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POLYMERS USED IN PHARMACEUTICS

Recent advances in controlled drug delivery systems have been possible mainly due to the advances in polymer chemistry. Without understanding polymers, it is rather difficult to understand the mechanisms of controlled drug delivery and controlled release dosage forms. We will cover basic polymer chemistry to understand how various polymers are used to make controlled release drug delivery systems.

I. SHORT HISTORY OF POLYMERS

Plastic is a generic term that the public uses in place of polymer. The word 'plastic' means any of numerous organic synthetic or processed materials that are mostly thermoplastic or thermosetting polymers of high molecular weight and that can be molded, cast, extruded, drawn, or laminated into objects, films, or filaments. Since the term 'polymer' is more widely used in the scientific area, we will use it instead of 'plastic.'

The first (semi)synthetic polymer ever made was guncotton (cellulose nitrate) by Christian F. Schönbein in 1845. When cotton wool was dipped into a mixture of fuming nitric and sulfuric acids, then squeezed, washed, and dried, the stuff, when lighted, had much more bang than gunpowder did. The guncotton was too explosive to be useful. Based on cellulose nitrate, in 1862 Alexander Parkes invented a new material called Parkesine, which was used to make a number of articles such as buttons, combs, knife handles, and pens. After that, John Wesley Hyatt developed 'celluloid,' a name by the inventor's brother for fake ivory. 'Celluloid' was originally a trade name but became a generic name that described camphor plasticized cellulose nitrate (*i.e.*, nitrocellulose or guncotton), a modified natural polymers. The initial goal of developing Celluloid was to make artificial billiard balls replacing ivory. There was a public announcement offering a \$10,000 prize for anyone who could produce a substitute for ivory suitable for making billiard balls. The use of alcohol as a solvent and camphor as a plasticizer in making celluloid made it extremely flammable. Celluloid possessed unique properties, as compared to other hard materials used at that time, such as flexibility, weakness, and scratchability. In 1869, cellulose acetate was produced by treating cellulose with acetic acid instead of nitric acid. Cellulose acetate produced at that time was soluble only in very toxic solvents. In 1905, it was found out that hydrolysis of cellulose acetate made it soluble in acetone, which was relatively easy to handle. The first commercial production of cellulose acetate

fibers began after World War I under the trade name Celanese. Cellulose acetate, viscose, or cuprammonium cellulose was used to make rayon, the regenerated man-made fibers.

Not long after the synthesis of celluloid a new popular plastic called 'Bakelite' was invented. In 1872, Adolf von Bayer discovered a new polymer based on phenols and aldehydes. In 1909 Leo H. Baekeland used phenol-formaldehyde (along with phenoxy resin, epoxy resin, acrylic resin, or ketone resin) to produce Bakelite which was the first totally synthetic polymer. Bakelite was used to cheaply duplicate millions of parts used in automotive and electrical industries, and to make other household items such as cameras, telephones, and plugs. Bakelite was incredibly strong and undestructable. While the fundamental properties and mechanisms of polymerization of Bakelite were not understood, people found uses for it without any problem.

The popularity of plastics was rising with the advent of other synthetic polymers, such as poly(methylmethacrylate) in 1932, polyethylene in 1933, poly(vinyl chloride) in 1933, polystyrene in 1933, nylon in 1935, Teflon[®] in 1938, and synthetic rubber (*i.e.*, Silly Putty[®]) in 1942. All these polymers played significant roles during World War II. Polyethylene was used to make radar equipment for airplanes. British air forces used polyethylene to insulate electrical parts of radars since it was light enough to be installed in the airplanes without adding weight. Synthetic rubber, which could be made in one hour as compared to 7 years for natural rubbers, was used to make tires and other military supplies. Teflon[®] was used in making atomic bombs. It was applied to separate isotopes of uranium with extremely high temperature. Nylon was used to make parachutes, replacing silk which had to be imported from Japan. All these new synthetic polymers contributed to winning World War II.

The polymer that affected the public and polymer scientists in the most significant way was probably nylon 6,6. Nylon was the first polymer which was synthesized with a good understanding of the molecular structure. Wallace Hume Carothers synthesized nylon in 1935, and a patent application for nylon 6,6 was filed in 1937. Just 19 days after applying for the patent in 1937, Carothers committed suicide owing to depression over feelings of failure. He thought that he had spent too many resources without producing anything useful. Certainly, the world did not, does not, and will not agree with him. Nylon was presented as a material which is stronger than steel, but finer than spiderweb. Other candidate names for nylon were Elastra and Silf. Nylon stocking made their official debut at the 1939 World's Fair in New York. On May 15, 1940, when nylon stockings were first marketed, 5 million pairs of the sheer leg wear were sold. The discovery of nylon sparked a material revolution in polyester fabrics including Dacron[®] which launched the leisure suit.

After World War II, polymers were used for peacetime applications and the post-war generation grew up with plastic (Meikle, 1995). Polymers could be made into a variety of sizes and shapes often with elegant designs and colors. In the five decades since the end of World War II, plastic has crept unceasingly, and often invisibly, into our homes, cars, offices, even

our bodies. Baby boomers played with hula hoops and Frisbees, Barbie dolls and Revell airplane models. Their families experienced a flood of new plastic products such as Tupperware[®], garbage pails and laundry baskets, Melamine[®] dishes, and appliance housings (Meikle, 1995). In those days, plastic was used to produce products that appeared to be genuine, and the term ‘plastic’ symbolized artificiality and disposability. The plastic age meant the era of the sham and the bogus. There is a famous line in the movie ‘The Graduate’ produced in the 1967: “I just want to say one word to you. Just one word: ‘plastics.’ There is a great future in it.” This line was intended to be a joke, since the perception of plastics at that time was that of something cheap and phony. It turns out, however, that there was really a great future in plastics, as we now know. Plastic made the 20th century a synthetic century (Fenichell, 1996).

In recent years, plastics have been used to develop devices for controlled drug delivery and devices replacing failing natural organs. Some of us have plastic hearts, valves, joints, limbs, etc. It is this plastic revolution which advanced the technologies in the 20th century. There will be an even greater future for plastics. Although the triumph of plastic in the past was based on the package over product, style over substance, and surface over essence, the triumph of plastic in the future will be based on product, substance, and essence themselves.

II. POLYMERS AND POLYMERIZATION

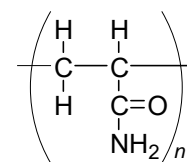
A. TERMINOLOGY

1. Monomers and Polymers

The word ‘polymer’ means ‘many parts.’ A polymer is a large molecule made up of many small repeating units. In early days of polymer synthesis, little was known about 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 (if one wishes to make) is that polymers are made of the repeating units while macromolecule are simply any large molecules and not necessarily made of repeating units. Thus, polymers are one kind of macromolecule. In general, the term ‘macromolecule’ is used as a synonym for polymer. If a molecule has a molecular weight larger than 5,000 daltons (5 kDa), it may be called a polymer. The field of polymer chemistry was recognized as represented by the awarding of additional Nobel prizes to polymer chemists: Karl Ziegler and Giulio Natta (for studying polymer tacticity and catalytic polymerization) in 1963 and Paul Flory (for studying polymer gels) in 1974. Flory was a former coworker of Wallace Hume Carothers who synthesized nylon.

A monomer is a small molecule which combines with other molecules of the same or different type to form a polymer. When it is necessary to draw the structures of polymer molecules for any reason, it becomes immediately obvious that drawing complete structures of polymer molecules is impossible. Since polymer molecules are made up of the same repeat-

ing units, they are normally drawn by showing only one repeating unit, (*i.e.*, a monomer). For example, the structure of polyacrylamide can be drawn using a monomer structure in a bracket as shown at the right. The subscript n (or any other symbol such as x , or i) outside the bracket represents the number of repeating units in the polymer molecule. The number is known as the degree of polymerization (DP). Thus, the molecular weight (M) of a polymer molecule can be calculated by the following equation:



$$M = (DP) \cdot M_0$$

where M_0 is the formula weight of the repeating unit.

2. Oligomers

Term	Example	Number of Units
Monomer		1
Dimer		2
Trimer		3
Multimer		5–30
Oligomer		30–100
Polymer		> 200

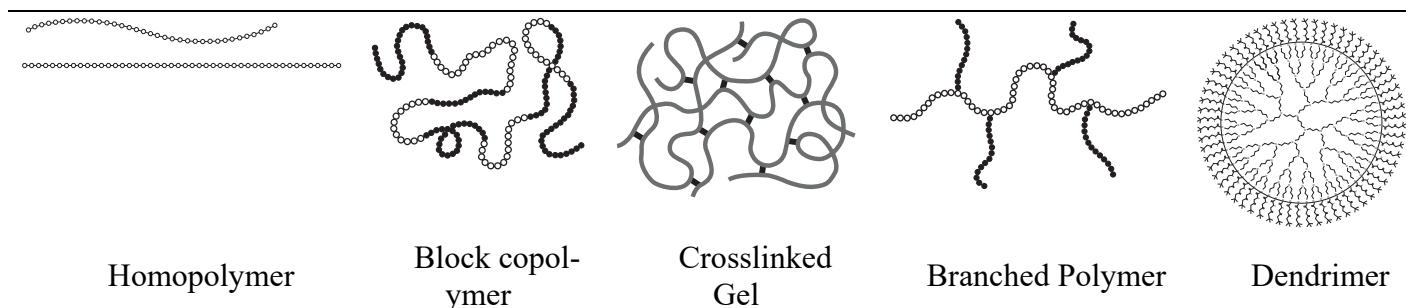
3. Polymer Architecture

Linear polymers in 1930s (homopolymer, random copolymer, block copolymer)

Crosslinked gels in 1940s

Branched polymers in 1960s (graft copolymer)

Dendritic polymers in 1980s



4. Molecular Weight

Number average molecular weight (M_n)

Weight average molecular weight (M_w)

Polydispersity index = M_w/M_n

Example:

A batch of poly(acrylic acid) is made of two monodisperse fractions. The molecular weights of the two fractions are 100 000 and 400 000. Each fraction has the same number of molecules (*i.e.*, the mole fraction is the same for both fractions).

a) What is the number average molecular weight of the polymer?

$$M_n = (0.5)(100\,000) + (0.5)(400\,000) = 250,000$$

b) What is the weight average molecular weight of the polymer?

Weight fraction of the fraction:

$$100,000 = 100,000 / (100,000 + 400,000) = 0.2$$

$$M_w = (0.2)(100,000) + (0.8)(400,000) = 340,000$$

c) What is the polydispersity index?

$$\frac{M_w}{M_n} = \frac{340\,000}{250\,000} = 1.36$$

5. Polyelectrolytes

The term ‘polyelectrolyte’ refers to polymer systems consisting of a macroion (*i.e.*, a macromolecule carrying covalently bound cationic or anionic or both groups) along with low molecular counterions (Dauzerberg *et al.*, 1994). The presence of counterions maintains the electroneutrality.

Polyacid (anionic polyelectrolyte): DNA, poly(acrylic acid), poly(styrene sulfonate)

Polybase (cationic polyelectrolyte): poly(ethylene imine)

6. Hysteresis of Gel Temperature

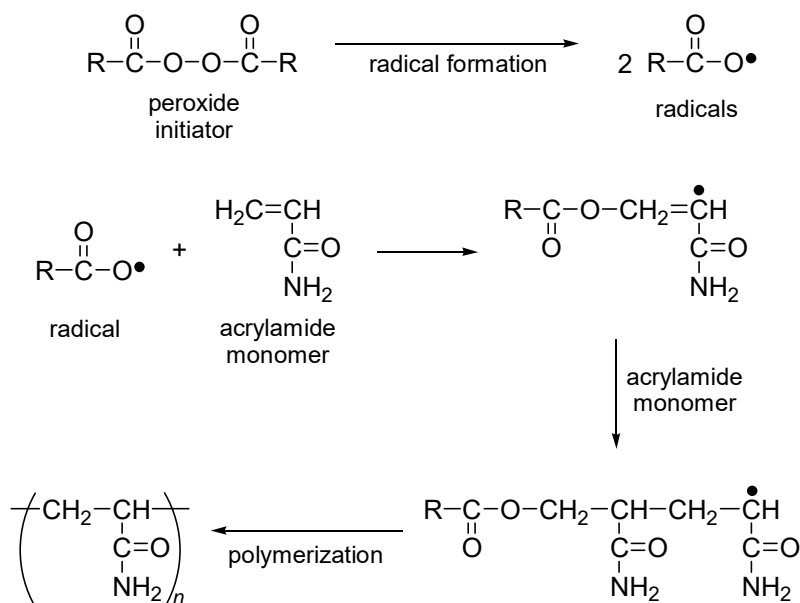
The sol-gel transformation (also known as thermoreversible gelling and remelting) can be repeated many times. The energy necessary for gelling and melting thermoreversible gels increases as the polymer concentration increases. For this reason, the gelling or melting temperature is a function of the polymer concentration. The energy necessary for melting a gel is usually greater than that available at the gelling temperature. This means that the melting occurs at higher temperature than the gelling temperature. The difference between the gelling and melting temperatures is known as the hysteresis effect.

B. POLYMERIZATION

Polymerization is a chemical reaction in which the product molecules are able to grow indefinitely in size so long as reactants (monomers) are supplied. There are many different polymerization methods, but the following two methods are most widely used.

1. Free-Radical Polymerization

Free-radical polymerization is also known as chain polymerization or addition polymerization. The following example shows vinyl polymerization of acrylamide, a vinyl monomer. To start the polymerization of monomers, there must be an initiator. An initiator, peroxide in the example below, dissociates into radicals. Each radical then attacks a vinyl monomer to produce another radical which attacks another vinyl monomer at the end of the monomer chain. This process continues until all the monomers are consumed. The key to this polymerization is that vinyl monomers are bifunctional. During polymerization, each monomer is added to the growing polymer chain and there is no loss of small molecules during polymerization.



2. Condensation Polymerization (Step-Reaction Polymerization)

The following example shows the condensation polymerization of nylon. The diamine is dissolved in water and the diacid chloride in tetrachloroethylene. Since the two solutions do not mix with each other, they form two layers, with tetrachloroethylene at the bottom. At the interface of the two solutions, the two monomers interact to form polymers. The formed polymers can then be gently removed from the interface, and monomers continue polymerization to result in continuous removal of polymers in the fiber form (see Figure 5.1). There are no radicals involved in this polymerization. As shown in the polymerization scheme (Figure 5.2), certain atoms in the monomers become removed from the monomer during polymerization so that they are absent in the repeating unit of the polymer.

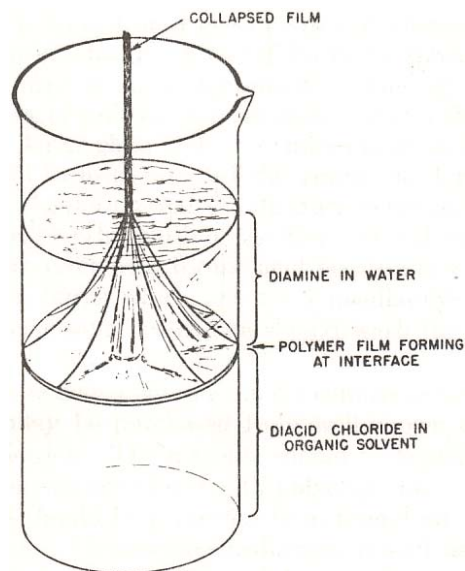
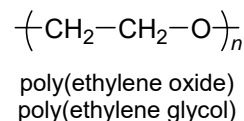


Figure 5.1 Formation of a nylon film (Morgan & Kwolek, 1959).

drugs can be immobilized by electrostatic interaction for controlled release.

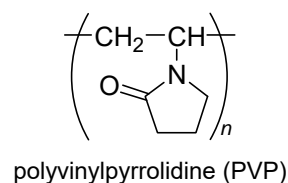
2. Poly(Ethylene Oxide) or Poly(Ethylene Glycol)

When the molecular weight of the polymer is larger than 10,000, it is usually called poly(ethylene oxide) or PEO. Polymers with molecular weight smaller than 10,000 are called poly(ethylene glycol) or PEG. However, this distinction is not absolute and PEO and PEG are used interchangeably. PEGs are marketed as Polyglycol, Carbowax[®] (Union Carbide), and Sentry[®] for the pharmaceutical industry. PEGs with a molecular weight less than 1,000 are liquid. Those with higher molecular weights are waxy solids. A mixture of PEGs and polysorbate 80 is known as polybase.



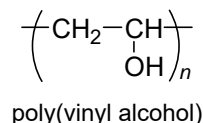
3. Polyvinylpyrrolidone

PVP is used to make Betadiene (iodine complex of PVP), an antiseptic which has lower toxicity than iodine itself. It was also used as a plasma extender during World War II. Aqueous solutions of PVP are used for granulation.



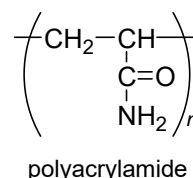
4. Poly(Vinyl Alcohol)

Poly(vinyl alcohol) (PVA) is used in making water-soluble packaging materials.

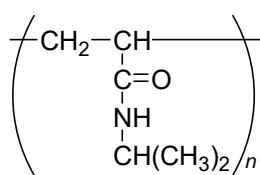


5. Polyacrylamide

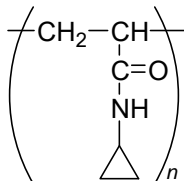
Polyacrylamide is widely used in gel electrophoresis to separate protein molecules based on their molecular weights. The monomer, acrylamide, is known to cause cancer, so it is important to wear gloves, eye protection, and dust mask and use in a fume hood. Wash thoroughly after handling. Skin contact, inhalation, or ingestion may cause nervous system disorders. In case of contact, flush with water for 15 minutes. Millions of scientists have made polyacrylamide for electrophoresis without any problem.



6. Poly(*N*-Isopropylacrylamide) and Poly(*N*-Cyclopropylmethacrylamide)



poly(*N*-isopropylacrylamide)



poly(*N*-cyclopropylmethacrylamide)

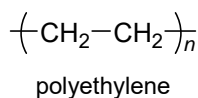
Polyacrylamide derivatives containing hydrophobic pendant groups have reverse temperature sensitivity. They are water-soluble at low temperature, but become water-insoluble at high temperature. This is due to the delicate balance between hydrogen bonding and hydrophobic interaction properties of various groups on the polymer backbone. Depending on the

temperature, one of the two interactions dominates, and it determines the water-solubility.

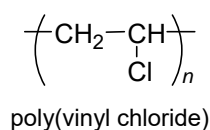
B. SYNTHETIC WATER-INSOLUBLE POLYMERS

The following polymers are examples of water-insoluble polymers. They may be soluble in selected organic solvent under certain conditions.

1. Polyethylene

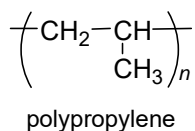


The structure of polyethylene indicates that the polymer was derived from ethylene. If the structure has only one methylene group, then it is polymethylene which is made from CH_2N_2 . Polyethylene is used to make plastic bottles, greenhouse cover, and Glad[®] wrap.



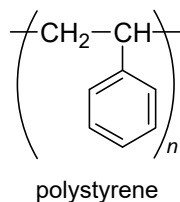
2. Poly(Vinyl Chloride)

Poly(vinyl chloride) (PVC) was first used to make a 12-inch long-playing phonograph record in 1948. It is also used to make credit cards without which nobody can survive. The plasticized PVC is used to make garden hoses, laboratory tubing, shower curtains, diaper covers, rain coat, and blood bags. Triaryl phosphate and dibutyl phthalate are often used as plasticizers.



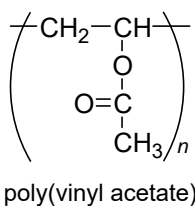
3. Polypropylene

Polypropylene is used to make high strength automotive and appliance items. A thin sheet of polypropylene is also used as a shrink packaging material for tight packing. PVC and other polypropylene films are also used as heat shrinking materials.



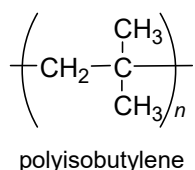
4. Polystyrene

Polystyrene is used to make petri dishes or bottles for cell culture.



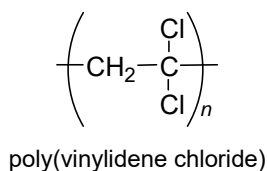
5. Poly(Vinyl Acetate)

Poly(vinyl acetate) (PVAc) is used in making chewing gums.



6. Polyisobutylene

Polyisobutylenes are elastomeric polymers commonly used for making pressure-sensitive adhesives (PAS) for transdermal drug delivery systems. The amorphous characteristics with low glass transition temperature (at -62°C) makes it very tacky. Usually tackifiers (such as rosin ester resins) are added to increase the polarity of the polyisobutylene formulation for strong adhesion.



7. Poly(Vinylidene Chloride)

Copolymer with PVC [poly(vinyl chloride-co-vinylidene chloride)] is used to make Saran Wrap, which clings to almost any material, such as bowls, dishes, pots and even itself. This clingy covering changed the American kitchen by maintaining the freshness of food at home.

8. Polytetrafluoroethylene

Polytetrafluoroethylene, or Teflon[®], is the superhero of polymers. It has high temperature stability, high chemical resistance, and high surface lubricity. Teflon was used to make nonsticky kitchen pans (Silverstone[®]) in the 1960s. If Teflon[®] is nonsticky, then how can it be coated on the surface of a kitchenware? First, Teflon[®] particles are mixed with adhesive particles, and a slurry of particles in water are placed on the mold. They are then baked at high pressure to fuse particles together and form a continuous layer. Teflon[®] is stretched to make Gore-Tex[®], the water-resistant, breathable clothing. Gore-Tex[®] is also used as biomaterials (e.g., artificial vascular graft).

9. Poly(Methyl Methacrylate)

Poly(methyl methacrylate) (PMMA) is used to make windows in airplanes. PMMA is also used to make hard contact lenses. Commercial products are Plexiglas[®] (Rohm & Hass) and Lucite[®] (Du Pont). Lucite is frequently used for the embedment of specimen of many kinds for purpose of preservation and display.

10. Poly(Hydroxyethyl Methacrylate)

Poly(hydroxyethyl methacrylate) (PHEMA) is used to make soft contact lenses.

11. Polybutadiene

This is used to make tires.

12. Polychloroprene

Polychloroprene [poly-(2-chloro-1,3-butadiene)] (Trade name: Neoprene) is frequently used as septums for injectable, plungers for syringes, and valve components. Polychloroprene replaces natural rubber containing mercaptobenzothiozole to which many people have hypersensitivity.

13. Polyisoprene

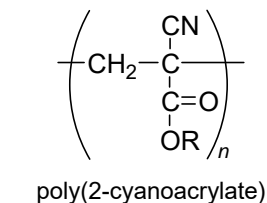
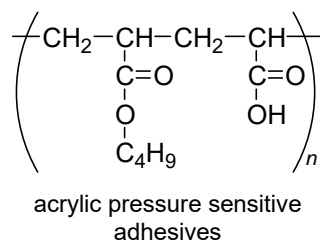
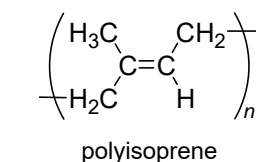
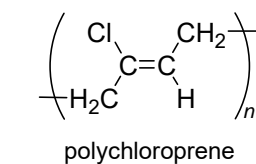
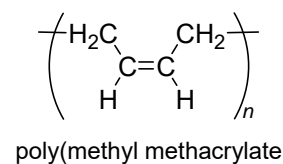
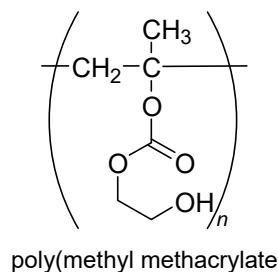
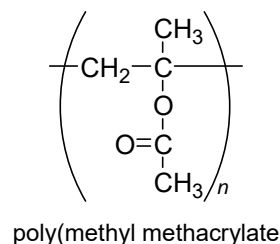
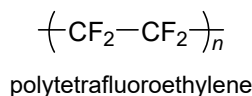
Please note that polyisoprene is natural rubber and so it does not belong to synthetic polymer section. But it is shown here for a comparison with polychloroprene.

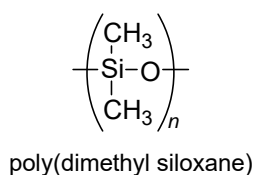
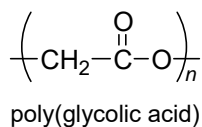
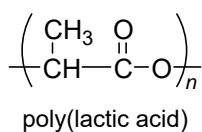
14. Acrylic Pressure Sensitive Adhesives

These are used as skin adhesives in transdermal patches.

15. Poly(2-Cyanoacrylate)

Unlike conventional adhesives that require heat, pressure, catalysts, or evaporation of solvent, the 2-cyanoacrylates polymerize at room temperature without solvent or catalyst. Thus, it has been widely used as 'instant glues' in industry, as biodegradable tissue adhesives in surgery, or as drug carriers in the form of nano- and microparticles.



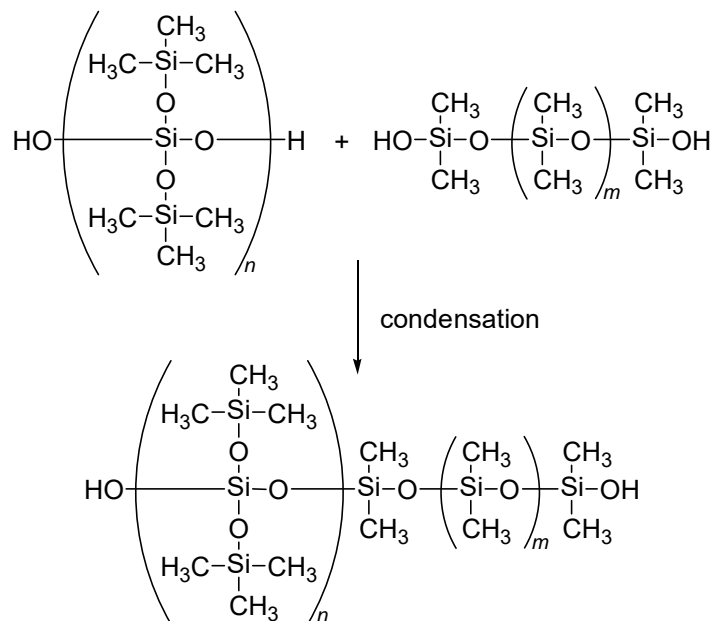


16. Poly(Lactic Acid) & Poly(Glycolic Acid)

Living cells produce energy by converting the energy stored in food into energy the cells can use by a chemical reaction called respiration. Aerobic respiration requires oxygen. Reaction between oxygen and glucose results in carbon dioxide, water, and energy. If the cells in our body (*e.g.*, cells in our muscle) use oxygen faster than our lungs can take it in, the cells start to use anaerobic respiration to provide an extra energy. Anaerobic respiration turns glucose into lactic acid and energy. It is the lactic acid that causes muscle ache and cramp. Lactic acid can be removed by supply of oxygen.

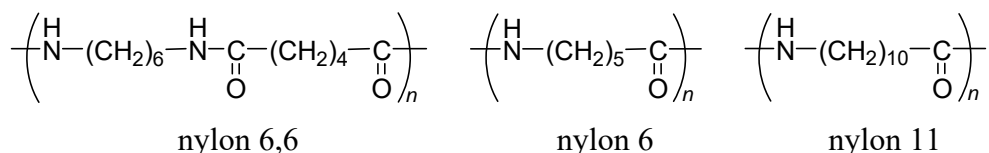
17. Poly(Dimethyl Siloxane)

Silicone rubber has been used to make a variety of different products ranging from athletic mouth piece or pacifier to therapeutic devices. It is often used in making masks in movie industry. Silly putty is made of silicone rubber (dimethyl polysiloxane crosslinked by borosiloxane). When silly putty is squeezed slowly, it will escape through the fist like modelign clay, and when dropped, it bounces like rubber. It is this property that allowed silicone rubber to be used as artificial body parts including reconstructed breast following mastectomy. Medical grade silicone rubber is used to make controlled release drug delivery systems such as Norplant[®] subdermal implant. The term 'medical grade' simply indicates that the polymer is better than the industrial grade and it does not guarantee the polymer is safe.



Polysiloxane and trimethylsiloxy silicate resin are used for making silicone pressure-sensitive adhesives (Tan & Pfister, 1999).

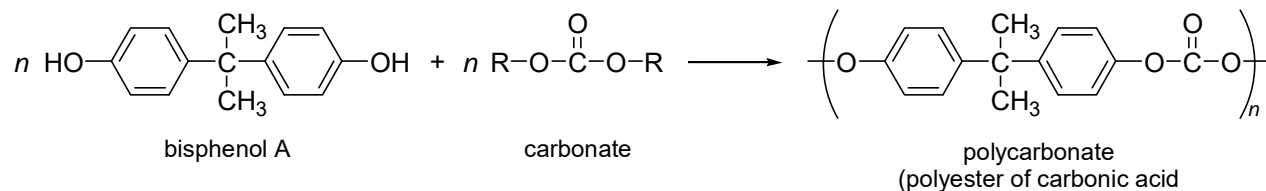
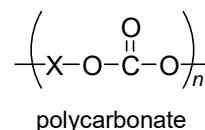
18. Nylons



Nylon 6,6, or poly(hexamethylene adipamide), is made from hexamethylenediamine and adipic acid ($\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$). It is used to make nylon stockings. To make high molecular weight polymers (which was called super polyamide), the reactants have to be extremely pure. The reaction produces long chains if water is removed to shift the equilibrium to favor large chains (Seymour & Carraher, 1990). Heating the purified salt from the diamine and diacid results in high molecular weight nylon 6,6. Examples of other nylons are nylon 6 (polycaprolactam) and nylon 11 (poly(11-aminoundecanoic acid)).

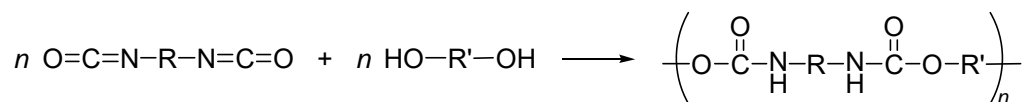
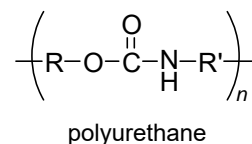
19. Polycarbonate

Polycarbonate is commonly used to make cases for biomedical and pharmaceutical products.

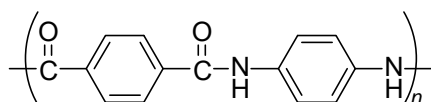


20. Polyurethane

Spandex fiber (a polyurethane) has been used in stretchy garments including the skimpy swimwear, aerobic wear, and elastic-waist jeans. Polyurethanes are used in blood pumps, artificial heart, and vascular grafts. Polyurethane foams have been used widely in various applications ranging from biomedical to industrial products.



21. Kevlar®

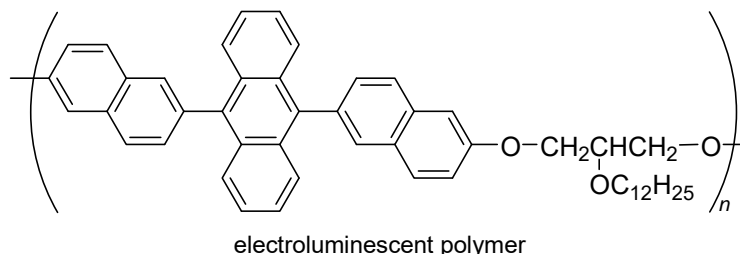


Discovery of a solvent allowed making of Kevlar® aramid fiber, which has been used to build spacecraft and bulletproof vests.

22. Electrically Conductive Polymers

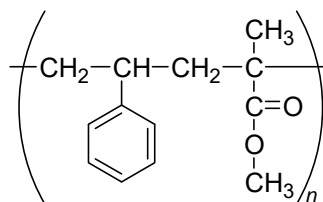
The 2000 Nobel Prize in chemistry was awarded to Alan MacDiarmid, Alan Heeger, and Hideki Shirakawa for their discovery in 1977 that an

organic polymer can conduct electricity. Properly constructed, certain polymers are able to conduct electricity and emit light (electroluminescent polymers). The construction of polymer-based light-emitting diodes (LEDs) is thus possible.



Conducting polymers are being used as antistatic coatings and corrosion inhibitors, radar-absorbing coating on stealth bombers, and mobile phone displays based on a light-emitting polymer. Other applications of conducting polymers that could emerge in coming years include light-weight batteries for cars, electromagnetic shielding, ultrathin computer monitors and television sets, artificial nerves, and sensors.

23. Copolymers

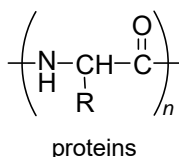


When two different types of monomers are used to make polymers, they are called copolymers. The name of the monomer with higher concentration comes before the other. If styrene and methyl methacrylate copolymer is made with higher concentration of styrene, it is called 'poly(styrene-co-methyl methacrylate).' Poly(ethylene-co-vinyl acetate) is a copolymer with higher concentration of ethylene. The copolymer can also be called using monomer names (*e.g.*, ethylene vinyl acetate copolymer (EVA copolymer)).

IV. STRUCTURES OF NATURAL POLYMERS

Natural polymers can be classified into three subclasses: proteins; polysaccharides; and nucleotides. Proteins and polysaccharides have been widely used to develop controlled release dosage forms, while nucleotides are not widely used for the same purpose.

A. PROTEINS



Proteins are polypeptides with the following general structure.

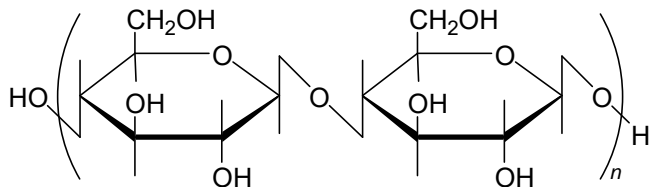
Proteins can be water-soluble as well as water-insoluble. Examples of water-soluble proteins are albumin, fibrinogen, and gelatin. Collagen is the major component of skin, tendon, and cartilage. Collagen is not water-

soluble at neutral pH, but can be dissolved in acidic aqueous solution. Collagen is injected to remove wrinkles. Since collagen is degradable by enzymes, it has to be injected again after a few months.

B. POLYSACCHARIDES

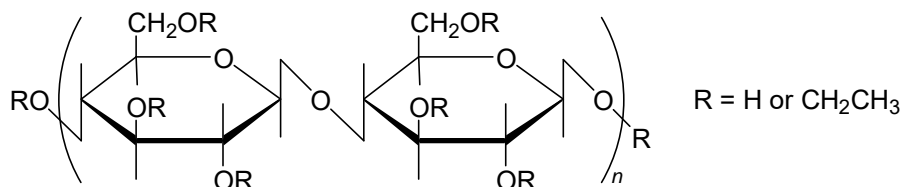
1. Cellulose and Cellulose Derivatives

a. Cellulose



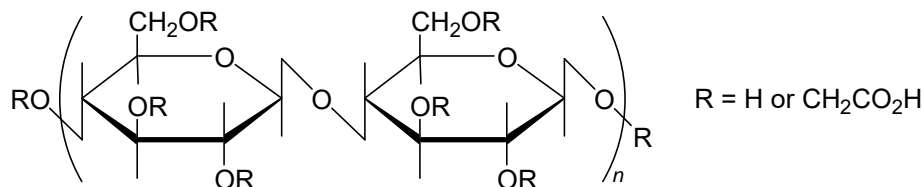
Not soluble in water. Cellulose is the most abundant polymer on earth. The structure suggests that cellulose can be water-soluble, but it is not. This is due to the extensive hydrogen bonding between individual cellulose molecules.

b. Ethylcellulose



Not soluble in water. Ethylcellulose is widely used in an aqueous coating system for sustained release applications. Ethylcellulose forms a relatively impermeable barrier. To make a flexible membrane, ethylcellulose is plasticized using either dibutyl sebacate and oleic acid. Usually, ammoniated water is used for the system. Ammonia is used to stabilize the dispersed polymer. Ethocel[®] from Dow is commercially available. Ethylcellulose colloidal dispersion of submicron particle size of ethylcellulose is sold as Aquacoat[®] aqueous polymeric dispersions from FMC. (*Degree of substitution)

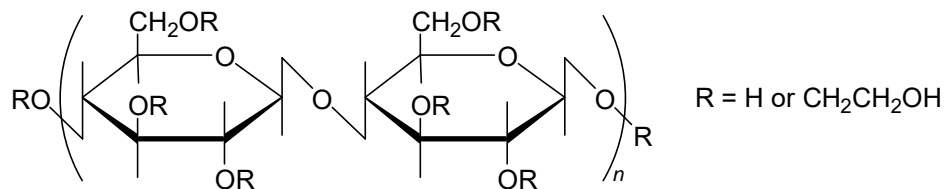
c. Carboxymethylcellulose



Water-soluble. Degree of substitution of the carboxymethyl group varies. Crosslinked sodium carboxymethylcellulose (CMC) is known as Croscarmellose Sodium in NF. A commercial product known as Ac-Di-

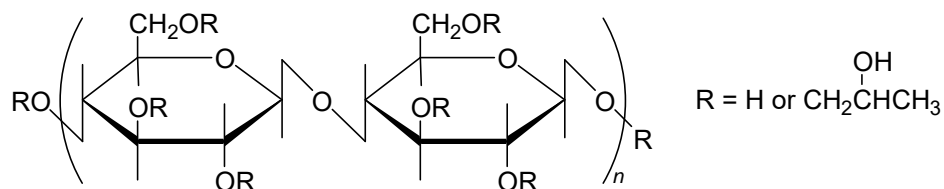
Sol[®] is available from FMC Corp. The name Ac-Di-Sol[®] came from ‘Accelerates DisSolution.’

d. Hydroxyethylcellulose



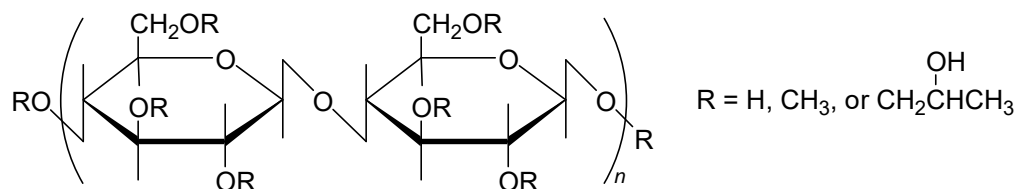
Water-soluble.

e. Hydroxypropylcellulose



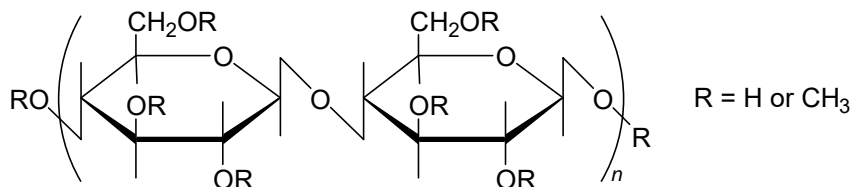
Water-soluble at low temperature, and is used for film coating.

f. Hydroxypropylmethylcellulose



Soluble in water below 60°C and in organic solvents. Methocel[®] is an aqueous system of hydroxypropylmethylcellulose (HPMC) used for tablet coating from Dow Chemical. Polymers, such as HPMC, have been spray applied onto tablets in heated conventional sugar coating pans and it has reduced tablet coating time from days to hours.

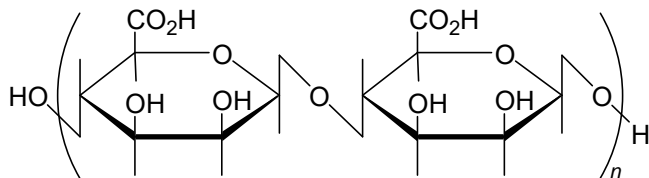
g. Methylcellulose



Soluble in cold water only. Commercially available under the names of Methocel[®] A (Dow Chemical) or Citrucel[®] (Merrel Dow)). It swells and disperses slowly in cold water to form a clear-to-opalescent, viscous, colloidal dispersion. It is practically insoluble in acetone, chloroform, ethanol, ether, saturated salt solutions, toluene and hot water. It is soluble in

glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform.

2. Alginic Acid

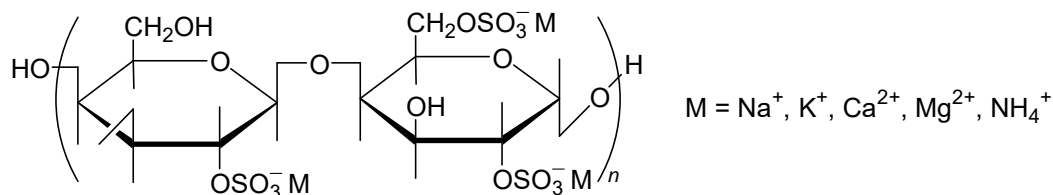


Alginic acid is a naturally occurring hydrophilic colloidal polysaccharide obtained from the various species of brown seaweed (Phaeophyceae). It is a linear copolymer consisting mainly of residues of β -1,4-linked D-mannuronic acid and a α -1,4-linked L-glucuronic acid. These monomers are often arranged in homopolymeric blocks separated by regions approximating an alternating sequence of the two acid monomers. The thick, jellylike substance is used as a stabilizer and thickener in a wide variety of commercially processed foods (*e.g.*, ice creams, puddings, flavored milk drinks, pie fillings, soups and syrups) and in pharmaceutical preparations as a stabilizing agent, suspending agent, tablet binder, tablet disintegrant, and viscosity-increasing agent.

Alginic acid is used in a variety of oral and topical pharmaceutical products. It is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions. In tablet and capsule formulations, it is used as both a binder and a disintegrating agent at concentrations of 1–5% w/w.

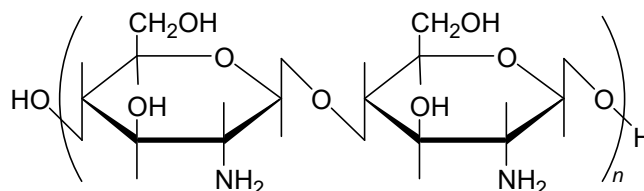
In the area of controlled release, the preparation of indomethacin sustained-release microparticles from alginic acid (alginate)–gelatin hydrocolloid coacervate systems has been investigated. In addition, as controlled-release systems for liposome-associated macromolecules, microspheres have been produced encapsulating liposomes coated with alginic acid and poly-L-lysine membranes. Mechanical properties, water uptake, and permeability properties of a sodium salt of alginic acid have been characterized for controlled-release applications. In addition, sodium alginate has been incorporated into an ophthalmic drug delivery system for pilocarpine nitrate. Also used generally as a hydrophilic matrix agent for controlled-release applications.

3. λ -Carrageenan



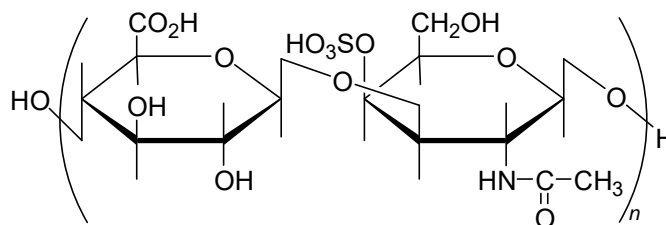
λ -Carrageenan (lambda-carrageenan) is a nongelling polymer typically used at levels of 0.7% w/v or less and provides viscosity to liquids and exhibits some modification of release of drugs from solution.

4. Chitosan



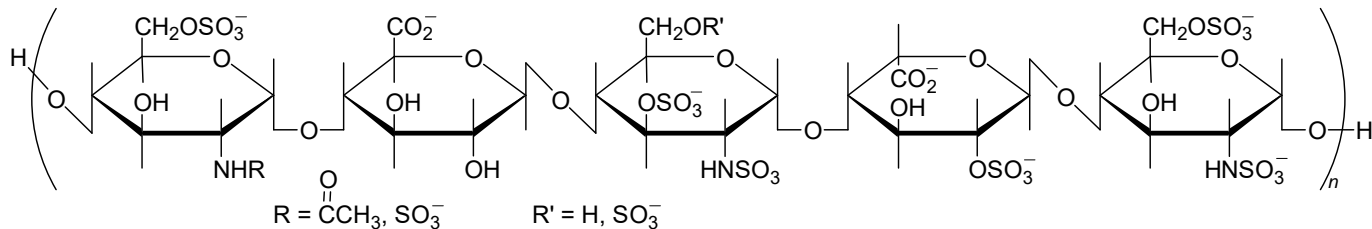
Chitosan is obtained from chitin which is abundant in shrimp, crab and lobster shells. Chitin is the second most abundant polymer on earth. It is used in cosmetics and has been investigated as a component of pharmaceutical formulations for controlled drug delivery applications, a component of mucoadhesive dosage forms, and rapid release dosage forms.

5. Chondroitin-4-Sulfate

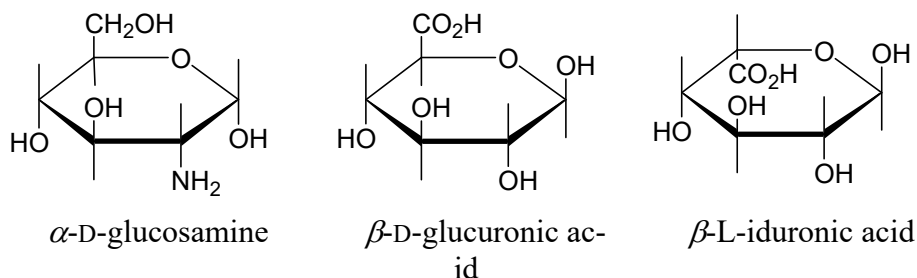


Chondroitin sulfate belongs to a family of complex polysaccharides called glycosaminoglycans or GAGs (formerly called mucopolysaccharides). Chondroitin sulfate consists of a long chain of repeating units of disaccharides called chondrosines composed of D-glucuronic acid and D-galactosamine. Depending on where these chondrosine units bind to each other determines the type of chondroitin. Chondroitin sulfate A (also called chondroitin-4-sulfate) is more numerous than chondroitin sulfate C (chondroitin-6-sulfate). Depending on how the chondroitin sulfate is prepared, there can be anywhere from 15–150 of these repeating chondrosine units. Commercially available chondroitin products are a mixture of chondroitin A and C. The major source of chondroitin sulfate commercially is from the cartilaginous rings of bovine trachea (the windpipe in cattle). Another, rather expensive source is shark cartilage. Chondroitin sulfate may be indicated for the prevention and treatment of osteoarthritis. It may be used by itself or in combination with glucosamine sulfate. There is some preliminary clinical evidence that chondroitin sulfate may be helpful for atherosclerosis, though more research will be required before this can be clearly demonstrated.

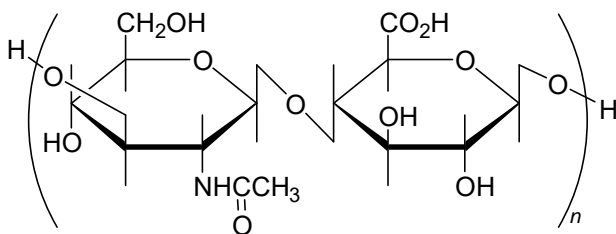
6. Heparin



Heparin is a heterogeneous mixture of variably sulfonated polysaccharide chains composed of repeating units of D-glucosamine and either L-iduronic acid or D-glucuronic acid with molecular weights ranging from 6–30 kDa. It is biosynthesized and stored in mast cells of various animal tissues, particularly liver, lung, or gut. Commercial heparin is isolated from beef lung or pork intestinal mucosa. The sodium salt is used as an anticoagulant.

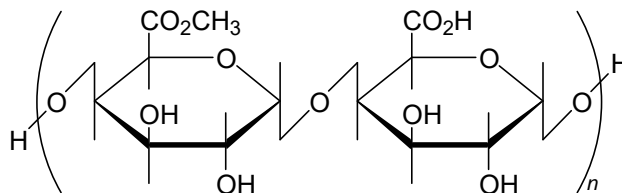


7. Hyaluronic Acid



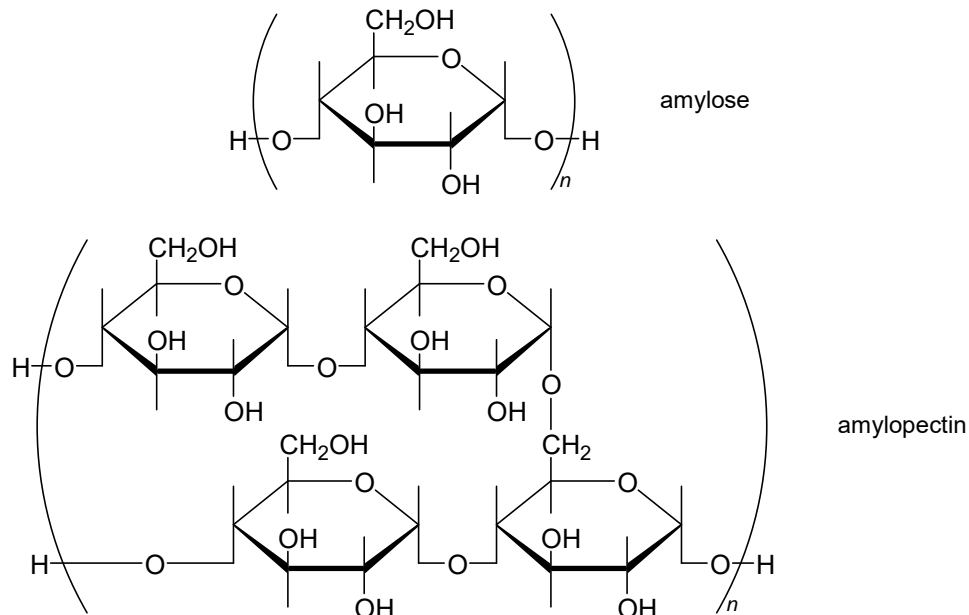
Hyaluronic acid is used as an essential ingredient in cosmetics. Bio-Performance Advanced Super Revitalizer (Cream) N[®] (Shiseido) contains 0.12–0.15% hyaluronic acid. A mixture of hyaluronic acid and carboxymethylcellulose has been used to make a commercial product known as Seprafilm[™] (Genzyme) that is applied for reduction of scar tissue as a result of abdominal or pelvic surgery.

8. Pectinic Acid



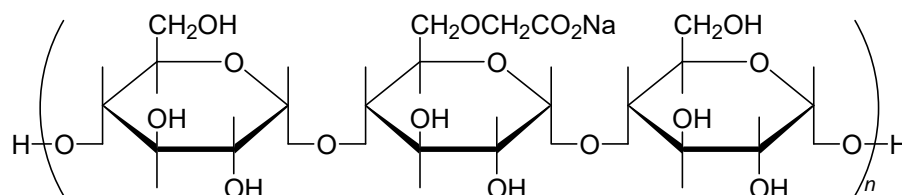
Protopectin is the insoluble pectin precursor present in green fruit especially lemon and orange rind. During ripening it is converted to pectinic acid and subsequently to pectin. Pectinic acid is a polymer of galacturonic acid with a variable amount of methylation. Pellets of pectinic acid might be suitable for drug release at sites throughout the entire gastrointestinal tract if combined with suitable film coatings.

9. Starch



Starch is obtained from a variety of sources (*e.g.*, maize, potato, rice, tapioca, wheat, and corn) and consists of amylose and amylopectin, two polysaccharides based on α -glucose. Starch is used as a glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, and a tablet binder.

10. Sodium Starch Glycolate



Sodium starch glycolate (Explotab[®], Primojel[®], Vivastar P[®]) is widely used as a tablet and capsule disintegrant in oral dosage forms. It is commonly used in tablet prepared by direct compression or wet granulation. Disintegration occurs by a rapid uptake of water followed by rapid and enormous swelling.

C. DNA AND RNA

DNA is the basic hereditary material included in all cells and contains the information necessary for protein production. DNA is a linear polymer consisting of nucleotide units that are comprised of a phosphate group, a deoxyribose sugar, and one of four bases: adenine (A), thymine (T), guanine (G), and cytosine (C). A duplex of DNA is formed by two complementary chains that are arranged in an anti-parallel manner. In normal DNA, the bases form complementary pairs: A—T and G—C.

RNA is a linear polymer similar to DNA but contains ribose instead of deoxyribose sugars. In addition, the RNA contains the base uracil (U) instead of thymine (T). RNA can form double stranded duplexes, but typically RNA is single stranded and can form complex and unusual shapes. tRNA is the key molecule involved in the translation of genetic information to proteins. Ribozyme is an RNA that has catalytic activity.

D. DIETARY FIBERS

Dietary fibers are plant substances that are indigestible in the digestive system. The current definition of dietary fibers accepted by the American Association of Cereal Chemists is “the remnants of edible plant cell, polysaccharides, lignin, and associated substances resistant to (hydrolysis) digestion by the alimentary enzymes of humans.” Examples of dietary fibers are listed in Table 2.1. Dietary fibers are divided into water-soluble and insoluble fibers. Soluble fibers are commonly found in high amounts in fruits and vegetables, soybean meal fiber, psyllium, and the β -glucans in oat bran, while insoluble fibers are found in corn, rice, wheat, and oat hulls. The American Dietetic Association recommends 20–35 g/d of dietary fiber for an adult, but most adults are known to consume roughly half of that. Many epidemiological studies have indicated that high-fiber diets are associated with reduced risks of coronary heart disease, diabetes, and colon cancer. Soluble fibers, especially guar, pectin and gum arabic, were shown to reduce serum cholesterol levels in clinical studies. Chitosan is claimed to increase levels of high-density lipoprotein, but more study is

Table 2.1 Examples of dietary fibers

alginate	corn bran	oat extract	rice bran
amaranth bran	fenugreek fiber	oat fiber	rice extract
arabic gum	fruit fiber	oligosaccharides	soy
barley	β -glucan	pea fiber	vegetable
cellulose	guar	pectin	wheat bran
chitosan	inulin	psyllium	
citrus fiber	oat bran	resistant starch	

necessary to confirm such beneficial effect of chitosan. Insoluble fibers have been linked with reduced risks of certain types of cancer. Some undigestible polysaccharides, such as inulin (abundant in chicory), are known to function as prebiotics that support beneficial probiotic intestinal flora, such as bifidobacteria, in humans.

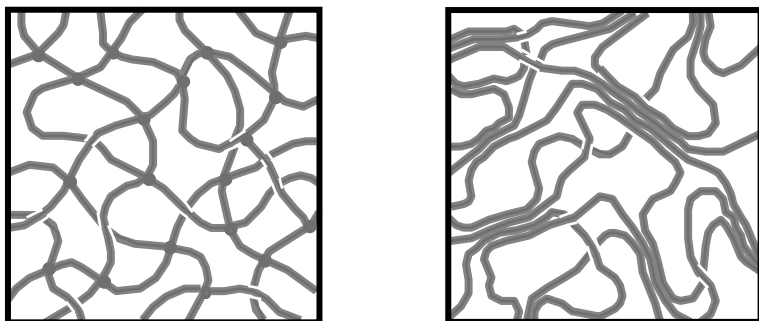
Since many compounds that are not classified as dietary fibers have been shown to be highly beneficial in maintaining a healthy gut microflora, the definition of dietary fibers may have to be revised. Polysaccharides obtained from non-edible plants, oligosaccharides which are not measured by the current method for measuring total dietary fiber, and synthetic polymers are not included in the definition of dietary fibers at all. These, however, may provide the same, or even better, benefits.

V. HYDROGELS

Certain materials, when placed in excess water, are able to swell rapidly and retain large volumes of water in their swollen structures. The materials do not dissolve in water and maintain three dimensional networks. Such aqueous gel networks are called hydrogels (also called aquagels). Hydrogels are usually made of hydrophilic polymer molecules which are crosslinked either by chemical bonds or other cohesion forces such as ionic interaction, hydrogen bonding or hydrophobic interactions. Hydrogels are elastic solids in the sense that there exists a remembered reference configuration to which the system returns even after being deformed for a very long time.

A hydrogel swells for the same reason that an analogous linear polymer dissolves in water to form an ordinary polymer solution. If a hydrogel, for any reason, dissolves in aqueous solvent, then the gel has become a hydrosol, which is a dispersion of colloidal particles in water. From a general physicochemical point of view, hydrosol is simply an aqueous solution. Many polymers can undergo reversible transformation between hydrogel and hydrosol. Chemical crosslinking of dispersed particles in hydrosols will result in irreversible hydrogel. It is noted that a gel is an infinitely large macromolecule, or supermacromolecule, which forms a network extending from one end to the other and occupying the whole reaction vessel.

The term hydrogel implies that the material is already swollen in water. The dried hydrogel is called xerogel or dry gel. During the drying process water evaporates from a gel and the surface tension causes collapse of the gel body. Thus, the gel shrinks to only a small fraction of its swollen size. If water is removed without disturbing the polymer network, either by lyophilization (*i.e.*, freeze drying) or by extraction with organic solvents, then the remaining material is extremely light with high porosity. Such a dehydrated hydrogel is called aerogel. When a hydrogel is made by introducing gas (air, nitrogen, or carbon dioxide) bubbles during hydrogel formation, the formed hydrogel contains very large pores. These hydrogels are called superporous hydrogels. Hydrogels can be divided into chemical and physical gels depending on the nature of the crosslinking. Figure 5.3 shows chemical and physical gels.



Random coil polymer

Figure 5.3 Chemical (A) and physical (B) gels. In chemical gels, polymer chains are crosslinked by covalent bonds. Polymer chains in physical gels are crosslinked by non-covalent bonds.

A. CHEMICAL GELS

Chemical gels are those which have covalently crosslinked networks. Thus, chemical gels will not dissolve in water or other organic solvent unless covalent crosslinks are cleaved. At least two different approaches can be used to form chemical gels. First, chemical gels can be made by polymerizing water-soluble monomers in the presence of bi- or multi-functional crosslinking agents. Second, chemical gels can be prepared by crosslinking water-soluble polymers using typical organic chemical reactions which involve functional groups of the polymers.

If a chemical gel is made of hydrophilic monomers, then the hydrogel will swell upon temperature increase and it is called thermoswelling hydrogels. Most hydrogels belong to this category. On the other hand, some hydrogels made of relatively hydrophobic monomers undergo shrinkage upon temperature increase and known as thermoshrinking gels. The thermoshrinking hydrogels undergo thermally reversible swelling and deswelling. Since the deswelling occurs rather dramatically by a minute temperature change, the phenomenon is often called the gel collapse. The gel collapse (*i.e.*, volume phase transition of gels) is similar to the coil-globule transition of polymer chains in poor solvents. The temperature which induces gel collapse corresponds to a lower critical solution temperature (LCST) of the uncrosslinked polymer.

B. PHYSICAL GELS

Physical gels (also called physical networks, association networks or pseudo gels) are the continuous, disordered three-dimensional networks formed by associative forces capable of forming noncovalent crosslinks. The point covalent crosslinks often found in synthetic polymer networks are replaced by weaker and potentially more reversible forms of chain-chain interactions. These interactions include hydrogen bonding, ionic association, hydrophobic interaction, stereocomplex formation, crosslinking by the crystalline segments, and solvent complexation. Because of

noncovalent nature of the crosslinks, physical gels are reversible between the gel and sol states.

In physical gels, a substantial fraction of a polymer chain is involved in the formation of stable contacts between polymer chains. Association of certain linear segments of long polymer molecules form extended ‘junction zones.’ This is distinguished from the chemical gels which have well defined point crosslinks. Figure 5.4 shows an example of physical gels with junction zones.

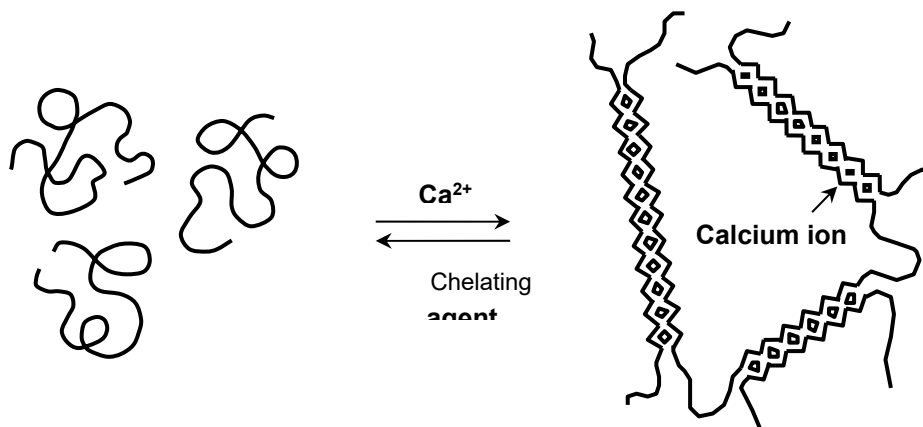


Figure 5.4 Gelation of sodium alginate in the presence of calcium ions. A number of calcium ions crosslink carboxylate ions on two alginate chains by forming junction zones.

1. Slime—an example of a physical gel

Making of slime based on poly(vinyl alcohol) (Casassa, Sarquis, & Van Dyke, 1986; Sarquis, 1986; Tonelli, 2001)

i. Prepare the following solutions:

4% PVA: Add 4 g of poly(vinyl alcohol) (PVA) to 100 mL hot water heated to 70 °C and stir until solution clears. (Please do not boil). Cool the solution to room temperature. The solution will look like a thick, viscous corn syrup.

4% Sodium Borate: Add 4 g of sodium borate to 100 mL of water with stirring to dissolve. (Borax, $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$)

ii. Measure 50 mL of PVA solution into a cup or a beaker.

iii. In a second cup place 5–10 mL of sodium borate solution. A color can be introduced by adding (*e.g.*, a drop of food coloring).

iv. Pour sodium borate solution into PVC solution while stirring vigorously with a glass rod or spoon.

- (a) What did you observe after addition of borate into the PVA solution?
- (b) What do you think is the mechanism? (*i.e.*, What kind of reaction occurred?)

- (c) Take the gel out of the beaker, roll it into a cylinder, and hang a portion of the gelled cylinder over the edge of the desktop. What did you observe?
- (d) Roll the extended gel cylinder into a ball and drop it on the desk surface from a height of 60–100 cm (2–3 feet). What did you observe?
- (e) Roll the gel into another cylinder and attempt to abruptly extend the cylinder by quickly pulling on both of its ends. Were you able to extend the gel?
- (f) Why do you think that the same PVA gel behaved three different ways in three different experiments?

2. Inverse thermosensitive hydrogels

Some physical gels are sensitive to temperature changes. Those physical gels which undergo melting (*i.e.*, dissolution of gels into sols) is called thermomelting gels. Widely known examples are gelatin and agarose. They form gels at low temperatures but melt at high temperatures. On the other hand, some physical gels melts at low temperature, but gels at high temperature. They are known as thermogelating hydrogels. Gels with thermogelation properties usually have hydrophobic side groups. As temperature increases, the hydrophobic interactions among side groups increase and as a result gel is formed. Polymers, such as methylcellulose, hydroxypropylmethylcellulose, or certain PEO/PPO/PEO triblock copolymers, dissolve only in cold water forming a viscous solution. On raising the temperature these solutions thicken or gel.

C. INTERPENETRATING NETWORKS

Interpenetrating network (IPN) is a polymer blend containing two networks which are interpenetrating each other (Figure 5.5). To make IPN, a crosslinked polymer is swollen with a second monomer, together with crosslinking agents, followed by its polymerization. When two different types of polymers are mixed, phase separation usually occurs owing to polymer incompatibility. But such a phase separation is limited to a fine scale in IPN owing to the interlocking of the networks, often having a cellular type of morphology. If only one polymer network is covalently crosslinked and the other type of polymer chains are not crosslinked, it is called semi-IPN.

D. SMART HYDROGELS

Hydrogels that can respond to environmental changes, such as changes in pH, temperature, salt concentration, salt type, solvent composition, or pressure, are collectively known as smart (or intelligent) hydrogels. The unique properties of smart hydrogels are ideal for making sensors and modulated drug delivery systems (see Chapter 12). Examples of smart hydrogels are shown below.

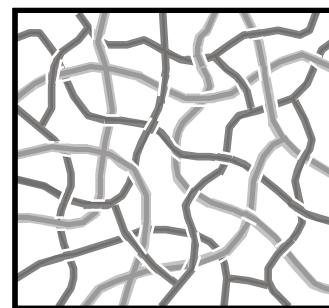


Figure 5.5 An example of interpenetrating network (IPN). Two different polymer networks interpenetrate each other.

VI. HYDROGEN BONDING AND HYDROPHOBIC INTERACTIONS

A. HYDROGEN BONDING

A hydrogen bond occurs when two electronegative atoms, such as nitrogen and oxygen, interact with the same hydrogen. The hydrogen is normally covalently attached to one atom, the donor, but interacts electrostatically with the other, the acceptor. This interaction is due to the dipole between the electronegative atoms and the proton. The strength of a hydrogen bond is between 2 and 10 kcal/mol.

There is a geometric component involved in hydrogen bonds, and for single donor acceptor systems, such as $N-H\cdots O$, the strongest hydrogen bonds are collinear. Electrostatic calculations suggest that deviation of 20° from linearity leads to a decrease in binding energy of approximately 10%. In double acceptor systems, bifurcated hydrogen bonds with non-linear angles are preferred.

B. HYDROPHOBIC INTERACTIONS

Hydrophobic interactions are considered to be the major driving force for the folding of globular proteins. These interactions result in the burial of the hydrophobic residues in the core of the protein. It is exemplified by the fact that oil and water do not mix. The thermodynamic factors that give rise to the hydrophobic effect are complex and still incompletely understood. The free energy of transfer of a non-polar compound from some reference state, such as an organic solution, into water, ΔG_{tr} , is made up of an enthalpy, ΔH , and entropy, $-\Delta TS$, term. At room temperature, the enthalpy of transfer from organic solution into aqueous solution is negligible; the interaction enthalpies are the same in both cases.

The entropy however is negative. Water tends to form ordered cages around the non-polar molecule and this leads to a decrease in entropy. At high temperatures ($\sim 110^\circ\text{C}$) these cages are no longer any stronger than bulk water, and the entropy contribution tends to zero. The enthalpy of transfer, however, is now positive (unfavourable). Because the temperature dependence of entropy and enthalpy are not the same, there is some temperature at which the hydrophobic effect is strongest, and the effect decreases at temperatures above and below this temperature. The decrease in the strength of the hydrophobic effect with decreasing temperatures is probably the major cause of cold-denaturation in proteins.

VII. MELTING TEMPERATURE AND GLASS-TRANSITION TEMPERATURE

A. CRYSTALLINITY AND MELTING TEMPERATURE

Some polymers crystallize if polymer chains are able to pack together in a regular array. For example, polypropylene molecules fit together in such a way that intermolecular attractions stabilize the chains in a regular lattice or crystalline state.

Melting temperature is a temperature at which crystalline polymers start segmental motion. Above the melting temperature, polymer molecules are in continuous motion and the wriggling molecules can slip past one another.

B. GLASS AND GLASS-TRANSITION TEMPERATURE

In many cases, the structure of polymers is so irregular that crystalline structure cannot be formed. Such polymers form a glass instead of crystals. A glass is a solid material existing in a non-crystalline (*i.e.*, amorphous) state. Glass formation is due either to such rapid cooling from the melt that crystallization is prevented by quenching or to the lack of structural regularity in the molecules of the glass-forming material. At a low temperature, rotation around single bonds of the polymer chain becomes very difficult such that the polymer molecules become trapped in a chaotic, disordered, entangled state to form amorphous polymers. Glass-forming materials exhibit their typical hard, but brittle, glassy properties at temperatures considerably below the glass-transition temperature. Glasses are hard and stiff materials but are of low strength owing to a lack of molecular mobility in the network structures. A glass signifies a state matter rather than a chemical composition.

1. Inorganic and Organic Glasses

The best known and traditional glassy materials are inorganic glasses. Most inorganic glasses are based on the acidic oxides, such as SiO_2 (giving silicate glasses, such as quartz) and B_2O_3 (giving borate glasses). Commercial glasses are silicate based.

Amorphous organic polymers can also show glassy properties and are sometimes referred to as organic glasses. Polystyrene and poly(methyl methacrylate) (Plexiglas[®] from Rohm and Hass; Lucite[®] from DuPont) are good examples. Lucite[®] and Plexiglas[®] acrylic resins are frequently used for the embedment of specimen of many kinds for purpose of preservation and display.

2. Plasticizer

A plasticizer is a material that enhances the flexibility of the polymer with which it is mixed. It acts to facilitate relative movement of polymer molecules. The addition of a plasticizer to a polymer makes it more flexible, workable, or stretchable. The addition of a plasticizer to a polymer results in a reduction in the glass-transition temperature of the mixture. The plasticizer may be a liquid or solid or another polymer. Examples of plasticizers are glycerin, glyceryl triacetate (triacetin), dimethyl (or diethyl or dibutyl) phthalate, butylbenzylphthalate, diisononyl phthalate, di-(2-ethylhexyl) (or dibutyl) adipate, dibutyl sebacate, dibutyl subacetate, trioctylphosphate, poly(ethylene glycol), and propylene glycol.

Poly(vinyl chloride) (PVC) is a hard solid material used to make credit cards, pipes, house siding, etc. It is also used to make flexible blood bags. To make flexible PVC bags, a plasticizer is added. For example, mixing PVC with about 50–100 parts by weight of phthalate ester plasticizers

converts the polymer into leathery products. Diisononyl phthalates have been used at levels as high as 55% by weight to make PVC toys soft and pliable. Some PVC toys, such as teething rings and rattles, are designed to be chewed, and chewing may cause leaching small amounts of phthalates into children's mouths. Although the leached phthalate may not reach a level high enough to pose a risk of cancer or liver damage or interfere with the development of young children, it is necessary to avoid such unnecessary exposure by young children.

Since plasticizers reduce the stiffness of the polymer molecules, they increase the diffusion rate of drug molecules through the polymeric matrix or polymeric membranes (Baker & Heller, 1989). Nitro-Dur[®] has a matrix of PVP and poly(vinyl alcohol) plasticized by glycerol. Another commercial nitroglycerin transdermal patch from Health Chem contains a matrix of poly(vinyl chloride)–poly(vinyl acetate) copolymer which is plasticized by di-(2-ethylhexyl)phthalate and isopropyl palmitate. Colloidal silicon dioxide is used as an inert filler. The EVA copolymer in Ocuser[®] is plasticized with dioctylphthalate (Baker & Heller, 1989).

3. Glass-Transition Temperature T_g

The glass transition (glass-to-rubber transition or rubber-to-glass transition) is the dominant transition in amorphous polymers, which also occurs at the highest temperature (except when a liquid transition also occurs). At T_g , glassy polymers start segmental motion. Glass transitions also occur in the amorphous regions of crystalline polymers.

The temperature at which the transition occurs is the glass-transition temperature (T_g). Since the transition occurs over a temperature range, T_g is more precisely the temperature at which the maximum rate of change of the property being observed occurs. Since the transition is a manifestation of molecular motion, the value of T_g is dependent on the rate of testing.

Amorphous polymers at temperatures well below the T_g value are hard, stiff, glassy materials, although they may not necessarily be brittle. On the other hand, at temperatures well above T_g , polymers are rubbery. This is why the alternative name glass–rubber transition is given. Rubber (or elastomer) is a polymer which recovers completely and very quickly from great extension, up to 1000% or more. Rubber is elastic at normal temperatures but at extremely low temperatures (*e.g.*, in liquid nitrogen at $-196\text{ }^\circ\text{C}$) it becomes brittle and shatters into pieces when tapped with a hammer.

T_g values for linear organic polymers range from about $-100\text{ }^\circ\text{C}$ to above $300\text{ }^\circ\text{C}$. Although some organic polymers may be expected to have T_g values considerably above $300\text{ }^\circ\text{C}$, decomposition of the polymer occurs before the T_g is reached so that its value cannot be observed. Table 2.2 lists glass-transition temperatures of selected polymers. From the table, it should be obvious which polymers we can use to make chewable dosage forms.

Table 2.2 Glass-Transition Temperatures of Selected Polymers

Polymer	T_g ($^\circ\text{C}$)
Poly(ethylene oxide)	-55
Polyethylene	-20
Poly(vinyl chloride) (plasticized)*	-20
Poly(vinyl acetate)	25
Poly(ethyl methacrylate)	65
Poly(vinyl chloride)	87
Polystyrene	100
Poly(methyl methacrylate)	105

* Plasticized with dioctyl phthalate.

C. THERMOPLASTICS AND THERMOSETS

A thermoplastic polymer is a polymer that softens without chemical change and can be made to flow when it is heated. It hardens on cooling and retains the shape imposed at elevated temperature. Examples are polystyrene, polyethylene, and poly(vinyl chloride). The heating and cooling cycle can be repeated many times.

Thermosetting polymer is a polymer that can undergo chemical change to produce network polymer (*i.e.*, chemical crosslinking). Once a thermoset polymers are formed, they do not soften upon heating below their decomposition temperature.

D. HOT-MELT EXTRUSION TO MAKE THIN MEMBRANES

Hot-melt extrusion has been used for making films or fibers of polymers, such as high density polyethylene, dimethylaminoethyl methacrylate, neutral methacrylic acid esters, and hydroxylpropylcellulose. The main component of hot-melt extrusion equipment is an extruder, which is typically composed of a feeding hopper, barrel, screw, die, screw driving unit and a heating/cooling device (McGinity *et al.*, 2001).

Different zones of the barrel are pre-set to specific temperatures (see Figure 5.6). The active ingredients, the thermoplastic polymers and other processing aids, are blended before feeding into the barrel of the extruder through the hopper. A rotating screw then transfers the materials inside the heated barrel. The use of polymeric carriers usually requires the incorporation of a plasticizer into the formulation. This is to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the stability and physicochemical properties of the final product. The choice of a suitable plasticizer will depend on many factors such as plasticizer-polymer compatibility and plasticizer stability. Plasticizers used in hot-melt extruded systems are triacetin, citrate esters (*e.g.*, triethylcitrate), lidocaine HCl, and low molecular weight polyethylene glycols. One of the functions of plasticizers is to improve the flexibility, for example, of the films used in transdermal products.

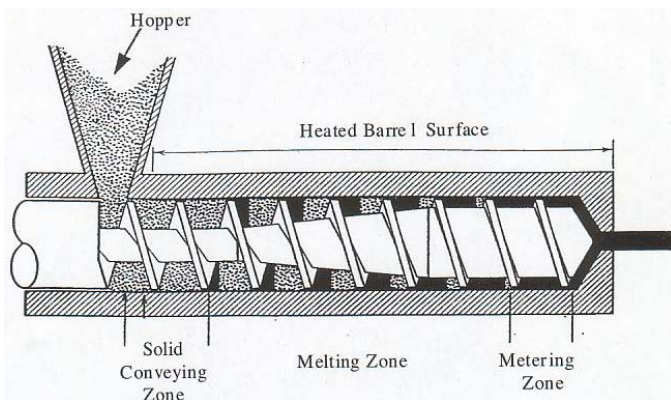


Figure 5.6 Schematic of an extruder illustrating various functional zones including the hopper, solid conveying zone, melting zone, metering zone, and die (McGinity *et al.*, 2001).

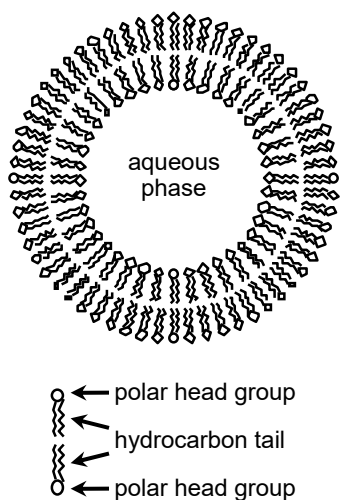


Figure 5.7 Schematic description of unilamellar liposome. Each phospholipid molecule consists of a hydrophilic (or polar) head group and a hydrophobic tail. The presence of two tails results in bilayer structure that is the same as the bilayer of cell membranes.

VIII. LIPOSOMES

A. PHOSPHOLIPID LIPOSOMES

Liposomes are vesicles composed of naturally occurring or synthetic phospholipids. Vesicles are spherical or ellipsoidal closed bilayer structures. The bilayer structure can be single- or multi-compartment. The size can also vary from smaller than $1\ \mu\text{m}$ to larger than $10\ \mu\text{m}$. The typical diameters of small unilamellar, large unilamellar, and multilamellar liposomes are $0.1\ \mu\text{m}$, $1\ \mu\text{m}$, and $5\ \mu\text{m}$, respectively. Schematic description of a unilamellar liposome is shown in Figure 5.7. The preparation of liposomes is shown schematically in Figure 5.8; examples of phospholipids are shown in Figure 5.9. Research on liposomes was quite active decades ago, as liposomes were used as a model for cellular bilayer. Recently, liposomes have been used for drug delivery and a few commercial products have been available. AmBisome[®], a liposomal formulation of amphotericin B from Gilead, was approved for use in the treatment of patients with systemic fungal infections.

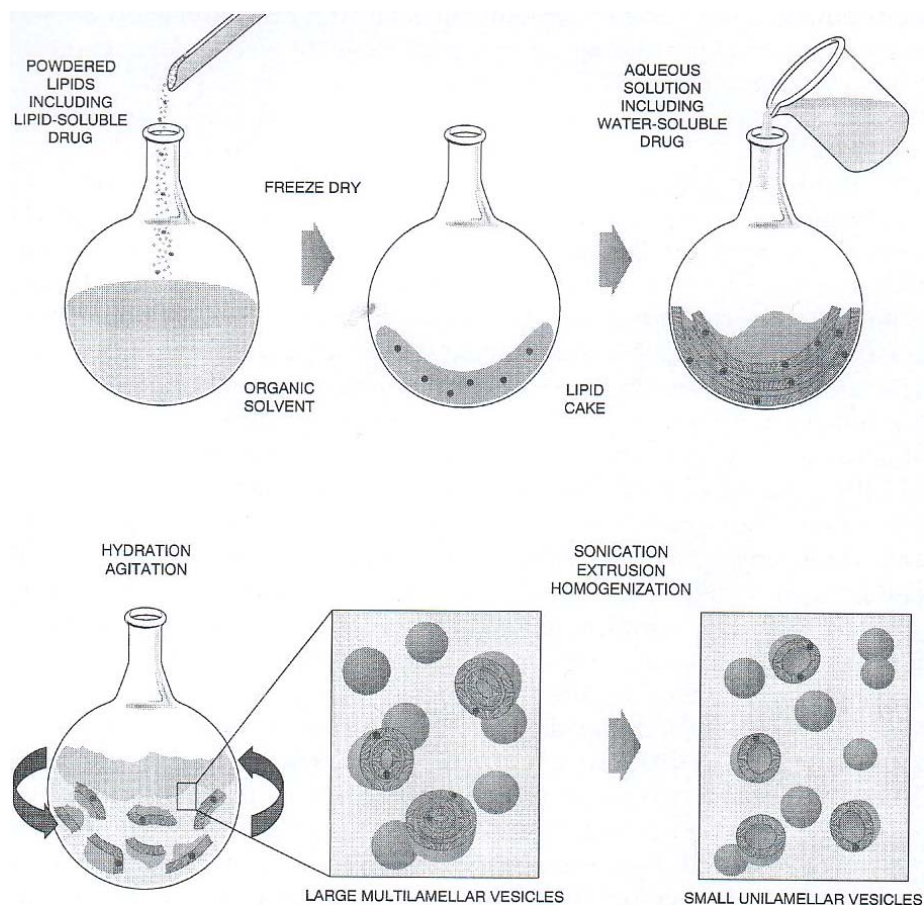


Figure 5.8 Schematic presentation of liposome preparation. Dry (or organic solutions of) lipids are dissolved (mixed) in an organic solvent. Following rotary evaporation and vacuum the thin lipid film is suspended in aqueous solution during shaking. LMVs are formed which can be sized down into SUVs by sonication or homogenization. (From DD Lasic *Sci. Am Sci Med* **3** 34–43 1996.)

Cochleates are solid, multilayered, crystalline structures composed of negatively charged lipid and divalent cations. They can be used to deliver peptides, proteins, and nucleic acids.

B. POLYMER-BASED LIPOSOMES (POLYMERSOMES)

Amphiphilic diblock copolymers in water can self-assemble into various ordered mesophases, notably lamellar structures (see Figure 5.10). Vesicles made from amphiphilic diblock copolymers, such as polyethyleneoxide–polyethylene (EO₄₀–EE₃₇), are called polymersomes (Discher *et*

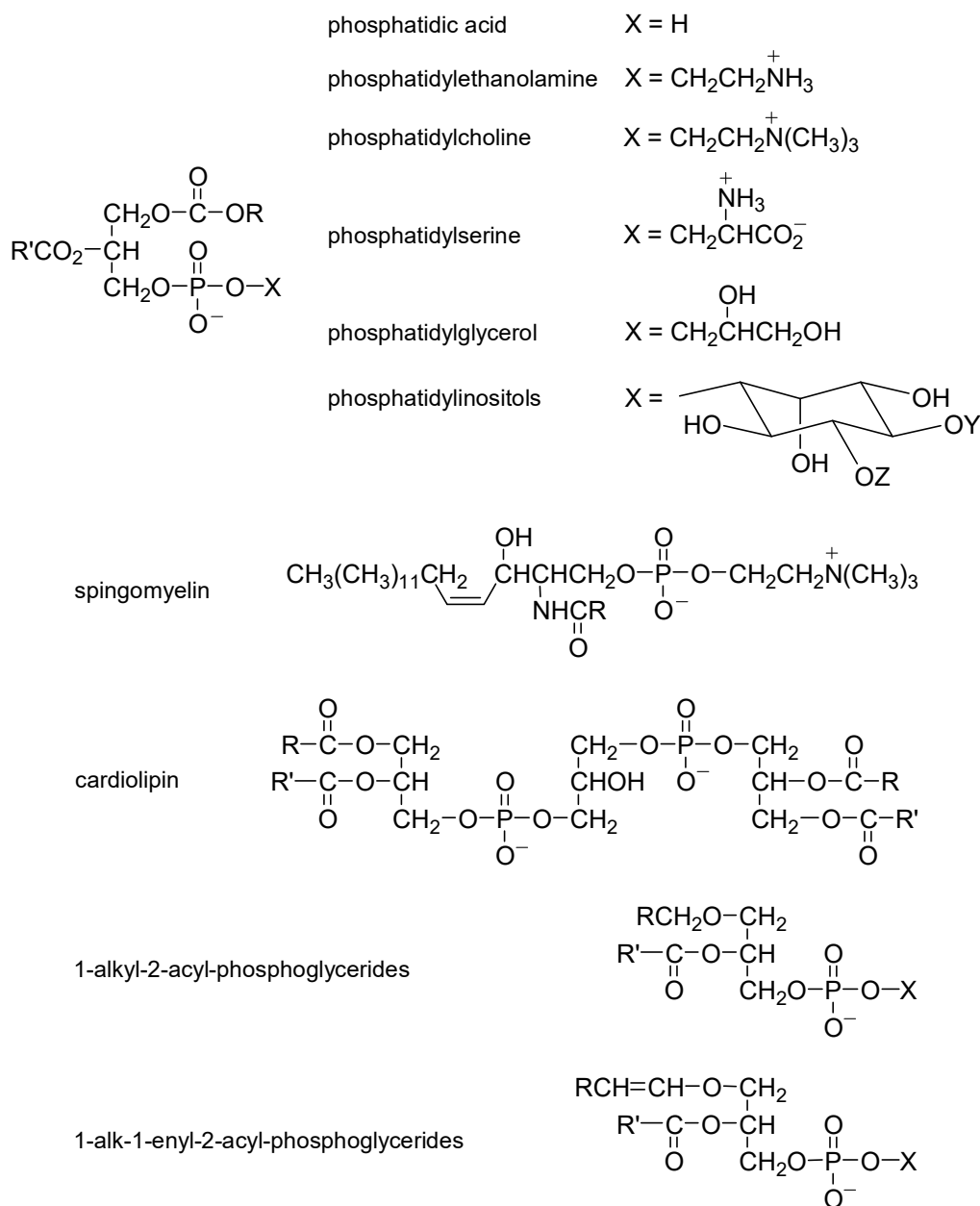


Figure 5.9 Typical phospholipids and fatty acid chains encountered in liposome work.

al., 1999). The polymersome membrane was at least ten times less permeable to water than common phospholipid bilayers.

IX. MICELLES

A. MICELLES OF SMALL MOLECULAR WEIGHT MOLECULES

Micelles are aggregates of detergent molecules in aqueous solution. Detergents are water-soluble, surface-active agents composed of a hydrophilic head group and a hydrophobic or lipophilic tail group. They can also align at aqueous/nonaqueous interfaces, reducing surface tension, increasing miscibility, and stabilizing emulsions.

Physical parameters are often used to describe detergents and determining their usefulness in pharmaceutical applications. The minimum concentration for self-aggregation of detergent molecules is known as the critical micellar concentration (CMC). The average number of detergent molecules in a micelle is called the aggregation number. Even above the CMC, micelle may not form if the temperature is too low. The minimum

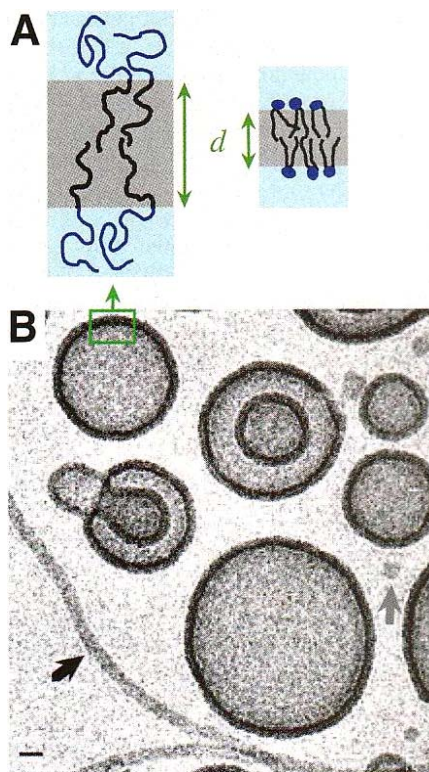


Figure 5.10 Molecular assemblies and copolymer structures in water. (A) Schematic representation of diblock copolymer EO₄₀–EE₃₇, also designated OE-7, with chain structure: *tert*-butyl-(CH₂CH(C₂H₅))₃₇(CH₂CH₂O)₄₀H. The number-average molecular weight is ~3900 g/mol. For a simple comparison of relative hydrophobic core thickness *d*, a bilayer of typical lipids are schematically shown next to the assembly of copolymers. (B) Aqueous suspensions of OE-7 vesicles in dominant coexistence with rod-like (black arrow) and spherical (gray arrow) micelles. Observations were made by cryo-TEM; the scale bar at lower left is 20 nm and the mean lamellar thickness is ~8 nm (Discher *et al.*, 1999).

Table 2.3 Selected examples of various micelle-forming detergents

Anionic	sodium dodecyl sulfate (SDS), deoxycholic acid, sodium
Cationic	hexadecyltrimethylammonium bromide
Zwitterionic	Lecithins (L- α -phosphatidylcholine)
Nonionic	Brij [®] 35 (polyoxyethylene 23 lauryl ether), Pluronic [®]

temperature for self-aggregation is called the critical micellar temperature (CMT). If temperature is increased higher than the CMT, some detergents aggregate into larger structures to scatter light, and the solution begins to look cloudy. This temperature is called the cloud point temperature (CPT). Examples of detergents are listed in Table 2.3.

B. POLYMERIC MICELLES

If a polymer is made of block copolymers of hydrophilic and hydrophobic segments, it tends to form a micelle. The hydrophilic polymer segment can be any water-soluble polymer, and the hydrophobic polymer segment can be any water-insoluble polymer.

C. NIOSOMES

Niosomes are unilamellar or multilamellar vesicles where, in an aqueous solution, they are enclosed in highly-ordered bilayers made up of nonionic surfactants with or without cholesterol or dicetyl phosphate and exhibit a behavior similar to liposomes *in-vivo* (Namdeo & Jain, 1996). Niosomes are supposed to give desirable interactions with human skin when applied in topical preparations by improving especially the horny layer characteristics, both by reducing trans-epidermal water loss and by increasing smoothness via replenishing lost skin lipids (Junginger, Hofland, & Bouwstra, 1991). Niosomes preparations constitute a more recently developed drug delivery system formed by hydration of mono- or di-alkyl surfactants that present chemical and physicochemical differences to liposomes, including a better stability and easier handling that makes them attractive as a vesicle-system for antigen release (Baillie *et al.*, 1985).

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ANSWERS

- (a) What did you observe after addition of borate into the PVA solution?

The PVA solution will go through a remarkable transformation into a gel.

- (b) What do you think is the mechanism? (*i.e.*, what kind of reaction occurred?)

PVA polymer strands are crosslinked by the borate through a complex structure of hydrogen bonds. The borate ions $[B(OH)_4^-]$ generated upon dissolution of borax are able to establish tetrafunctional interactions with the hydroxyl groups on PVA chains, thereby forming temporary, physical cross-links and generating the gel (*i.e.*, swollen network) structure. The borate ion cross-links are physical and not covalent and may be disrupted if sufficiently strained.

- (c) Take the gel out of the beaker, roll it into a cylinder, and hang a portion of the gelled cylinder over the edge of the desktop. What did you observe?

The PVA cylinder gel underwent the slow, irreversible elongation, eventually extending to the floor without rupture.

- (d) Roll the extended gel cylinder into a ball and drop it on the desk surface from a height of 60–100 cm (2–3 feet). What did you observe?

The gel ball bounces elastically several times before sticking to and spreading across the desk surface.

- (e) Roll the gel into another cylinder and attempt to abruptly extend the cylinder by quickly pulling on both of its ends. Were you able to extend the gel?

If pulled quickly enough, the gel cylinder will fail in a brittle manner with very little extension and sharp, flat fracture surfaces.

- (f) Why do you think that the same PVA gel behaved three different ways in three different experiments?

To summarize, the highly swollen PVA/borax gel responded in three distinct manners when stressed: (i) It flowed irreversibly when acted upon by gravity as it hung over or rested on the desk, (ii) it behaved elastically as it bounced several times on the desktop, and (iii) it evidenced brittle failure when rapid extension was attempted. Thus the response of the PVOH gel depended sensitively on the frequency of the deformational force. The temporary borate ion-hydroxyl group, physical cross-links were disrupted and reformed permitting overall irreversible flow of the gel under the steady, low-frequency gravitational force. When the PVOH ball was dropped on the desk, the brief time of impact with the desk was not sufficient to allow the disruption and reformation of the physical cross-links, so the gel ball behaved elastically by bouncing. The attempt to rapidly extend the PVOH gel cylinder led to brittle fracture, because the large extensional force was applied for a time insufficient to permit disruption and reformation of the temporary cross-links and achieve plastic flow or to even allow the PVOH chains between the cross-links to adopt more extended conformations and thereby respond elastically. In each instance the PVOH chains of the temporary, physical network attempted to change their conformations, thereby altering their sizes and shapes in response to stresses of various magnitudes and duration or frequency. Because of their large sizes and temporary connectivity, the PVA chains are unable to respond instantaneously and instead exhibit frequency- or time-dependent responses.