline state. With increased temperature, the crystal cells (crystallites) start to melt and the whole

polymer mass suddenly melts at a certain temperature. Above the melting temperature, polymer molecules are in continuous motion and the molecules can slip past one another.

In many cases, the structure of a polymer is so irregular that crystal formation is thermodynamically infeasible. Such polymers form glass instead of crystal domains. A glass is a solid material existing in a noncrystalline (i.e., amorphous) state. Amorphous structure is formed due to either rapid cooling of a polymer melt in which crystallization is prevented by quenching or due to the lack of structural regularity in the polymer structure. Rotation around single bonds of the polymer chains becomes very difficult at low temperatures during rapid cooling; therefore, the polymer molecules forcedly adopt a disordered state and form an amorphous structure. Amorphous or glassy polymers do not generally display a sharp melting point; instead, they soften over a wide temperature range.8

Example 20-5

Crystalline and Amorphous

Polystyrene and poly (vinyl acetate) are amorphous with melting range of 35°C to 85°C and 70°C to 115°C, respectively. On the other hand, poly (butylene terephthalate) and poly (ethylene terephthalate) are very crystalline with sharp melting range of 220 and 250°C to 260°C, respectively.

Polymer strength and stiffness increases with crystallinity as a result of increased intermolecular interactions. With an increase in crystallinity, the optical properties of a polymer are changed from transparent (amorphous) to opaque (semicrystalline). This is due to differences in the refractive indices of the amorphous and crystalline domains, which lead to different levels of light scattering. From a pharmaceutical prospective, good barrier properties are needed when polymers are used as a packaging material or as a coating. Crystallinity increases the barrier properties of the polymer. Small molecules like drugs or solvents usually cannot penetrate or diffuse through crystalline domains. Therefore, crystalline polymers display better barrier properties and durability in the presence of attacking molecules. Diffusion and solubility are two important terms that are related to the level of

crystallinity in a polymer. On the other hand, a less crystalline or an amorphous polymer is preferred when the release of a drug or an active material is intended. Crystallinity in a given polymer depends on its topology and isomerism (linear versus branched; isotactic versus atactic), polymer molecular weight, intermolecular forces, pendant groups (bulky versus small groups), rate of cooling, and stretching mode (uniaxial versus biaxial). Another unique property of a crystalline polymer or a polymer-containing crystalline domains is anisotropy. A crystal cell displays different properties along longitudinal and transverse directions. This causes the polymer to behave like an anisotropic material.

 **Key Concept**

Anisotropy

Take a roll of toilet paper from your bathroom and try to tear it apart from two directions perpendicular to each other. What will you observe?

If you tear it along the roll direction (its length), it will easily tear apart and the tear line will be smooth and even. On the other hand, tearing in the other direction would be very difficult and the tear line will appear as a random irregular corrugated line. Why is this?

Toilet paper is manufactured using a process that applies a force along the roll direction. Because of the applied force, the chains are aligned in the direction of the force. When you try to tear the tissue in this direction, there is no barrier to the force and the material does not resist. On the other hand, tearing the tissue requires cutting the chains in the perpendicular direction that implies resistance from the material. This is **anisotropy,** which means material properties are different in different directions. Pharmaceutical tablets are generally compressed in one direction, which might affect drug release or tablet properties throughout.

Thermal Transitions

Thermal transitions in polymers can occur in different orders. In other words, the volume of a polymer can change with temperature as a first- or second-order transition. When a crystal melts, the polymer volume increases significantly as the solid turns to a liquid. The melting temperature (T_m) represents a first-order thermal transition in polymers. On the other hand, the volume of an amorphous polymer gradually changes over a wide temperature range or so-called glass transition temperature. This behavior represents a second-order thermal transition in polymers. As shown in Figure 20-9, T_m and T_g of a given polymer can be detected by differential scanning calorimetry (DSC) as an endothermic peak and a baseline shift, respectively. These two thermal transitions reflect the structural movement of the crystalline and amorphous regions of a polymer chain.

Glass Transition Temperature

T_g is an expression of molecular motion, which is dependent on many factors. Therefore, the T_g is not an absolute property of a material and is influenced by the factors affecting the movement of polymer chains. At temperatures well below the T_g, amorphous polymers are hard, stiff, and glassy although they may not necessarily be brittle. On the other hand, at temperatures well above the T_g, polymers are rubbery and might flow. The T_g values for linear organic polymers range from about -100°C to above 300°C. Even though some organic polymers are expected to have T_g values above

300°C, they decompose at temperatures below their transition temperatures. From a pharmaceutical standpoint, T_g is an important factor for solid dosage forms. For example, a chewable dosage form needs to be soft and flexible at mouth temperature of about 37°C. This means the polymer used as a chewable matrix should be softened at this temperature. Pharmaceutically acceptable polymers with their T_g values close to the service temperature of 37°C would be the best candidates. Nicotine gum (Nicorette) gum is used as an aid in smoking cessation. It works by providing low levels of nicotine, which lessens the physical signs of withdrawal symptoms. The nicotine is released into the mouth as the patient chews the gum. After placing a piece of the Nicorette gum into the mouth the patient should chew it slowly several times. The patient should stop chewing it once he or she notices a tingling sensation or a peppery taste in the mouth. At this point the nicotine is being released and the patient

should “park” the gum in the buccal area (in other words, between the cheek and the gum) and leave it there until the taste or tingling sensation is almost gone. The patient can resume chewing a few more times and then stop once the taste comes back. The patient should repeat this for about 30 min or until the taste or tingling sensation does not return. The reason that the patient “parks” the gum is because the release of nicotine should be slow and constant chewing will release the nicotine too quickly resulting in nausea, hiccups, or stomach problems. The patient should also avoid drinking or eating at this time. You have most likely experienced how gum behaves differently when you drink cold water or hot tea. This is all reflected in glass–rubber transition of the chewable matrix.

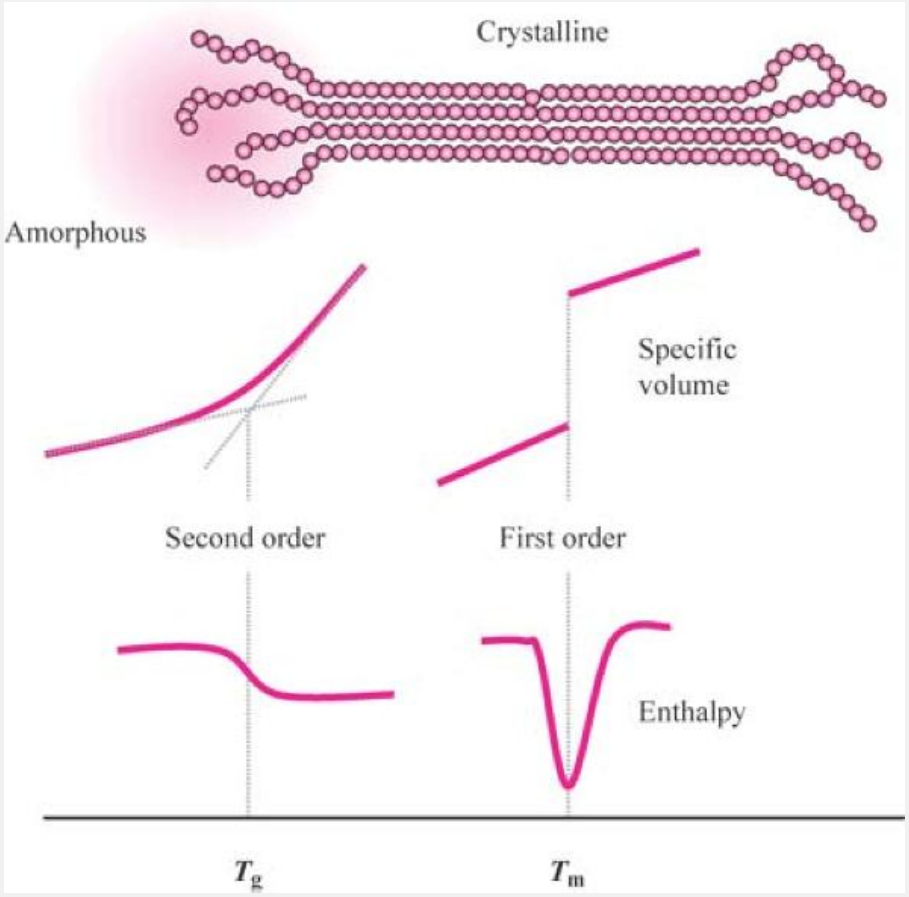


Fig. 20-9. Thermal transitions in polymers.

As mentioned before, the T_g of a polymer is dependent on many factors and the most important ones are discussed here. Segmental motion in polymers is facilitated by the empty space in between the polymer chain ends, also called the *free volume*. As the free volume increases, polymer segments gain more freedom to move and this affects the temperature at which the movement occurs. For example, low- and high-density polyethylenes are different in terms of the size of the free volume inside their structures. At a given weight, a low-density polymer occupies more volume as compared with its high-density counterpart. This means the polymer chain in general and the chain segments in particular can move with more ease resulting in a lower T_g value.

T_g and the length of the polymer chain: Long polymer chains provide smaller free volume than their shorter counterparts. Since more free volume corresponds to lower T_g values, polymers containing short chains or having lower molecular weight possess lower T_g values.

T_g and polymer chain side group: A side group may be bulky or polar. Because of its steric hindrance, higher temperature is needed to induce segmental motion in polymers containing bulky groups. For example, polystyrene and polypropylene are only different in terms of their side groups, phenyl versus

methyl, respectively. The larger size of the phenyl group results in the much higher T_g value of polystyrene, 100°C as opposed to -20°C for polypropylene. On the other hand, polar side groups provide stronger intermolecular interactions that significantly affect the segmental motion of the polymer chains. Poly (vinyl chloride) is similar to polyethylene except hydrogen is replaced by one chlorine atom. Since chlorine is more polar than hydrogen, the PVC polymer displays a much higher T_g of 100°C compared to -120°C for polyethylene.

T_g and polymer chain flexibility: Flexible polymer chains display higher entropy (desire to move) than rigid chains. Flexible and rigid chains behave similar to liquid and solid, respectively. Groups such as phenyl, amide, sulfone, and carbonyl either inside the backbone or as a side group hanging on the backbone affect the overall polymer flexibility. For example, poly (ethylene adipate) and poly (ethylene terephthalate) are structurally very similar except for the phenylene residue in phthalate versus the butylene residue in adipate. This results in almost a 100°C difference in T_g values of the two polymers (-70°C versus 69°C, respectively).

T_g and polymer chain branching: Linear polymer chains possess smaller free volume as opposed to their branched counterparts. Therefore, higher T_g values are expected for linear polymers. On the other hand, branches in branched polymers impose hindrance or restriction to segmental motion, for which higher T_g values are expected. Therefore, branching has no obvious effect on the $T_g$unless the whole structure of the polymer is known.

T_g and polymer chain cross-linking: Compared to cross-linked chains, linear chains have a higher entropy and the desire to move; hence, they display low T_g values. Adding cross-links to linear polymer chains limits chain movement resulting in less entropy at a given temperature and hence a higher T_g value. For very highly cross-linked polymers, T_g values are expected to be very high to the extent that the

polymer starts to decompose before it shows any segmental motion.

T_g and processing rate: In order to prepare polymer products, the polymer needs to be processed at different temperatures or pressures that can significantly affect the molecular motion in polymers. Therefore, the rate of processes such as heating, cooling, loading, and so on and so forth might be considered when evaluating the T_g value of a given polymer. Kinetically speaking, if the rate of the process is high (fast cooling, fast loading), the polymer chains cannot move to the extent that they are expected to. They virtually behave like rigid chains with lower tendency to move, which results in reading high T_g values. For instance, when a differential scanning calorimeter is used to measure the T_g of a polymer, different T_g values may be observed if the same polymer is heated up at different heating rates. This implies that the heating rate has to be very realistic and should be consistent with the conditions in which the polymer is expected to serve.

T_g and plasticizers: Plasticizer molecules can increase the entropy and mobility of the polymer chains. This is translated to lower $T_g$values for plasticized polymers compared with their nonplasticized counterparts.

Plasticized Polymers

A plasticizer is added to a polymer formulation to enhance its flexibility and to help its processing. It facilitates relative movement of polymer chains against each other. The addition of a plasticizer to a polymer results in a reduction in the glass transition temperature of the mixture. Since plasticizers increase molecular motion, drug molecules can diffuse through the plasticized polymer matrix at a higher rate depending on the plasticizer concentration.

Example 20-6

Plasticized Polymers

Fluoxetine (Prozac Weekly) (fluoxetine hydrochloride) capsules contain hydroxypropyl methylcellulose and hydroxypropyl cellulose acetate succinate plasticized with sodium lauryl sulfate and triethyl citrate. Omeprazole magnesium (Prilosec), a delayed release oral suspension, contains hydroxypropyl cellulose, hydroxypropyl methylcellulose, and methacrylic

acid copolymer plasticized with glyceryl monostearate, triethyl citrate, and polysorbate. Triacetin can be found in ranitidine HCl (Zantac) 150-tablet formulations, which contains hydroxypropyl methylcellulose as its polymer matrix. Dibutyl sebacate is found in methylphenidate HCl (Metadate) CD which contains polymers such as povidone, hydroxypropyl methylcellulose, and ethyl cellulose.

Molecular Weight

Addition of a monomer to a growing macroradical during polymer synthesis occurs by a diffusion or a random walk process. Monomers may or may not be added equally to the growing macroradicals. As a result, a polymer batch may contain polymer chains with different lengths (molecular weights) and hence different molecular weight distributions. A very narrow molecular weight distribution is very much desired for a polymer that is intended to be mechanically strong. On the other hand, a polymeric adhesive may have wide distribution of molecular sizes. In general, a given polymer cannot be identified as a molecule with a specific molecular weight. Since chains are different, the molecular weight of all chains should be considered and must be averaged to have a more realistic figure for molecular weight of a given polymer. There are different ways that molecular weights of a polymer can be expressed; by the number of the chains, by the weight of the chains (the chain size), or by viscosity. However, the two most common ways are number (M_n) and weight (M_w) average calculations. If all polymer chains are similar in size, then the number and weight average values will be equivalent. If chains are of different sizes, then weight average is distancing itself from the number average value. The term polydispersity (PD) indicates how far the weight average can distance itself from the number average. A PD value closer to 1 means the polymer system is close to monodispersed and all of the polymer chains are almost similar in size. The farther the value from 1 indicates that the polymer system is polydispersed and chains are different in size. Figure 20-10 shows the concept.

Consider that you have received two different batches of a same polymer as shown in Table 20-2. The first batch contains 2 chains of 50,000 g/mol and 10 chains of 20,000 g/mol in size. The second batch contains 2 chains of 100,000 g/mol and 10 chains of 10,000 g/mol in size. Calculations show both batches have the same number averages of 25,000 g/mol. Should you, as a pharmaceutical scientist, claim that the two batches are similar and you can use them interchangeably within your formulation? You continue with the calculation to find out the weight average values for the two batches. Surprisingly, two very different numbers, 30,000 g/mol and 70,000 g/mol, are found for the batch 1 and the batch 2,

respectively. This shows that the two batches are beyond a doubt different. Another important piece of data that can help you with your decision is PD which is the ratio of weight to number averages.*Polydispersity* of 2.8 versus 1.2 indicates that the batch 2 contains very different chains. If both polymer batches are soluble in water, they will definitely show different solubility behavior in the presence of water. The shorter chains are dissolved faster in water than longer chains. Drug release from these batches will certainly be different as they assume different PD values.

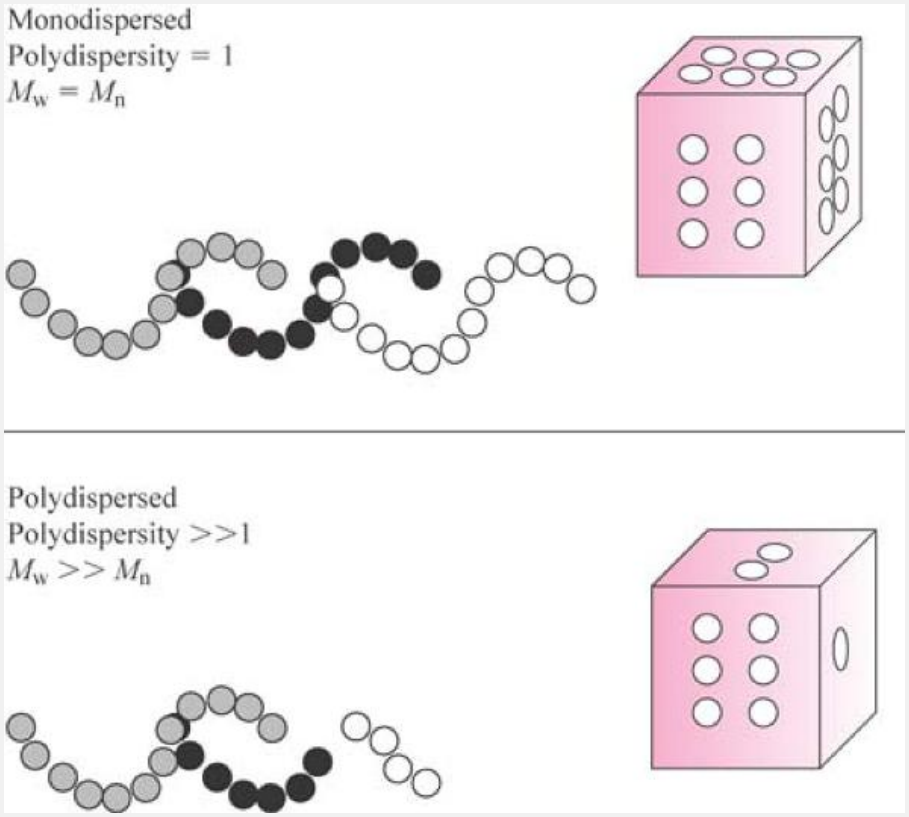


Fig. 20-10. Molecular weight distribution in polymer systems.

Key Concept

Number and Weight Averages

A research institute is planning to hire a good scientist who can publish a tangible number of high-quality manuscripts per year. The institute receives two resumes in which both scientists have claimed 20 publications a year. The applicants were then asked to submit more details about the journals in which they have published. Now, the institute knows not only the total number of publications but also the type and the number of journals they have published in. Journals were then categorized on the basis of their impact factor (IF) as very high, high, medium, and low. If the total number of publications is divided by the number of journals, both scientists score the same with an average of five publications per journal per year. The number will change if the impact factors of the journals are also considered in the calculation. So, the new calculation shows average numbers of 1.6 as opposed to 3.4 for the scientists 1 and 2, respectively. It looks like the institute has found a tool to discriminate between the achievements of the two scientists. These new numbers show that the scientist 2 is more capable in publishing high-quality manuscripts. A similar discussion is valid for different polymer chains (journals) with different molecular weights (impact factors). With number average, all chains are considered similar and the effect of their size is simply overlooked.

Journal	IF	Scientist 1	Scientist 2	N_1	W_1	N_2	W_2
Very high IF	20	2	8				
High IF	10	4	6	5	1.6	5	3.4
Medium IF	4	6	4				
Low IF	1	8	2				
Total	35	20	20				

Different techniques are used to calculate different averages. Since the number average relies on the number of polymer chains, technique to measure this should also rely on the number of species such as number of particles, and so on and so forth. It is well-known that colligative properties such as osmotic pressure and freezing point depression are dependent on the number of particles in the solution. Colligative properties were introduced earlier in the book. These techniques are very appropriate for calculating the average M_n of a given polymer. On the other hand, the weight average relies on the size of the molecules. Techniques such as light scattering are also reliant on the size of the molecules. Large- and small-sized molecules scatter light in a very different way. Therefore, it is reasonable to use a light-scattering technique to calculate the average M_w of a polymer.

TABLE 20–2
AVERAGE MOLECULAR WEIGHTS AND POLYDISPERSITY

Number of Chains	Batch 1	Batch 2
2	50,000 g/mol	100,000 g/mol
10	20,000 g/mol	10,000 g/mol

Batch 1			Batch 2		
M_n	M_w	PD	M_n	M_w	
25,000 g/mol	30,000 g/mol	1.2	25,000 g/mol	70,000 g/mol	2

$$\overline{M_n} = \frac{\sum M_i N_i}{N_i} = \frac{(M_1N_1) + (M_2N_2) + (M_3N_3) + (M_4N_4) + \cdots}{N_1 + N_2 + N_3 + N_4 + \cdots}$$

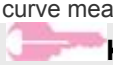
$$\overline{M_w} = \frac{\sum M_i^2 N_i}{\sum M_i N_i} = \frac{(M_1^2N_1) + (M_2^2N_2) + (M_3^2N_3) + (M_4^2N_4) + \cdots}{(M_1N_1) + (M_2N_2) + (M_3N_3) + (M_4N_4) + \cdots}$$

Table 20-2 Average Molecular Weights and Polydispersity

Mechanical Properties

Depending on their structure, molecular weight, and intermolecular forces, polymers resist differently when they are stressed. They can resist against stretching (tensile strength), compression (compressive strength), bending (flexural strength), sudden stress (impact strength), and dynamic loading (fatigue). With increasing molecular weight and hence the level of intermolecular forces, polymers display superior properties under an applied stress. As far as structure is concerned, a flexible polymer can perform better under stretching whereas a rigid polymer is better under compression.
P.503

A polymer is loaded and its deformation is monitored to measure its strength. Figure 20-11 shows the stress–strain behavior of different materials. For elastic materials such as metals and ceramics, the stress and strain (deformation) correlation is linear up to the failure point. Generally, these materials show high stress and very low elongation (deformation, strain) at their breaking point. Polymeric materials such as fibers and highly cross-linked polymers display elastic behavior, in other words, a linear stress/strain correlation up to their breaking point. With an increase in intermolecular forces within a fibrous product or cross-link density of a cross-linked polymer, the slope of the stress/strain line will become steeper. The sharper the slope, the higher the modulus. Modulus and stiffness are two terms that can be used interchangeably to demonstrate the strength of a polymer. Some polymeric materials do not display a sharp or abrupt breaking point. Instead, they yield at certain stresses and continue to deform under lower stresses before they finally break apart. Tough plastics show this typical behavior. Rubbers or elastomers on the other hand display completely different behavior, which depends on the level of cross-linking or curing. Generally, under very small stresses, they deform to a large extent to more than 10 to 15 times their original lengths. You may recall a rubber band when you stretch it from both ends. Highly cross-linked rubbers show very low deformation at their breaking point. In fact, cross-linking is the process by which properties of a rubber can be enhanced to a very tough plastic or even a fiber. Regardless of the polymer type (fiber, tough plastic, or rubber), certain amounts of energy are needed to break the polymer apart (in other words, toughness) and the area under the stress/strain curve measures it. The larger the area is, the tougher the polymer.



Key Concept

Molecular Weight Distribution

If you are planning to hire individuals for a cheerleading team, you may impose very strict requirements. For example they should all be 6-feet tall with a body mass index of 20. In the same sense, a soccer team might need a goalkeeper as well as a defense and forward, for each of which you may have different requirements. For example, height is very important for the goalkeeper position, whereas speed and accuracy is the most important requirement for the forward. In polymer terms, chain size distribution per se is not a bad or a good thing. Depending on the application, the polymer needs to have a sharp or wide size distribution. A polymer for an engineering application like the ones they use in aircrafts or spacecrafts may need to have a narrow size distribution, whereas for a general-purpose application you may use a polymer with a wider size distribution.

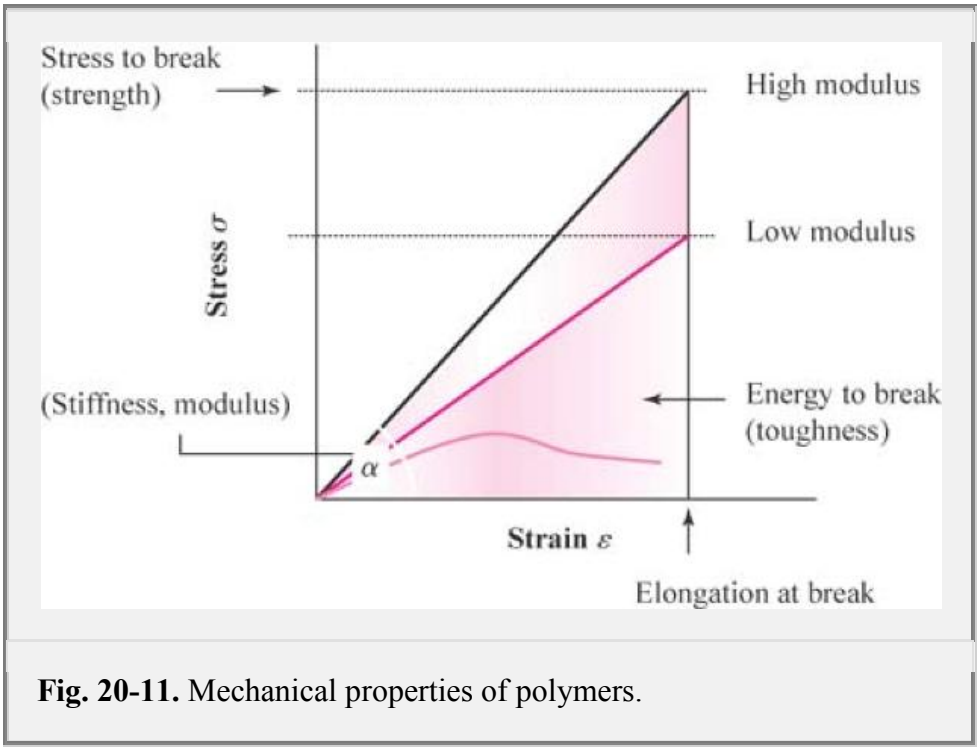


Fig. 20-11. Mechanical properties of polymers.

Viscoelastic Properties

Mechanical properties of a given polymer are generally measured at a fixed rate of loading, certain temperature or relative humidity, and so on and so forth. Polymers are neither a pure elastic nor a pure fluid material. They have the ability to store energy (display elastic behavior) and to dissipate it (display viscous behavior). For this reason, most polymers are viscoelastic materials. For example, poly (vinyl chloride) has a glass transition temperature of about 100°C. This means, it behaves like a solid at temperatures below its T_g and like a fluid at temperatures above its T_g. Since a typical PVC product is generally used at room temperature, its T_g is supposed to be well above the temperature of the environment in which it is expected to serve. In other words, a PVC product behaves like a solid or glass at any temperature (including its service temperature) below its T_g. Now, assume that your PVC product is expected to serve under a certain load (thermal, mechanical, etc.) and at certain temperature below its T_g, but for various periods of time. Such a loaded polymer, which originally behaves as a solid, or elastic may change its behavior upon a long-term loading. Over time, the polymer intermolecular forces will essentially become weaker and hence, the polymer becomes softer. This can be seen in the glass windows used in the old churches as they show different thicknesses from top to the bottom.
There are generally two methods to evaluate the viscoelasticity in polymers; the creep test and the stress relaxation test. With the former, the polymer is first loaded with a certain weight and its deformation is then monitored over the time. With the latter, the polymer is first deformed to a certain extent, and then its stress relaxation (internal stress) is monitored with the time.

Molecular Weight and Polymer Properties

Mechanical properties of a given polymer generally increase with an increase in molecular weight. Polymer melts and

polymer solutions are handled with more difficulty as their molecular weight increases. This is due to a phenomenon called entanglement, which affects the flow of the polymer chains. As molecular weight increases, polymer chains are more likely entangled into each other at certain molecular weights. This results in poor polymer flow either in solid state (as a melt) or in solution state (as a solution). For many applications, there is a working range of molecular weights that a given polymer in solid or solution state can successfully be processed.

Key Concept

Entanglement

Let us say that there are two laundry machines with the total capacity of each 20 lb and you separate your clothes into two small (shorts) and large (pants) groups, each weighing 20 lb. Once the laundry step is completed, the clothes are to be transferred into a dryer. An important observation to make is that more time will be spent to separate the large clothes from each other, which is not the case with the small clothes. This happens because large clothes have a tendency to tie into each other. Because of this, the washer should be loaded with a smaller number of large articles of clothing as it makes it easier to wash and dry them. In polymer terms, large molecular-weight polymers (large clothes) have a better affinity to tie into each other as opposed to their smaller molecular-weight counterparts (small clothes). This is called *entanglement*. This occurs after a certain molecular weight and affects the polymer properties in both the solution and solid states.

Variety of Polymers

Depending on their applications, polymers may be classified as rubbers, plastics, fibers, adhesives, and coatings. Each application requires a polymer to possess certain properties.

Rubbers

Rubbers are mostly used in tire manufacturing. A tire is a dynamic service environment that experiences friction with the ground surface; has to carry a heavy load of car weight and its passengers; and is exposed to ultraviolet radiation, ozone, oxygen (inside and outside of the tire), weathering conditions (wind, rain), and fatigue (dynamic loading and unloading). From a processing prospective, a tire is a composite of a few rubbers, metal, fiber, particulate fillers, and more. This requires rubber components of a tire to have excellent cohesive (strength) and adhesive (adhesion) properties. Rubbers have unique elongation properties, they can be stretched without failure, and they can be loaded with static and dynamic loads under very severe conditions. Just imagine for a moment, landing of a fully loaded cargo plane or a commercial aircraft. Different rubbers offer different properties. Those with double bonds (e.g., isoprene, butadiene) offer resiliency but are very susceptible to oxidation and ozonation. Those without double bonds (e.g., ethylene–propylene rubber) are very durable against weathering conditions. Some are very resistant to oil (e.g., chloroprene and nitrile) and some have excellent impermeability (e.g., isobutylene–isoprene rubber). Tube-in tires are still used in which the tube part is basically made of an air-impermeable rubber called butyl. Silicone is a very inert rubber with almost no affinity to any material. Therefore, silicone rubber is an excellent candidate for very durable parts such as implants in biomedical applications. Rubbers in general are not very strong in their raw form but they have a potential to be cross-linked and cured. None of the rubbers used in tires can serve this application without undergoing a curing process. Rubber is loaded with certain chemicals (curing agents) and is cured or cross-linked at high pressure and temperature. Generally speaking, the glass transition temperatures of the rubbery polymers (elastomers) are below the room temperature.

Plastics

Plastics on the other hand possess completely different properties. Their glass transition temperature is generally above the room temperature as opposed to elastomers as shown in Figure 20-12. Plastic parts are manufactured by techniques such as injection molding, extrusion, and thermoforming that require the plastic to be in its molten state. Plastics that are used in general applications such as packaging are generally cheap and are structurally weak. Polymers such as polyethylene, polypropylene, and polystyrene have only carbon in their backbone. The other groups of plastics which are used in engineering applications are required to be impact resistant, weather resistant, solvent resistant, and so on and so forth. These are generally heterogeneous plastics, which have elements other than carbon such as N, Si, and O in their backbone. Polyesters, polyamides, and polyacetals are engineering plastics with very high intermolecular forces and hence high melting point.

Fibers

Polymers for fibrous products are required to have a crystalline structure with a very sharp melting point. For this application, polymers need to be meltable and spinnable. Polypropylene fibers are used for plastic baskets, they are weak, and do not possess any specific properties. On the other hand, Kevlar fibers are used for bulletproof jackets. This application requires the fiber to have very strong

intermolecular forces. In manufacturing fibers, both general and engineering plastics are used. Examples of fiber-forming materials are cellulose acetate, rayon, polypropylene, nylon, polyester, polyamide, and polyacrylonitrile.

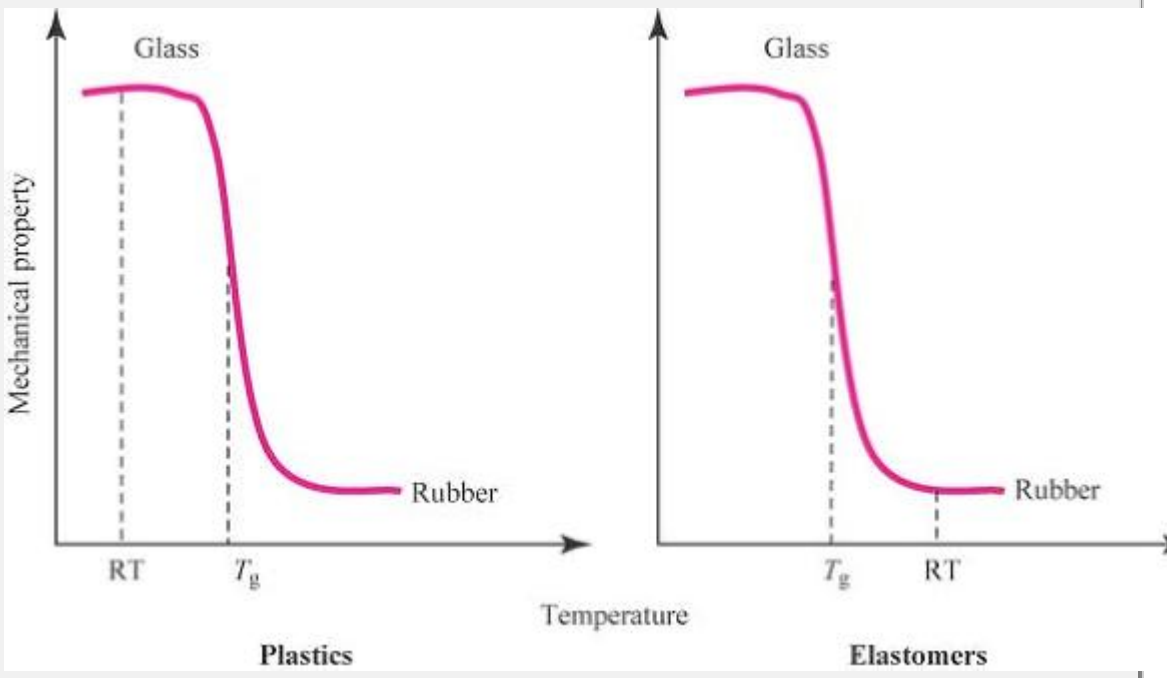


Fig. 20-12. Plastics and elastomers.

Adhesives and Coatings

The required properties of polymers for adhesive and coating applications are tackiness and adhesiveness. This means that adhesive forces (interaction with a second material) should be in balance with cohesive forces (interaction with itself). Both forces increase with the molecular weight of the polymer as molecular interactions increase between the same or different molecules due to increased surface area. Structurally speaking, the cohesive forces within a polymer can be modulated by changing its molecular weight, crystallinity, or addition of a second material such as plasticizers or oils. The adhesive intended for a nonpolar adherent should be nonpolar as well. On the other hand, very polar adhesive materials such as epoxy and cyanoacrylate are suggested for very polar adherents including metals. Generally speaking, the rule of thumb “like dissolves like” is simply applied to polymers for adhesive and coating applications. Like plastics, adhesives can be categorized as general and engineering (structural). The difference is the level of intermolecular forces within the adhesive structure. Structural adhesives are generally used for engineering application such as in air and aerospace industries where high quality, durability, and strength are the basic requirements. To ensure that these requirements are met, the adhesive undergoes special treatment such as curing. Cyanoacrylate-based adhesives or silicone adhesives are generally cured by absorbing moisture from the air. Epoxy adhesives are generally supplied as two components and cured in the presence of a third component (primary, secondary, and tertiary amines). Polyester adhesives are cured using peroxides and catalyzed by amines. The curing process increases the cohesive forces at the expense of adhesive forces. Since

an adhesive should possess a balance of cohesive and adhesive properties, the curing process should also be optimized.

Coating and adhesive applications rely on similar concepts. A successful adhesive or coating process requires that the matrix onto which the adhesive is applied to be fully covered by the polymer material, which is generally applied in an emulsion form. Coatings are used for protection purposes. A successful adhesive application requires careful understanding of the properties of the adhesive and adherents since an adhesive is generally trapped in between two or more materials. For coating applications, the coating polymer is generally exposed to a second environment such as air, oxygen, water, stomach fluid, intestinal fluid, solvents, and so on and so forth. This requires a thorough understanding of the coated matrix, coating material, as well as the service environment in which the material is expected to serve. Examples of coating materials are poly (vinyl acetate), acrylate esters, ethyl cellulose, and so on and so forth.

Polymers as Rheology Modifiers

Polymer chains are in a coiled conformation at rest, and they assume extended conformation once they are loaded. In applications where increased viscosity of the solution is desirable, the goal is to increase the chain end-to-end distance under a given load. In dissolution of a polymer and polymer swelling, the load originates from the interaction of a polymer and a solvent as well as concentration gradient of ions inside the polymer structure and the solution. Apparently longer end-to-end distances are potentially obtained if the polymer chains are longer and have more interaction with the solvent. In case of water as a solvent, the more hydrophilic polymer will be better. On the other hand, a more lipophilic polymer would be more desirable when the dissolution or swelling medium is organic. Figure 20-13 shows how different polymer chains and solutions display different rheological behavior, which is characterized by the volume occupied by the polymer chains. Because of their hydrophilicity and high molecular weight, gums are the candidate of choice for increasing the viscosity of the aqueous solutions or dispersions.

Key Concept

Polymer Structure and Solution Viscosity

Your cotton-based clothes get wetter on a rainy day as compared to plastics. So, if you go for a daylong trip on a rainy day, you might want to wear a poncho which is 100% plastic in order to repel the water. In polymer terms, polymers with water-loving functional groups make more and closer contacts with water, which causes molecules of water to move slower, which means they generate more viscosity.

Hydrogels

The concept of an end-to-end distance is also applied in swellable polymers. As mentioned earlier, the driving force for the dissolution and swelling processes are similar. Certain materials, when placed in excess water, are able to swell rapidly and retain large volumes of water in their structures. Such aqueous gel networks are called hydrogels. These are usually made of a hydrophilic polymer that is cross-linked either by chemical bonds or by other cohesion forces such as ionic interaction, hydrogen bonding, or hydrophobic interactions. Hydrogels behave like an elastic solid in a sense that they can return to their original conformation even after a long-term loading.

A hydrogel swells for the same reason as its linear polymer dissolves in water to form a polymer solution or hydrosol. From a general physicochemical standpoint, a hydrosol is simply an aqueous solution of a polymer. Many polymers can undergo reversible transformation between hydrogel and hydrosol. When a hydrogel is made by introducing gas (air, nitrogen, or carbon dioxide) during its formation, it is called a porous hydrogel.

A hydrogel swells in water or in any aqueous medium because of positive forces (polymer–solvent interaction, osmotic, electrostatic) and negative forces (elastic) acting upon the polymer chains as shown in Figure 20-14. Dissolution of a polymer in a solvent is an entropy-driven process that happens

spontaneously. A dry hydrogel is in its solid state and has the tendency to obtain more freedom as it goes into solution. If a polymer structure is nonionic, the major driving force of swelling will be polymer–solvent interactions. As the ion content of a hydrogel increases, two very strong osmotic and electrostatic forces are generated within the hydrogel structure. The presence of ions inside the gel and the absence of the same ions in the solvent trigger a diffusion process (osmosis) by which water enters the polymer structure until the concentration of the ion inside the gel and the solvent becomes equivalent. In fact, the polymer diffuses into water to balance its ion content with the surrounding solution. Polymer chains carrying ions are charged either negatively (anionic) or positively (cationic). In either case, similar charges on the polymer backbone will repel each other upon ionization in an aqueous medium. This creates more spaces inside the hydrogel and more water can be absorbed into its structure. Since swelling in many applications is a desirable property (e.g., in superabsorbent baby diapers or superdisintegrants in pharmaceutical solid dosage forms), the infinite dilution of the polymer needs to be restricted. Linking polymer chains to each other can do this, generating elastic forces and causing less entropy.

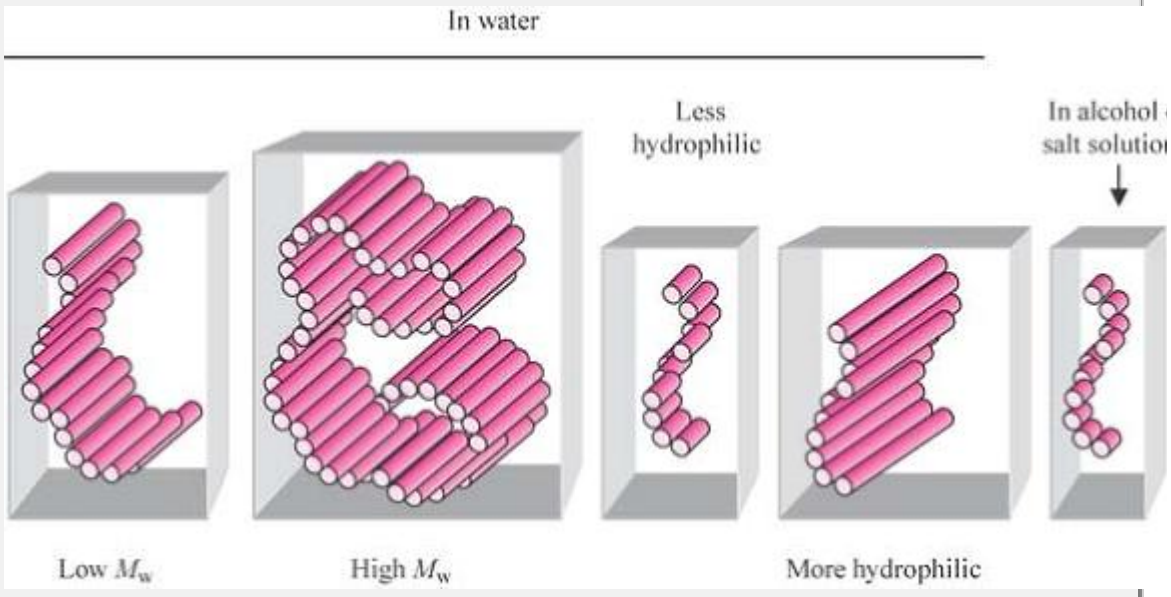


Fig. 20-13. Polymers as rheology modifier.

Example 20-7
Superdisintegrants
In pharmaceutical solid dosage forms, a superdisintegrant is generally used to help the dosage form with a proper disintegration. The concept behind this is the osmotic pressure that is generated by either hydrophilicity (as in vinyl pyrrolidone) or ionic (as in carboxymethyl cellulose) nature of the structure. Sodium starch glycolate (Explotab, Primojel, Vivastar P), cross-linked poly (vinyl pyrrolidone) (Crospovidone), and cross-linked sodium salt of carboxymethyl cellulose (Ac-Di-Sol, Croscarmelose) are widely used as a tablet and capsule disintegrant in oral dosage forms.

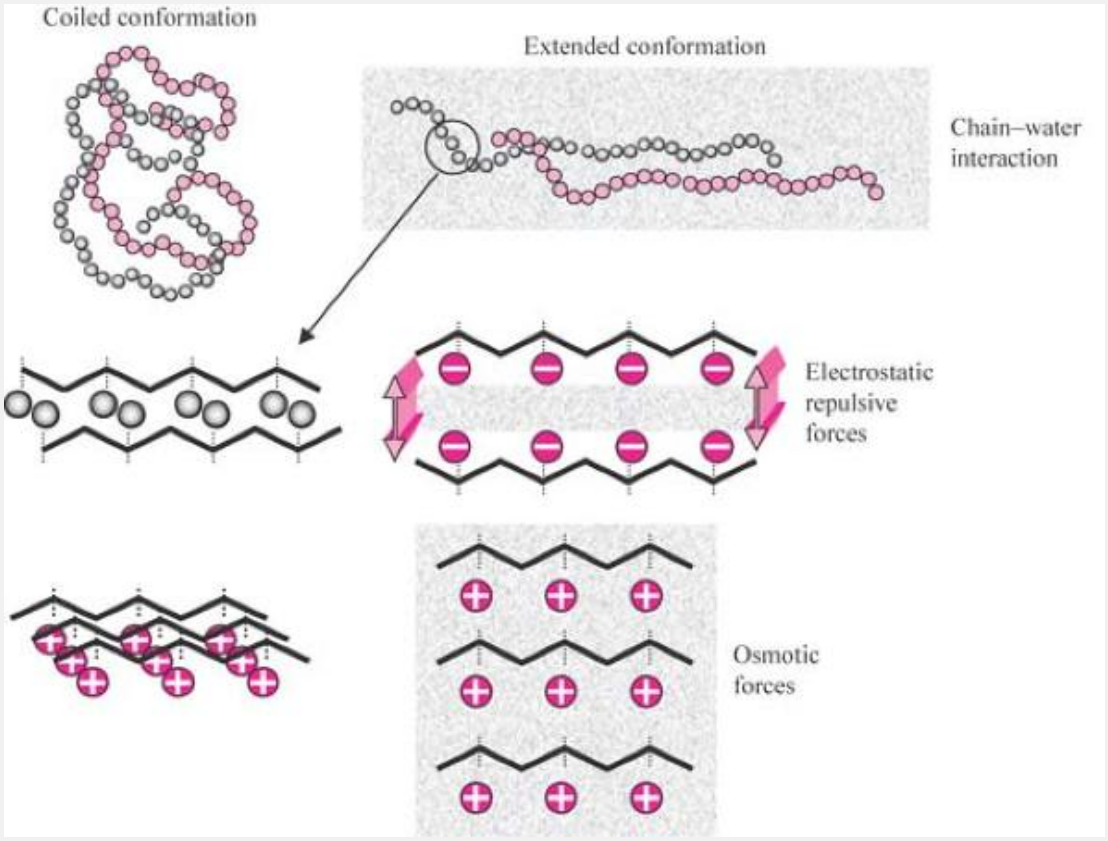


Fig. 20-14. Swelling forces in hydrogels.

Example 20-8
Osmotic Tablet and Pump

Alza's Oros and Duros technologies are based on an osmosis concept. Oros provides 24 hr controlled drug release that is independent of many factors such as diet status. Tablets using Oros technology as shown in Figure 20-15 are made of two sections coated with a semipermeable material. The upper section contains drug and the lower section contains the osmotic agent either a salt or a water-soluble/swellable polymer. The membrane allows water or the aqueous medium to enter into the osmotic agent compartment. In the presence of water, osmotic pressure pushes the bottom compartment upward which in turn forces the drug through a laser-drilled orifice on top of the tablet. Since 1983, this technology has been used in a number of prescription and over-the-counter products marketed in the United States, including nifedipine (Procardia XL), glipizide (Glucotrol XL), methylphenidate, oxybutynin, and pseudoephedrine (Sudafed 24 Hour). Duros technology is utilized in implants that deliver drugs over a very long period. Leuprolide implant (Viadur) osmotic implant is based on Alza's Duros pump technology which delivers leuprolide acetate over a year long period.

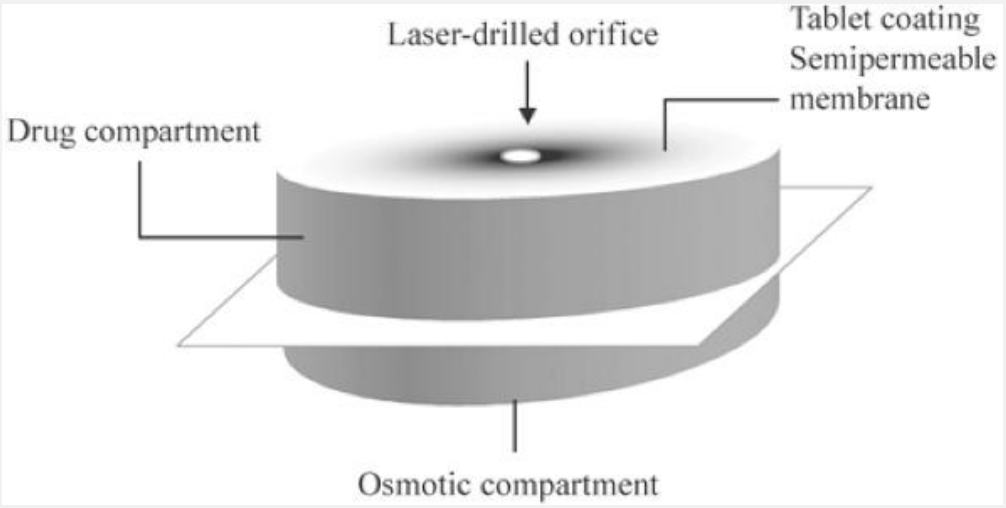


Fig. 20-15. An osmotic tablet based on Oros technology.

Depending on the nature of cross-linking, a hydrogel is classified as chemical or physical.

Chemical Gels

Chemical gels are those that are covalently cross-linked. Therefore, chemical gels will not dissolve in water or other organic solvent unless the covalent cross-links are broken apart. At least two different approaches can be used to form chemical gels, either by adding an unsaturated olefinic monomer carrying more than one double bond (e.g., *N*,*N*′-methylene bisacrylamide, ethylene glycol dimethacrylate) or by reacting the functional groups on the polymer backbone. The first approach is used to make water swellable gels or hydrogels. In general, cross-linking through double bond is energetically favored as less energy is required to break a double bond than to react the functional groups. Cross-linked polymers of acrylic acid, sodium acrylate, and acrylamide have found extensive application in hygiene and agricultural industries as water absorbent polymers. These can absorb urine in diapers or can retain the water in the soil.

As far as the swelling is concerned, temperature has often a positive effect on the swelling process. Most chemical gels especially those made of hydrophilic chains can swell more in warmer solutions. These gels are so-called thermoswelling chemical gels. On the other hand, some hydrogels made of relatively hydrophobic monomers shrink upon increase in temperature, and they are known as thermoshrinking chemical gels. The thermoshrinking hydrogels undergo thermally reversible swelling and deswelling. The temperature at which this sharp transition occurs is corresponded to a lower critical solution temperature of the non–cross-linked polymer.

Physical Gels

Hydrogen bonding, hydrophobic interaction, and complexation are three major tools in preparing a physical gel. A hydrogen bond is formed when two electronegative atoms, such as nitrogen and oxygen interact with the same hydrogen, N–H···O. The hydrogen is covalently attached to one atom, the donor, but interacts electrostatically with the other, the acceptor. This type of interaction occurs extensively in poly (vinyl alcohol), for example. Although its structure suggests an easy dissolution in water, a poly (vinyl alcohol) at molecular weight more than 100,000 g/mol is water insoluble. In order to dissolve the polymer, the hydrogen bonds need to be broken and that requires the solution to be heated up to 80°C to 90°C.

Hydrophobic interactions are considered to be the major driving force for the folding of thermoresponsive hydrogels and globular proteins. The existence of hydrophobic groups will change the hydrophilic lipophilic balance (HLB) of the polymer that in turn affects its solubility in water. The more hydrophobic groups within the hydrogel structure, the more temperature dependent the swelling will be. As the number of hydrophobic group increases, the solubility–insolubility transition or swelling–deswelling transition shifts to a lower temperature. Polymers, such as methylcellulose, hydroxypropyl methylcellulose, or certain PEO/PPO/PEO triblock copolymers, dissolve only in cold water and form a viscous solution. Once the solution temperature increases up to a certain point, these solutions become thicker by forming a gel.

Complexation may happen between two oppositely charged groups of different polymer structures or via metal ions. In water, alginic acid with negatively charged groups and chitosan with positively charged groups can form a complex. The solubility of the complex is generally dependent on the pH of the dissolution medium and the pK_a of the polymers. On the other hand, alginic acid carrying negatively charged carboxyl groups can form insoluble complexes with divalent and trivalent ions such as calcium, aluminum, and iron. These complexes are also reversible and pH dependent. Hydrogels either chemical or physical are also known as smart, intelligent, or responsive as they react to the environmental changes such as pH, temperature, salt concentration, salt type, solvent composition, or pressure. The unique properties of responsive hydrogels are ideal for making sensors and modulated drug delivery systems.

Polymers for Pharmaceutical Applications

In a traditional pharmaceutics area, such as tablet manufacturing, polymers are used as tablet binders to bind the excipients of the tablet. Modern or advanced pharmaceutical dosage forms utilize polymers for drug protection, taste masking, controlled release of a given drug, targeted delivery, increase drug bioavailability, and so on and so forth.

Apart from solid dosage forms, polymers have found application in liquid dosage forms as rheology modifiers. They are used to control the viscosity of an aqueous solution or to stabilize suspensions or even for the granulation step in preparation of solid dosage forms. Major application of polymers in current pharmaceutical field is for controlled drug release, which will be discussed in detail in the following sections. In the biomedical area, polymers are generally used as implants and are expected to perform long-term service. This requires that the polymers have unique properties that are not offered by polymers intended for general applications. Table 20-3provides a list of polymers with their applications in pharmaceutical and biomedical industries.

In general, the desirable polymer properties in pharmaceutical applications are film forming (coating), thickening (rheology modifier), gelling (controlled release), adhesion (binding), pH-dependent solubility (controlled release), solubility in organic solvents (taste masking), and barrier properties (protection and packaging).

From the solubility standpoint, pharmaceutical polymers can be classified as water-soluble and water-insoluble (oil-soluble or organic soluble). The cellulose ethers with methyl and hydroxypropyl substitutions are water-soluble, whereas ethyl cellulose and a group of cellulose esters such as cellulose acetate butyrate or phthalate are organic soluble. Hydrocolloid gums are also used when solubility in water is desirable. The synthetic water-soluble polymers have also found extensive applications in pharmaceutical industries, among them polyethylene glycol, polyethylene glycol vinyl alcohol polymers, polyethylene oxide, polyvinyl pyrrolidone, and polyacrylate or polymethacrylate esters containing anionic and cationic functionalities are well-established.

Cellulose-Based Polymers

Although cellulose itself is insoluble in water, its water-soluble derivatives have found extensive applications in pharmaceutical dosage forms. The structure of cellulose is shown in Figure 20-16. Methyl cellulose, CMC, and hydroxypropyl methylcellulose are the most common cellulose-based polymers with methyl, carboxymethyl, and

hydroxypropyl/methyl substitution, respectively. Table 20-4 shows how functional group substitution results in different cellulose-based polymers with different properties.

Table 20-3 Polymers in Pharmaceutical and Biomedical Applications

Water-Soluble Synthetic Polymers	
Poly (acrylic acid)	Cosmetic, pharmaceuticals, immobilization of cationic drugs, base for Carbopol polymers
Poly (ethylene oxide)	Coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent
Poly (ethylene glycol)	M_w <10,000; liquid (M_w <1000) and wax (M_w >1000), plasticizer, base for suppositories
Poly (vinyl pyrrolidone)	Used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
Poly (vinyl alcohol)	Water-soluble packaging, tablet binder, tablet coating
Polyacrylamide	Gel electrophoresis to separate proteins based on their molecular weights, coagulant, absorbent
Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide)	Thermogelling acrylamide derivatives, its balance of hydrogen bonding, and hydrophobic association changes with temperature
Cellulose-Based Polymers	
Ethyl cellulose	Insoluble but dispersible in water, aqueous coating system for sustained release

	applications
Carboxymethyl cellulose	Superdisintegrant, emulsion stabilizer
Hydroxyethyl and hydroxypropyl celluloses	Soluble in water and in alcohol, tablet coating
Hydroxypropyl methyl cellulose	Binder for tablet matrix and tablet coating, gelatin alternative as capsule material
Cellulose acetate phthalate	Enteric coating
Hydrocolloids	
Alginic acid	Oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrant
Carrageenan	Modified release, viscosifier
Chitosan	Cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
Hyaluronic acid	Reduction of scar tissue, cosmetics
Pectinic acid	Drug delivery
Water-Insoluble Biodegradable Polymers	
(Lactide-co-glycolide) polymers	Microparticle–nanoparticle for protein delivery
Starch-Based Polymers	

Starch	Glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder
Sodium starch glycolate	Superdisintegrant for tablets and capsules in oral delivery
Plastics and Rubbers	
Polyurethane	Transdermal patch backing (soft, comfortable, moderate moisture transmission), blood pump, artificial heart, and vascular grafts, foam in biomedical and industrial products
Silicones	Pacifier, therapeutic devices, implants, medical grade adhesive for transdermal delivery
Polycarbonate	Case for biomedical and pharmaceutical products
Polychloroprene	Septum for injection, plungers for syringes, and valve components
Polyisobutylene	Pressure sensitive adhesives for transdermal delivery
Polycyanoacrylate	Biodegradable tissue adhesives in surgery, a drug carrier in nano- and microparticles
Poly (vinyl acetate)	Binder for chewing gum
Polystyrene	Petri dishes and containers for cell culture
Polypropylene	Tight packaging, heat shrinkable films, containers

Poly (vinyl chloride)	Blood bag, hoses, and tubing
Polyethylene	Transdermal patch backing for drug in adhesive design, wrap, packaging, containers
Poly (methyl methacrylate)	Hard contact lenses
Poly (hydroxyethyl methacrylate)	Soft contact lenses
Acrylic acid and butyl acrylate copolymer	High T_g pressure–sensitive adhesive for transdermal patches
2-Ethylhexyl acrylate and butyl acrylate copolymer	Low T_g pressure–sensitive adhesive for transdermal patches
Vinyl acetate and methyl acrylate copolymer	High cohesive strength pressure–sensitive adhesive for transdermal patches
Ethylene vinyl acetate and polyethylene terephthalate	Transdermal patch backing (occlusive, heat sealable, translucent)
Ethylene vinyl acetate and polyethylene	Transdermal patch backing (heat sealable, occlusive, translucent)
Polyethylene and polyethylene terephthalate	Transdermal patch backing (when ethylene vinyl acetate copolymer is incompatible with the drug)

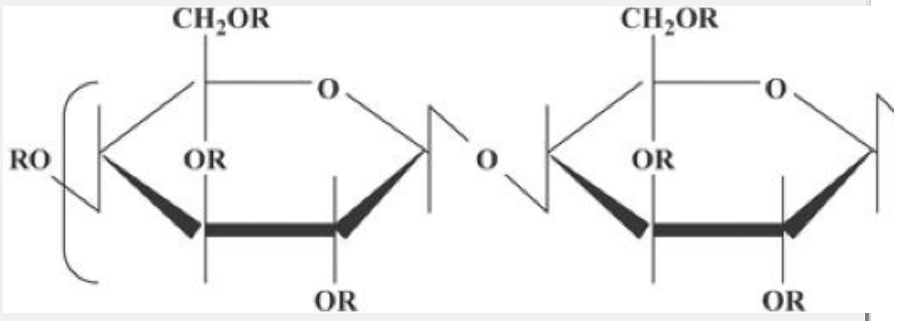


Fig. 20-16. Cellulose structure.

Methocel polymers including pure methylcellulose and hydroxypropyl-substituted methylcellulose display thermogelling property in water. As the temperature of the solution increases, the hydrophobic groups of these polymers start to aggregate, as a result the polymer solution will assume a cloudy appearance. The cloud point temperature for the pure methyl cellulose (with no hydroxypropyl substitution) is about 50°C. As more methyl groups are substituted with hydroxypropyl groups, which have better solubility in water, the cloud point temperature shifts to higher temperature (60°C–85°C for the Methocel E, F, and K). Generally speaking, cloud point temperature is critically dependent on the methyl substitution. On the other hand, aqueous viscosity of the Methocel polymers is more dependent on the polymer molecular weight than its methyl/hydroxypropyl content.

Table 20-4 Cellulose-Based Polymers

R	Polymer	Characteristics
H	Cellulose	Water-insoluble due to excessive hydrogen bonding
H and CH_3	Methyl cellulose (MC)	Soluble in cold water only; commercially available as Methocel A (Dow Chemical); swells and disperses slowly in cold water to form a colloidal dispersion; practically insoluble in ethanol, saturated salt solutions, and hot water; soluble in glacial acetic acid, displays thermogelling property
H and CH_2CH_3	Ethyl cellulose	Water-insoluble; aqueous coating

	(EC)	system for sustained release applications; impermeable barrier; plasticized EC composed of dibutyl sebacate and oleic acid; Ethocel is commercially available from Dow; Ethyl cellulose latex, Aquacoat, is also available from FMC Corp
H and CH_2COOH	Carboxymethyl cellulose (CMC)	Water-soluble; variable degree of substitution; cross-linked CMC is water-swellable and known as croscarmellose sodium in National Formulary (NF); FMC Corp. supplies cross-linked CMC (Ac-Di-Sol; Accelerated Dissolution) as tablet superdisintegrant
H and CH_2CH_2OH	Hydroxyethyl cellulose (HEC)	Soluble in water and in alcohol
H and $CH_2CHOHCH_3$	Hydroxypropyl cellulose (HPC)	Water-soluble at low temperature; film-coating application
H and CH_3 and $CH_2CHOHCH_3$	Hydroxypropyl methylcellulose (HPMC)	Soluble in water below 60°C and in organic solvents; Dow Chemical supplies HPMC as Methocel (such as E, F, K) for tablet coating; HPMC coating replaced sugar coating with the advantage of much shorter coating time; possess thermogelling property; is also used as capsule material to substitute the animal-based gelatin

Hydrocolloids

Various hydrocolloids or polysaccharide gums are originated from a variety of sources as summarized in Table 20-5.

Most gums are hydrophilic and contain very long polymeric chains as well as different functional groups. These features are very attractive in many pharmaceutical processes such as coating, stabilization,

thickening, binding, solubilization, and disintegration. Gums behave differently in water and aqueous solutions. Almost all display thickening property, whereas some show gelling property. Although thickening is a desirable property for solution, suspension, and emulsion dosage forms, gelling property is utilized in drug encapsulation for controlled delivery applications. Gums such as guar gum can provide excellent thickening property, whereas gums including alginate and chitosan can offer a gelling property in the presence of ions. Similar to synthetic polymers, gums can be blended to provide superior properties through

synergy, which cannot be achieved by individual gum alone. On the negative side, gums are obtained from natural sources with different assay and qualities. Therefore, as opposed to synthetic polymers, the batch-to-batch consistency and quality would be a major challenge for pharmaceutical suppliers. Besides, gums are a good platform for bacteria growth, which limits their shelf life and requires sterilization.

Table 20-5 Hydrocolloids from Different Sources

Plant Exudates	Seed Gum	Seaweed Extract	Microbial	Plant Extract	Animal-Based
Gum arabic	Guar	Agar	Xanthan	Pectin	Chitosan
Karaya	Locust bean	Carrageenan	Gellan	Konjac	Gelatin
Tragacanth	Psyllium	Alginate	Curdlan		
Ghatti					

Polysaccharides and their derivatives can be used as a rate controller in sustained release formulations due to their gelling property.9 Gums can easily be derivatized to change their solution properties. For instance, chitosan is only soluble in acidic water, but its carboxymethyl derivative is soluble at a wider pH range. Gums offer a wide range of molecular weights that also affect their dissolution properties. They are biodegradable and their chemical composition varies greatly.10 The physicochemical properties of polysaccharide solutions and gels have recently been reviewed for pharmaceutical and food applications.11 Polysaccharides are claimed to effectively treat local colon disorders if they are used in colon-targeting delivery systems, which utilize the colonic microflora.12 Inulin, amylase, guar gum, and pectin are specifically degraded by the colonic microflora and used as polymer drug conjugates and coating. It has been shown that drug release in the colon can be maximized if the hydrophobicity of the gums is modified chemically or physically using other conventional hydrophobic polymers.13 In cancer therapy, polysaccharides are used as immune-modulators. A few fungal polysaccharides, either alone or in combination with chemotherapy and/or radiotherapy, have been used clinically in the treatment of various cancers.9 It was suggested that iron stabilized into a polysaccharide structure can be used to treat anemia. The product can also be used in resonance imaging as well as in separation of cells and proteins utilizing magnetic fields due to its magnetic properties.14

Alginic acid is a linear polysaccharide that mainly consists of two building blocks of mannuronic (M) and guluronic (G) acid residues. Alginic acid and its salts are anionic polymers that can offer gelling

properties. Since they contain carboxyl group, they can easily undergo a complexation reaction in the presence of ions. Depending on its source, the mannuronic and guluronic contents of the alginate product can be different. Between the two building blocks, the G blocks are responsible for the gelling property; as such, a product rich in G block offers stronger gel in the presence of ions, in particular, calcium. Excipient suppliers provide different grades of alginate with broad range of G/M ratios. Apparently, the mechanical property of the alginate gel is determined by the G/M contents of the product, the type of ion (monovalent, divalent, trivalent), the concentration of ion in the solution, as well as the duration of the gelling process. For the encapsulation purposes, all these factors have to be considered in designing a tailor-made delivery system. Alginic acid and its derivatives have found applications as a stabilizing agent, binding agent, drug carrier, and so on and so forth. The antibiotic griseofulvin, which is supplied as oral suspension, contains sodium alginate stabilized with methylparaben. Alginic acid and ammonium calcium alginate can be found in metaxalone tablets. Alginate microbeads can be used to entrap drugs, macromolecules, and biological cells. For this application, parameters such as calcium salt, other hardening agents, and different drying methods have been studied.15 Islets of Langerhans embedded into alginate encapsulates can be transplanted without the risk of protein contamination and immune system suppression.16

Carrageenan is a sulfated linear polysaccharide of galactose and anhydrogalactose. It carries a half-ester sulfate group with the ability to react with proteins. If carrageenan is used in a solution containing proteins, the solution becomes gel or viscous due to a complex formation between carrageenan and charged amino acids of the protein. Therefore, a formulation scientist should be aware of any incompatibility issues which might jeopardize the stability of the drug solution, suspension, or emulsion. Depending on the concentration and location of the sulfated ester groups, carrageenan can be found in three different grades of kappa, iota, and lambda. Kappa carrageenan can form a strong and brittle gel, especially in the presence of potassium ions or if blended with locust bean gum. If a drug formulation requires a softer and more elastic gel, iota carrageenan can be used. Both kappa and iota carrageenan can be used for controlled delivery application as they display gelling properties under certain circumstances. If a drug formulation needs to be thickened and does not contain proteins of any source, a lambda carrageenan can be utilized. Donepezil hydrochloride orally disintegrating tablets and cefpodoxime proxetil oral suspension contain carrageenan. Carrageenan is shown to increase the permeation of sodium fluorescein through porcine skin as it changes the rheological

properties of the drug solution.17 In capillary electrophoresis, a sulfated polysaccharide such as carrageenan can be used to separate the enantiomers of weakly basic pharmaceutical compounds. Different enantiomers of racemic compounds such as propranolol and pindolol have been separated using carrageenan.18,19

Chitosan is obtained from chitin, the second most abundant natural polymer after cellulose, which can be found in shrimp, crab, and lobster shells. Chitosan is a cationic polymer and has been investigated as an excipient in controlled delivery formulations and mucoadhesive dosage forms because of its gelling and adhesive properties. The bitter taste of natural extracts such as caffeine has been masked using chitosan. Chitosan can potentially be used as a drug carrier, a tablet excipient, delivery platform for parenteral formulations, disintegrant, and tablet coating.20,21 From toxicity and safety standpoint, lower–molecular-weight chitosan (as an oligosaccharide) has been shown to be safer with negligible cytotoxicity on Caco-2 cells.22 During the encapsulation process using synthetic polymers, the protein is generally exposed to the conditions which might cause their denaturation or deactivation. Therefore, a biocompatible alternative such as chitosan is desirable for such applications.23 Because of its cationic nature, chitosan can make complexes with negatively charged polymers such as hyaluronic acid (HA) to make a highly viscoelastic polyelectrolyte complex. The complex has the potential to be used as cell scaffold and as a drug carrier for gene delivery.24 Gels based on chitosan and ovalbumin protein have been suggested for pharmaceutical and cosmetic use.25 In veterinary area, chitosan can be used in the delivery of chemotherapeutics such as antibiotics, antiparasitics, anesthetics, painkillers, and growth

promotants.26 As an absorption enhancer, a protonated chitosan is able to increase paracellular permeability of peptide drugs across mucosal epithelia. While trimethyl derivative of chitosan is believed to enhance the permeation of neutral and cationic peptide analogs, the carboxymethyl derivative of chitosan offers gelling properties in an aqueous environment or with anionic macromolecules at neutral pHs.27 Chitosan can also be mixed with nonionic surfactants such as sorbitan esters to make emulsion like solutions or creams.28 To prepare chitosan beads or microspheres, the chitosan matrix needs to be treated with an anionic compound like pentasodium tripolyphosphate. A sustained release dosage form of salbutamol sulfate bead can be prepared using chitosan in phosphate buffer.29

Pectin is a ripening product of green fruits such as lemon and orange skin. Protopectin is an insoluble pectin precursor present in such fruits, which is converted to pectinic acid and subsequently to pectin. The main component of pectin is D-galacturonic acid, which is in part esterified via methylation. Depending on its methoxyl content, pectin is classified as high methoxyl (HM, 50% or more esterification) and low methoxyl (LM, less than 50% esterification). Pectins can form a gel in an aqueous solution if certain conditions are existed. For instance, high methoxyl pectins require a minimum of 65% soluble solids and low pH (<3.5) to form a gel, whereas low methoxyl pectins require calcium and may form a gel at a much lower solid content, that is, 20%. Gelation and association of pectin chains in the presence of pH-reducing additives has also been reported.30 While pectin is generally known as a suspending and thickening agent, it is also claimed to reduce blood cholesterol levels and to treat gastrointestinal disorders.31 Pectin can be found in amlexanox oral paste.

Xanthan gum is found in a number of drug formulations including cefdinir oral suspension and nitazoxanide tablets. It is a highly branched glucomannan polysaccharide with excellent stability under acidic conditions. Xanthan is generally used in solution and suspension products for its thickening property. Because of its very rigid structure, its aqueous solution is significantly stable over a wide pH range. Similar to locust bean gum, xanthan gum is also nongelling but forms a gel once it is mixed with the locust bean gum. Concentrated xanthan gum solutions resist flow due to excessive hydrogen bonding in the helix structure, but they display shear-thinning rheology under the influence of shear flow. This feature of xanthan gum solutions is critical in food, pharmaceutical, and cosmetic manufacturing processes.32 Oxymorphone hydrochloride extended-release tablets contain TIMERx, which consists of xanthan gum, and locust bean gum for controlled delivery.33 Rectal delivery of morphine can be controlled using cyclodextrins as an absorption enhancer and xanthan as a swelling hydrogel. This combination produces a sustained plasma level of morphine and increases its rectal bioavailability.34

HA consists of *N*-acetyl-D-glucosamine and beta-glucoronic acid and has been used as fluid supplement in arthritis, in eye surgery, and to facilitate healing of surgical wounds. Solaraze gel for the topical treatment of actinic keratoses is composed of 3% sodium diclofenac in 2.5% HA gel.35 Sodium hyaluronate and its derivatives have been evaluated in vitro and in vivo for optimized delivery of a variety of active molecules such as antibiotic gentamicin and cytokine interferon.36 Hyaluronan is biocompatible and nonimmunogenic and has been suggested as a drug carrier for ophthalmic, nasal, pulmonary, parenteral, and dermal routes.37Sodium hyaluronate topical (Seprafilm), which is used to reduce scar tissue as a result of abdominal or pelvic surgery, is a bioresorbable membrane containing sodium hyaluronate.

Gum arabic or gum acacia is best known for its emulsifying property and its solution viscosity at very high solid concentration. Locust bean gum consists of mannose and galactose sugar units at a ratio of 4:1. Like almost all gum solutions, an aqueous solution of this gum displays shear-thinning rheology. It shows synergistic effect with xanthan and kappa carrageenan. Gellan gum has been used in pharmaceutical dosage forms as a swelling agent,38 as a tablet binder,39 and as a rheology modifier.40 Drug delivery behavior of scleroglucan hydrogels has been examined using theophylline as a model drug.41 As an alternative tablet binder to starch and polyvinyl pyrrolidone, seed galactomannan of Leucaena, a natural polysaccharide comparable to guar

gum, has been evaluated for poorly compressible drugs such as paracetamol.42 Schizophyllan, which is

secreted by fungus, has been evaluated as an immunostimulant (to suppress tumor growth), antitumor, antihepatitis, anti-HIV, and antiviral agent.[43,44] Sustained release formulations based on guaran,[45] in situ gel-forming ability of xyloglucan,[46] and borax–guar gum complexes for colon specific drug delivery have also been studied.[47]

One of the most recent applications of gums is in film forming. Recent concepts and products such as breath films, cough strips, flu, and sore throat strips have all been realized on the basis of film-forming ability of gums. Generally speaking, as opposed to branched gums, linear gums have more sites available for intermolecular hydrogen bonding; as a result, they offer better film-forming properties. Individual and blended gum products based on agar, alginate, κ-carrageenan, methyl cellulose, pectin, CMC, and guar can potentially be used in film dosage forms.

Polymers in Drug Delivery

Introduction

Pharmaceutical polymers are widely used to achieve taste masking; controlled release (e.g., extended, pulsatile, and targeted), enhanced stability, and improved bioavailability. Monolithic delivery devices are systems in which a drug is dispersed within a polymer matrix and released by diffusion. The rate of the drug release from a matrix product depends on the initial drug concentration and relaxation of the polymer chains, which overall displays a sustained release characteristic. Extended release alprazolam tablet is an example of monolithic products, in which extended or sustained delivery is provided by swelling and erosion of the polymer matrix. Alternatively, a drug can be released from a drug core through a porous or nonporous membrane. While drug release through a nonporous membrane is essentially driven by diffusion, porous membrane generates an extra path for the drug release, that is, through pores. The status of drug release from membrane systems can generally be modified via membrane thickness, use of plasticizers, pore structure (size, size distribution, and morphology), and filler tortuosity (filler orientation). Membrane systems have found applications in drug stability, enteric release, taste masking, and sustained release. Enteric-coated products are the ones that pass the stomach environment safely and release the drug at a higher pH environment of the intestine. These have to be coated with a pH-operative coating such as an anionic polymer. Examples of enteric-coated products are duloxetine, mesalazine, naproxen, omeprazole, and amino salicylic acid. Drugs such as lutein and lycopene are more stable in membrane dosage forms. Reservoir systems have been utilized to taste mask acetaminophen and caffeine. Potassium chloride and diltiazem are also offered sustained release property if formulated in a membrane system.

Synthetic Polymers

Synthetic polymers based on acrylic or methacrylic acids have found extensive applications in the drug delivery area to protect the drug or to release the drug in a controlled manner. These are classified as cationic, anionic, and neutral (nonionic) polymers. Despite the different solubility and swellability across the GI tract, the drug release from these matrices occurs through a diffusion process.

Cationic polymers: One of the most widely used cationic polymers for protective coating applications has dimethyl aminoethyl methacrylate for a functional group. As far as its purity is concerned, the polymer contains less than 3000 ppm of residual monomers including butyl methacrylate (<1000 ppm), methyl methacrylate (<1000 ppm), and dimethyl aminoethyl methacrylate (<1000 ppm). These are used as pH-dependent drug delivery platforms to protect sensitive drugs, to mask unpleasant tastes and odor, to protect the active ingredient from moisture, and also to improve drug storage stability. Eudragit E 100 is, for instance, supplied as a granule and is used in taste-masking applications where a low pH solubility (<5) is desirable.

Anionic polymers: Anionic polymers have methacrylic acid as a functional group and are generally used for drug delivery past the stomach into the duodenum, jejunum, ileum, or colon. As discussed in Chapter 10, since the pH of the fasted stomach is below pH 3 in nearly every healthy person and below pH 2 in most people, the stomach represents a harsh environment for many drugs. Since the methacrylic group dissociates at the higher pH of the small intestine and colon, anionic polymers such as Eudragit L 100-55 (with dissolution at pH 5.5) and Eudragit S 100 (with dissolution at pH >7.0) are highly desirable. Aqueous dispersions of these polymers (Eudragit L 30 D-55) are generally available for direct use in

enteric coating applications. Kollicoat MAE 30 DP (Fig. 20-17), a combination of methacrylic acid and ethyl acrylate (1:1) monomers, is supplied as a 30% aqueous dispersion. The polymer is used as a film-former in enteric coating of solid dosage forms.

Neutral polymers: Acrylate or methacrylate polymers with or without aminoethyl functionality are generally insoluble or have pH-independent swelling property. These are neutral acrylic polymers which are used for sustained release applications where insolubility of the polymeric drug carrier is very much desirable. Neutral polymers with added functionality are supplied as powder (e.g., Eudragit

RS PO), granule (e.g., Eudragit RS 100), and aqueous dispersions (e.g., Eudragit RS 30 D). Neutral polymers with no added functionality are supplied as aqueous dispersions (Eudragit NE30D, NM30D, and NE40D).

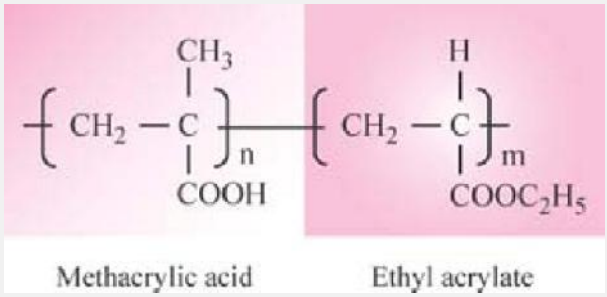


Fig. 20-17. A copolymer for an enteric tablet-coating application.

Biodegradable Polymers

Alternatively the drug can be released from a dosage form as a result of polymer erosion. Erosion occurs because of biodegradation or swelling and might happen within the bulk of the polymer or may be limited to the polymer surface at a time. Porous and nonporous platforms can provide bulk and surface erosion, respectively. Polymers with ester and amide functional groups are susceptible to a hydrolytic degradation in strong acidic and basic environment. When a polymer starts to erode from its surface, the drug imbedded within the polymer matrix will be released at a rate depending on the erosion rate of the polymer. If erosion happens in bulk, a much faster release is expected as an enormous number of hydrolysable sites are simultaneously cleaved up in water.

Biodegradable polymers are classified as natural-based and synthetic. Polysaccharides and protein-based polymers are obtained from the natural sources. Polyesters or copolyesters of lactic acid and glycolic acid, polycaprolactone, polyanhydrides, and polyethylene glycol are the most common synthetic biodegradable polymers, which are used for variety of pharmaceutical applications.

Example 20-9

Injectable Implant

Injectable implants have been developed on the basis of biodegradable polymers. Leuprolide (Eligard), a delivery system for prostate cancer, is supplied as an injectable suspension that utilizes the Atrigel technology for delivering the hormone leuprolide acetate. The delivery system consists of a biodegradable (lactide-co-glycolide) copolymer dissolved in a biocompatible solvent. The polymer gradually loses its organic solubility once it is injected

subcutaneously. Doxycycline (Atridox), a bioabsorbable delivery system for the treatment of periodontal disease, also uses Atrigel technology to deliver an antibiotic, doxycycline hyclate.

Alternatively, a drug may be released as a result of matrix swelling. The matrix is made of nonbiodegradable but erodible polymers, which control the drug delivery due to its swelling. A polymer in its swollen form is mechanically weak and can be eroded at different rates depending on the swelling feature of the matrix.48 A fast swelling hydrogel may undergo faster erosion and provide faster drug release compared with a slow swelling hydrogel. The release kinetics from a swellable matrix is generally zero-order.

Ion-Exchange Resins

These are polymeric materials with two characteristics; they swell in an aqueous medium and they contain complexable and ionizable groups. Ion-exchange resins are generally made of methacrylic acid, sulfonated styrene, and divinyl benzene (DVB). The acidic resins can be weak or strong. Weak acid resins are produced on the basis of methacrylic acid (containing COOH) monomer cross-linked with DVB. The counter-ion of the acidic carboxyl group is hydrogen (as in Polacrilex resin, Amberlite IRP64) or potassium (as in Polacrilin potassium, Amberlite IRP88). To make an ion-exchange resin with stronger acidity, the water-insoluble styrene is used as a monomer, which is sulfonated to become water compatible. Similarly, DVB is used to cross-link the polymer and the counter-ion of the sulfate group (SO_3) is generally sodium. The commercial product of sodium polystyrene sulfonate (Amberlite IRP69) is used to treat hyperkalemia. Cation exchangers are anionic polymers which contain carboxyl or sulfate groups with hydrogen, potassium, and sodium as counter-ions. On the other hand, cationic ion-exchange resins with the ability to exchange anions carry quaternary ammonium groups, $-N^{+}(R)3$ with chlorine as a counter-ion. Cholestyramine resin (Duolite AP143) is cationic styrene DVB polymer which is an anion exchanger and used to reduce cholesterol or to sequestrate the bile acid. Because of their unique properties, the ion-exchange resins are generally used for taste masking, drug stabilization, tablet disintegration, and sustained release applications.

Cationic or anionic drugs can be complexed into the structure of an ion-exchange resin due to its ionic structure. The stability of the complex inside the mouth masks the taste of the drug since the drug will not be free to interact with taste buds. The drug will be released in the gastric medium once the complex becomes unstable. Certain drugs have a poor shelf life due to their instability against moisture, light, heat, and so on and so forth. Shelf stability and bioavailability of these drugs increase when formulated with ion-exchange resins. The DVB–cross-linked potassium methacrylate copolymer possesses a very high swelling capacity in water. Although this polymer generally swells fast and to a high degree, its swelling properties are significantly affected by pH, the presence of salts, and the ionic strength of the aqueous solution. Nevertheless, the swelling pressure generated by this polymer is sufficient to disintegrate tablet dosage forms in an aqueous medium. These polymers can also provide a sustained or a zero-order release due to their high swelling capacity.

Chapter Summary

Polymers have been used as a main tool to control the drug release rate from the formulations. They are also increasingly used as taste-masking agent, stabilizer, and protective agent in oral drug delivery. Polymers can bind the particles of a solid dosage form and also change the flow properties of a liquid dosage form. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Polymers are macromolecules having very large chains, contain a variety of functional groups, can be blended with other low- and high–molecular-weight materials, and can be tailored for any applications. Understanding

the basic concepts of polymers provides a foundation for further understanding of drug products and designing of better delivery systems.

This chapter provides basic concepts behind the behavior of polymers in the solid and solution states. Chapter begins with a general introduction on polymers and continues with different types of polymer structure and polymerization methods to make them. The major polymer concepts and properties, such as synthesis, topology, crystallinity, thermal transitions, molecular weight (averages and distribution), swelling, entanglement, rheology, and mechanical properties, are discussed in detail. The chapter continues with a variety of polymer products including rubbers, plastics, fibers, adhesives, and coatings, and also highlights important properties of each group. The chapter concludes with major applications of polymers in pharmaceutical industry, such as ion-exchange resins. Many examples, pictures, and concept boxes have been added to better appreciate these topics. This chapter can serve as a valuable source of information for those with little or no background in polymers, researchers in the polymer, pharmaceutics and biomedical areas, as well as pharmacy students.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Chapter Legacy

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