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Der Pharmacia Lettre, 2010: 2 (1) 172-180
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ISSN 0975-5071

USA CODEN: DPLEB4

Emerging trends in pharmaceutical polymers

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Abstract

Polymer science implements its applications in pharmacy and in other areas even in space research. A detailed research review has been undertaken taking care of emphasis in the field of pharmacy. Verifications have been conducted with regard to the different levels of synthesis, structure, configuration and properties of these macromolecules. Mechanism of gelling is diagrammatically exhibited and applications of polymers in pharmacy which include different dosage forms, packaging etc. have been revived. An awareness regarding this also have been discussed. Physical and chemical properties of polymers depend on the structural configuration which can be used to alter the drug release. Rheological properties are influenced greatly by the degree of polymerization.

Keywords: vulcanization, polydisperse, cis, trans, elastomers, solvated, prosthesis, micro encapsulation, osmotic pumps, transdermal.

Introduction

Polymers are a large class of materials consisting of many small molecules (called monomers) that can be linked together to form long chains, thus they are known as macromolecules. A typical polymer may include tens of thousands of monomers. In the late 1830s, Charles Goodyear succeeded in producing a useful form of natural rubber through a process known as "vulcanization." Some 40 years later, Celluloid (a hard plastic formed from nitrocellulose) was successfully commercialized. Despite these advances, progress in polymer science was slow until the 1930s, when materials such as vinyl, neoprene, polystyrene, and nylon were developed. The introduction of these revolutionary materials began an explosion in polymer research that is still going on today. Unmatched in the diversity of their properties, polymers such as cotton, wool, rubber, Teflon and all plastics are used in nearly every industry. Since the early 1990s, a number of polymer-protein conjugates have been approved for medical use by the FDA[1]. Polymer based drug delivery system include polymer protein conjugates, polymer-drug conjugates, micelles consisting of polymeric surfactants and complexes of cationic polymers of DNA[2]. Natural and synthetic

polymers can be produced with a wide range of stiffness, strength, heat resistance, density, and even price. With continued research into the science and applications of polymers, they are playing an ever increasing role in society. In pharmacy natural polymers are getting much attention over synthetic and semi synthetic polymers because of their biocompatibility and immunocompatibility. Some major ground breaking discoveries related to polymer science is exhibited in table 1[3-5].

Table 1. Historical developments in pharmaceutical polymer science

Year	Historical developments
1830	Charles Goodyear succeeded in producing a useful form of natural rubber through a process known as "vulcanization."
1930	Materials such as vinyl, neoprene, polystyrene, and nylon were developed.
1970	Use of biomaterials in controlled drug release systems were evoked.
1974	Theeuwes and Higuchi involved the principles of osmotic pressure based drug delivery systems.
1990	Number of polymer-protein conjugates have been approved for medical use by FDA.
2000 till date	Emerging respirocytes incorporating polymers.

Writing Formulas for Polymeric Macromolecules

The repeating structural unit of most simple polymers not only reflects the monomer(s) from which the polymers are constructed, but also provides a concise means for drawing structures to represent these macromolecules. For polyethylene, arguably the simplest polymer, this is demonstrated by the following equation. Here ethylene (ethene) is the monomer, and the corresponding linear polymer is called high-density polyethylene (HDPE). HDPE is composed of macromolecules in which n ranges from 10,000 to 100,000 (molecular weight 2×10^5 to 3×10^6). If Y and Z represent moles of monomer and polymer respectively, Z is approximately $10^{-5} Y$. This polymer is called polyethylene rather than polymethylene, $(-\text{CH}_2-)_n$, because ethylene is a stable compound (methylene is not), and it also serves as the synthetic precursor of the polymer. The two open bonds remaining at the ends of the long chain of carbons (colored magenta) are normally not specified, because the atoms or groups found there depend on the chemical process used for polymerization. Unlike simpler pure compounds, most polymers are not composed of identical molecules. The HDPE molecules, for example, are all long carbon chains, but the lengths may vary by thousands of monomer units. Because of this, polymer molecular weights are usually given as averages. Two experimentally determined values are common: M_n , the number average molecular weight, is calculated from the mole fraction distribution of different sized molecules in a sample, and M_w , the weight average molecular weight, is calculated from the weight fraction distribution of different sized molecules. Since larger molecules in a sample weigh more than smaller molecules, the weight average M_w is necessarily skewed to higher values, and is always greater than M_n . As the weight dispersion of molecules in a sample narrows, M_w approaches M_n , and in the unlikely case that all the polymer molecules have identical weights (a pure monodisperse sample), the ratio M_w / M_n becomes unity.

Polymer Synthesis

Polymer synthesis is a complex procedure and can take place in a variety of ways. Addition polymerization describes the method where monomers are added one by one to an active site on the growing chain [6].

Initiation Reaction

The first step in producing polymers by free radical polymerization is initiation. This step begins when an initiator decomposes into free radicals in the presence of monomers. The instability of carbon-carbon double bonds in the monomer makes them susceptible to reaction with the unpaired electrons in the radical. In this reaction, the active center of the radical "grabs" one of the electrons from the double bond of the monomer, leaving an unpaired electron to appear as a new active center at the end of the chain. Addition can occur at either end of the monomer.

In a typical synthesis, between 60% and 100% of the free radicals undergo an initiation reaction with a monomer. The remaining radicals may join with each other or with an impurity instead of with a monomer. "Self destruction" of free radicals is a major hindrance to the initiation reaction. By controlling the monomer to radical ratio, this problem can be reduced.

Propagation Reaction

In the propagation stage, the process of electron transfer and consequent motion of the active center down the chain proceeds. In this diagram, (chain) refers to a chain of connected monomers, and X refers to a substituent group (a molecular fragment) specific to the monomer. For example, if X were a methyl group, the monomer would be propylene and the polymer, polypropylene. In free radical polymerization, the entire propagation reaction usually takes place within a fraction of a second. Thousands of monomers are added to the chain within this time. The entire process stops when the termination reaction occurs.

Termination Reaction

In theory, the propagation reaction could continue until the supply of monomers is exhausted. However, this outcome is very unlikely. Most often the growth of a polymer chain is halted by the termination reaction. Termination typically occurs in two ways: combination and disproportionation. Combination occurs when the polymer's growth is stopped by free electrons from two growing chains that join and form a single chain. Disproportionation halts the propagation reaction when a free radical strips a hydrogen atom from an active chain. A carbon-carbon double bond takes the place of the missing hydrogen. Disproportionation can also occur when the radical reacts with an impurity. This is why it is so important that polymerization be carried out under very clean conditions.

Living Polymerization

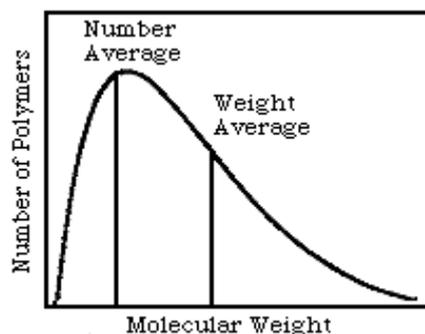
There exists a type of addition polymerization that does not undergo a termination reaction. This so-called "living polymerization" continues until the monomer supply has been exhausted. When this happens, the free radicals become less active due to interactions with solvent molecules. If more monomers are added to the solution, the polymerization will resume. Uniform molecular weights (low polydispersity) are characteristic of living polymerization. Because the supply of monomers is controlled, the chain length can be manipulated to serve the needs of a specific application. This assumes that the initiator is 100% efficient.

Statistical Analysis of Polymers

When dealing with millions of molecules in a tiny droplet, statistical methods must be employed to make generalizations about the characteristics of the polymer. It can be assumed in polymer synthesis, each chain reacts independently. Therefore, the bulk polymer is characterized by a wide distribution of molecular weights and chain lengths. The degree of polymerization (DP) refers to the number of repeat units in the chain, and gives a measure of molecular weight. Many important properties of the final result are determined primarily from the distribution of lengths and the degree of polymerization [7].

In order to characterize the distribution of polymer lengths in a sample, two parameters are defined: number average and weight average molecular weight. The number average is just the sum of individual molecular weights divided by the number of polymers. The weight average is proportional to the square of the molecular weight. Therefore, the weight average is always larger than the number average. The following graph shows a typical distribution of polymers including the weight and number average molecular weights.

Fig. 1: Distribution of polymers including weight and number average molecular weights



It is described that the molecular weight of a polymer can also be represented by the viscosity average molecular weight. This form of the molecular weight is found as a function of the viscosity of the polymer in solution (viscosity determines the rate at which the solution flows - the slower a solution moves, the more viscous it is said to be - and the polymer molecular weight influences the viscosity). The degree of polymerization has a dramatic effect on the mechanical properties of a polymer. As chain length increases, mechanical properties such as ductility, tensile strength, and hardness rise sharply and eventually level off (Fig 1).

Polymer Structure

Although the fundamental property of bulk polymers is the degree of polymerization, the physical structure of the chain is also an important factor that determines the macroscopic properties. The terms configuration and conformation are used to describe the geometric structure of a polymer. Configuration refers to the order that is determined by chemical bonds. The configuration of a polymer cannot be altered unless chemical bonds are broken and reformed. Conformation refers to order that arises from the rotation of molecules about the single bonds.

Configuration

The two types of polymer configurations are cis and trans. These structures can not be changed by physical means (e.g. rotation). The cis configuration arises when substituent groups are on the same side of a carbon-carbon double bond. Trans refers to the substituents

on opposite sides of the double bond. Stereo regularity is the term used to describe the configuration of polymer chains. Three distinct structures can be obtained. Isotactic is an arrangement where all substituents are on the same side of the polymer chain. A syndiotactic polymer chain is composed of alternating groups and atactic is a random combination of the groups. The following diagram shows two of the three stereo isomers of polymer chain.

Cross-Linking

In addition to the bonds which hold monomers together in a polymer chain, many polymers form bonds between neighboring chains. These bonds can be formed directly between the neighboring chains, or two chains may bond to a third common molecule. Though not as strong or rigid as the bonds within the chain, these cross-links have an important effect on the polymer. Polymers with a high enough degree of cross-linking have "memory." When the polymer is stretched, the cross-links prevent the individual chains from sliding past each other. The chains may straighten out, but once the stress is removed they return to their original position and the object returns to its original shape. One example of cross-linking is vulcanization . In vulcanization, a series of cross-links are introduced into an elastomer to give it strength. This technique is commonly used to strengthen rubber.

Classes of Polymers

Elastomers, or rubbery materials, have a loose cross-linked structure. This type of chain structure causes elastomers to possess memory. Typically, about 1 in 100 molecules are cross-linked on average. When the average number of cross-links rises to about 1 in 30 the material becomes more rigid and brittle. Natural and synthetic rubbers are both common examples of elastomers. Plastics are polymers which, under appropriate conditions of temperature and pressure, can be molded or shaped (such as blowing to form a film). In contrast to elastomers, plastics have a greater stiffness and lack reversible elasticity. All plastics are polymers but not all polymers are plastics. Cellulose is an example of a polymeric material which must be substantially modified before processing with the usual methods used for plastics. Some plastics, such as nylon and cellulose acetate, are formed into fibers (which are regarded by some as a separate class of polymers in spite of a considerable overlap with plastics). Every day plastics such as polyethylene and poly (vinyl chloride) have replaced traditional materials like paper and copper for a wide variety of applications.

Polymer Morphology

Molecular shape and the way molecules are arranged in a solid are important factors in determining the properties of polymers. From polymers that crumble to the touch to those used in bullet proof vests, the molecular structure, conformation and orientation of the polymers can have a major effect on the macroscopic properties of the material. The general concept of self-assembly enters into the organization of molecules on the micro and macroscopic scale as they aggregate into more ordered structures.

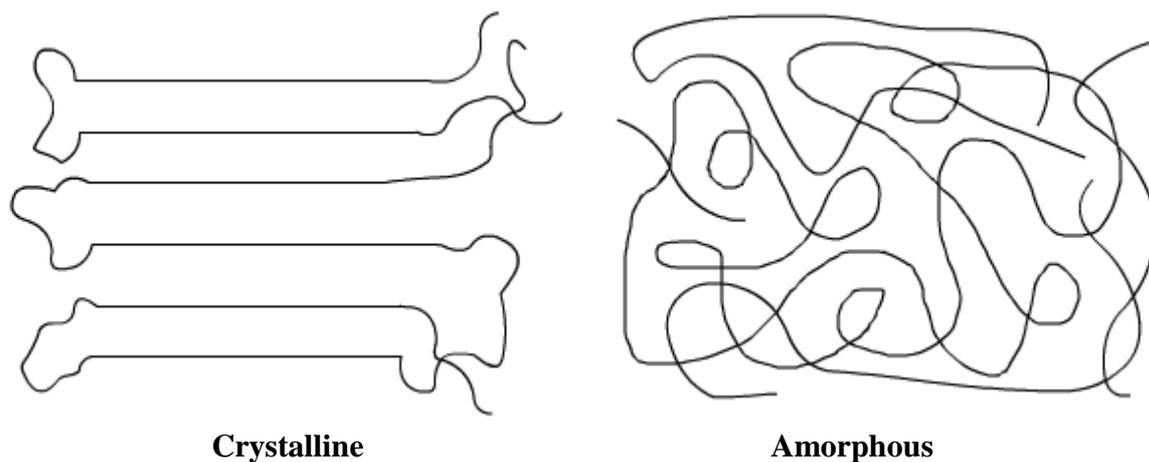
Crystallinity

We need to distinguish here, between crystalline and amorphous materials and then show how these forms coexist in polymers. Consider a comparison between glass, an amorphous material, and ice which is crystalline. Despite their common appearance as hard, clear material, capable of being melted.

An amorphous solid is formed when the chains have little orientation throughout the bulk polymer. The glass transition temperature is the point at which the polymer hardens into an amorphous solid. This term is used because the amorphous solid has properties similar to

glass. In the crystallization process, it has been observed that relatively short chains organize themselves into crystalline structures more readily than longer molecules. Therefore, the degree of polymerization (DP) is an important factor in determining the crystallinity of a polymer. Polymers with a high DP have difficulty organizing into layers because they tend to become tangled.

Fig. 2: Difference in morphology of amorphous and crystalline structure



The cooling rate also influences the amount of crystallinity. Slow cooling provides time for greater amounts of crystallization to occur. Fast rates, on the other hand, such as rapid quenches, yield highly amorphous materials. Subsequent annealing (heating and holding at an appropriate temperature below the crystalline melting point, followed by slow cooling) will produce a significant increase in crystallinity in most polymers, as well as relieving stresses.

Low molecular weight polymers (short chains) are generally weaker in strength. In most polymers, the combination of crystalline and amorphous structures forms a material with advantageous properties of strength and stiffness. Also influencing the polymer morphology is the size and shape of the monomers' substituent groups. If the monomers are large and irregular, it is difficult for the polymer chains to arrange themselves in an ordered manner, resulting in a more amorphous solid. Likewise, smaller monomers, and monomers that have a very regular structure (e.g. rod-like) will form more crystalline polymers (Fig 2).

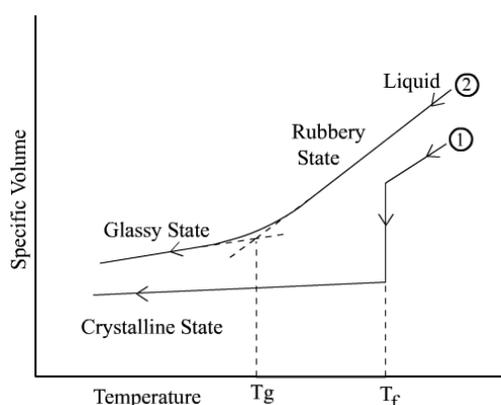
Polymer Glass Transition

As the temperature of a polymer drops below T_g , it behaves in an increasingly brittle manner. As the temperature rises above the T_g , the polymer becomes more rubber-like. Thus, knowledge of T_g is essential in the selection of materials for various applications. In general, values of T_g well below room temperature define the domain of elastomers and values above room temperature define rigid, structural polymers.

This behavior can be understood in terms of the structure of glassy materials which are formed typically by substances containing long chains, networks of linked atoms or those that possess a complex molecular structure. Normally such materials have a high viscosity in the liquid state. When rapid cooling occurs to a temperature at which the crystalline state is expected to be the more stable, molecular movement is too sluggish or the geometry too awkward to take up a crystalline conformation. Therefore the random arrangement

characteristic of the liquid persists down to temperatures at which the viscosity is so high that the material is considered to be solid. The term glassy has come to be synonymous with a persistent non-equilibrium state. In fact, a path to the state of lowest energy might not be available. To become more quantitative about the characterization of the liquid-glass transition phenomenon and T_g , we note that in cooling an amorphous material from the liquid state, there is no abrupt change in volume such as occurs in the case of cooling of a crystalline material through its freezing point, T_f . Instead, at the glass transition temperature, T_g , there is a change in slope of the curve of specific volume vs. temperature, moving from a low value in the glassy state to a higher value in the rubbery state over a range of temperatures. This comparison between a crystalline material (1) and an amorphous material (2) is illustrated in the figure below (Fig. No.3). Note that the intersections of the two straight line segments of curve (2) define the quantity T_g .

Fig. No. 3: Effect of temperature on morphology of polymers

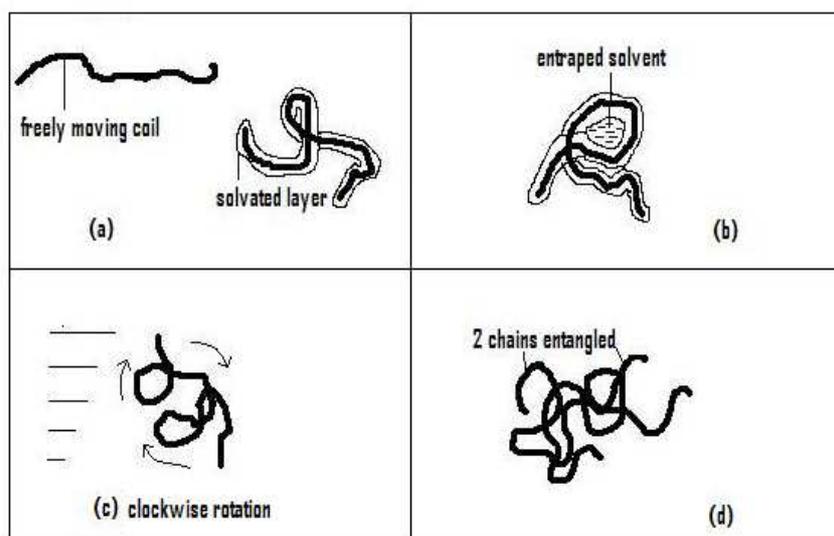


The specific volume measurements shown here, made on an amorphous polymer (2), are carried out in a dilatometer at a slow heating rate. In this apparatus, a sample is placed in a glass bulb and a confining liquid, usually mercury, is introduced into the bulb so that the liquid surrounds the sample and extends partway up a narrow bore glass capillary tube. A capillary tube is used so that relatively small changes in polymer volume caused by changing the temperature produce easily measured changes in the height of the mercury in the capillary. While the dilatometer method is the more precise method of determining the glass transition temperature, it is a rather tedious experimental procedure and measurements of T_g are often made in a differential scanning calorimeter (DSC). In this instrument, the heat flow into or out of a small (10 – 20 mg) sample is measured as the sample is subjected to a programmed linear temperature change. There are other methods of measurement such as density, dielectric constant and elastic modulus. Several approaches explain the thickening phenomena which alters the rheology of a polymer solution.

Formation of solvated layer – A random coil solution consists of approximately 0.01 % polymer and 99.9 % solvent. Methyl cellulose has 3-4 ether groups and 1-2 hydroxyl groups that are excessively hydrated in aqueous solution. Ether oxygen has two unshared electron pairs and therefore binds with 2 water molecules by hydrogen bond. Each of these water molecules can bond with additional water molecules. Thus surrounding the polymer chain there forms a sheath of water of hydration. These bonded solvated structures cannot move as freely as they were in an unbonded state (Fig 4a). **Solvent entrapment**- A portion of solvent is mechanically trapped and has to be dragged along when the macromolecule chain moves. Thus some of the non-solvating solvent forms part of the unit increasing its size and frictional

resistance contributing more thickening action (Fig 4b). Clock wise rotation – according to Newton solvent is of several thin layers. Relative motion of each layer is proportional to the distance from the walls of the container which is related to frictional resistance. Therefore, the top layer has maximum flow and the bottom layer is exhibiting the least velocity. The upper portion of the random coil is subjected to greater shear stress than the lower portion. The resulting couple causes the random coil to rotate clockwise which further increases the frictional resistance (Fig 4c). Interpenetration of neighbouring chains – Thermal agitation of solvent molecules and great chain flexibility causes the neighbouring polymer chains to penetrate and become entangled to form a mass which increases resistance [8].

Fig. No. 4: Different representations of approaches responsible for the thickening of polymer solution



Pharmaceutical and medical applications of polymers

Cardiovascular implants, Vascular Prostheses, Heart valve prostheses, Cardiac Replacement, Hard tissue Replacement, Dental Material, Orthopedic and Bone-Contacting materials, Soft Tissue Replacement, Wound Dressings And Artificial Skin, Applications of Polymeric Systems. In drug delivery, film coating, matrices, micro encapsulation and microspheres, rate limiting membrane and devices, implants of silicon rubber or any other polymeric material in drug is embedded can be designed by choice of polymer, membrane thickness and porosity, to release drug at pre selected rates, eroding systems, osmotic pumps for oral administration, gastroretentive mucoadhesive/ floating systems and excipients [9-15].

Conclusion

Poly macromolecules play an important role in enhancing the quality and standard of dosage form design and thus improving the patient compliance. Physical and chemical properties of polymers depend on the structural configuration which can be used to alter the drug release. Rheological properties are influenced greatly by the degree of polymerization. Proper modulation of the morphology can be suitable to reach the goal of a pharmacist in formulation.

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