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2.5 HYDROGELS

Nicholas A. Peppas

Hydrogels are water-swollen, cross-linked polymeric structures containing either covalent bonds produced by the simple reaction of one or more comonomers, physical cross-links from entanglements, association bonds such as hydrogen bonds or strong van der Waals interactions between chains (Peppas, 1987), or crystallites bringing together two or more macromolecular chains (Hickey and Peppas, 1995). Hydrogels have received significant attention because of their exceptional promise in biomedical applications. The classic book by Andrade (1976) offers some of the best work that was available prior to 1975. The more recent book and other reviews by Peppas (1987, 2001) addresses the preparation, structure, and characterization of hydrogels.

Here, we concentrate on some features of the preparation of hydrogels, as well as characteristics of their structure and chemical and physical properties.

CLASSIFICATION AND BASIC STRUCTURE

Depending on their method of preparation, ionic charge, or physical structure features, hydrogels maybe classified in several categories. Based on the method of preparation, they may be (i) homopolymer hydrogels, (ii) copolymer hydrogels, (iii) multipolymer hydrogels, or (iv) interpenetrating polymeric hydrogels. Homopolymer hydrogels are cross-linked networks of one type of hydrophilic monomer unit, whereas copolymer hydrogels are produced by cross-linking of two comonomer units, at least one of which must be hydrophilic to render them swellable. Multipolymer hydrogels are produced from three or more comonomers reacting together (see e.g., Lowman and Peppas, 1997, 1999). Finally, interpenetrating polymeric hydrogels are produced by preparing a first network that

is then swollen in a monomer. The latter reacts to form a second intermeshing network structure. Based on their ionic charges, hydrogels may be classified (Ratner and Hoffman, 1976; Brannon-Peppas and Harland, 1990) as (i) neutral hydrogels, (ii) anionic hydrogels, (iii) cationic hydrogels, or (iv) ampholytic hydrogels. Based on physical structural features of the system, they can be classified as (i) amorphous hydrogels, (ii) semicrystalline hydrogels, or (iii) hydrogen-bonded or complexation structures. In amorphous hydrogels, the macromolecular chains are arranged randomly. Semicrystalline hydrogels are characterized by dense regions of ordered macromolecular chains (crystallites). Finally, hydrogen bonds and complexation structures may be responsible for the three-dimensional structure formed.

Structural evaluation of hydrogels reveals that ideal networks are only rarely observed. Figure 1A shows an ideal macromolecular network (hydrogel) indicating tetrafunctional cross-links (junctions) produced by covalent bonds. However, in real networks it is possible to encounter multifunctional junctions (Fig. 1B) or physical molecular entanglements (Fig. 1C) playing the role of semipermanent junctions. Hydrogels with molecular defects are always possible. Figures 1D and 1E indicate two such effects: unreacted functionalities with partial entanglements (Fig. 1D) and chain loops (Fig. 1E). Neither of these effects contributes to the mechanical or physical properties of a polymer network.

The terms “cross-link,” “junction,” or “tie-point” (an open circle symbol in Fig. 1D) indicate the connection points of several chains. These junctions may be carbon atoms, but they are usually small chemical bridges [e.g., an acetal bridge in the case of cross-linked poly(vinyl alcohol)] with molecular weights much smaller than those of the cross-linked polymer chains. In other situations, a junction may be an association of macromolecular chains caused by van der Waals forces, as in the case of the glycoprotein network structure of natural mucus, or an aggregate formed by hydrogen bonds, as in the case of aged microgels formed in polymer solutions.

Finally, the network structure may include effective junctions that can be either simple physical entanglements of permanent or semipermanent nature, or ordered chains forming crystallites. Thus, the junctions should never be considered as points without volume, which is the usual assumption made when developing structural models for analysis of the cross-linked structure of hydrogels (Flory, 1953). Instead, they have a finite size and contribute to the deformational distribution during biomedical applications.

PREPARATION

Hydrogels are prepared by swelling cross-linked structures in water or biological fluids. Water or aqueous solutions may be present during the initial preparation of the cross-linked structure. Methods of preparation of the initial networks include chemical cross-linking, photopolymerization, or irradiative cross-linking (Peppas *et al.*, 2000).

Chemical cross-linking calls for direct reaction of a linear or branched polymer with at least one difunctional,

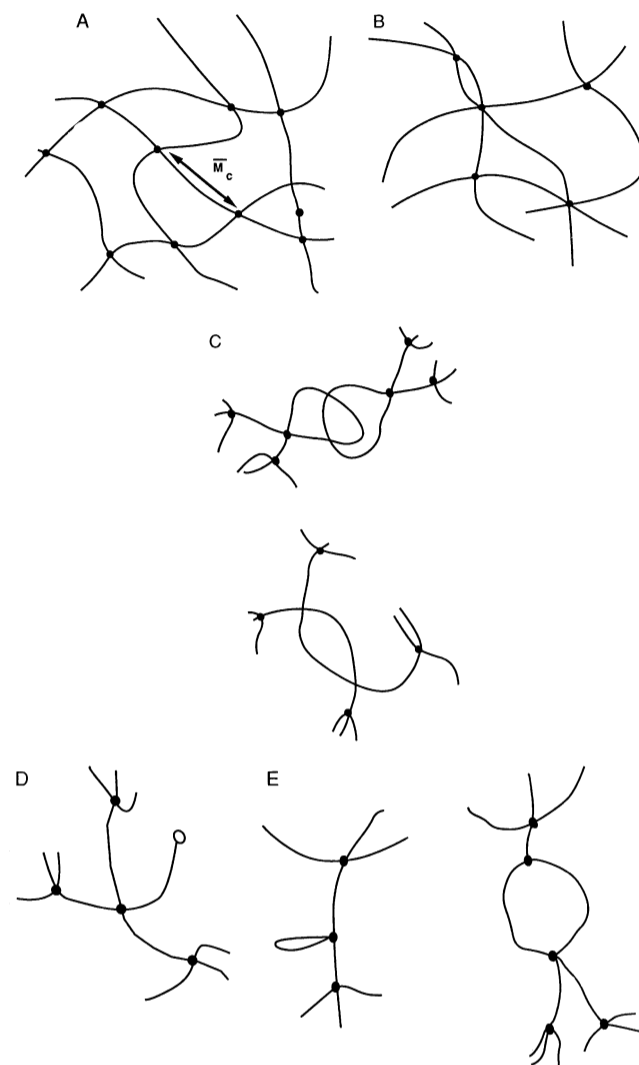


FIG. 1. (A) Ideal macromolecular network of a hydrogel. (B) Network with multifunctional junctions. (C) Physical entanglements in a hydrogel. (D) Unreacted functionality in a hydrogel. (E) Chain loops in a hydrogel.

small molecular weight, cross-linking agent. This agent usually links two longer molecular weight chains through its di- or multifunctional groups. A second method involves a copolymerisation-cross-linking reaction between one or more abundant monomers and one multifunctional monomer that is present in relatively small quantities. A third method involves using a combination of monomer and linear polymeric chains that are cross-linked by means of an interlinking agent, as in the production of polyurethanes. Several of these techniques can be performed in the presence of UV light leading to rapid formation of a three-dimensional network. Ionizing radiation cross-linking (Chapiro, 1962) utilizes electron beams, gamma rays, or X-rays to excite a polymer and produce a cross-linked structure via free radical reactions.

SWELLING BEHAVIOR

The physical behavior of hydrogels is dependent on their equilibrium and dynamic swelling behavior in water, since upon preparation they must be brought in contact with water to yield the final, swollen network structure. Figure 2 shows one of two possible processes of swelling. A dry, hydrophilic cross-linked network is placed in water. Then, the macromolecular chains interact with the solvent molecules owing to the relatively good thermodynamic compatibility. Thus, the network expands to the solvated state.

The Flory-Huggins theory can be used to calculate thermodynamic quantities related to that mixing process. Flory (1953) developed the initial theory of the swelling of cross-linked polymer gels using a Gaussian distribution of the polymer chains. His model describing the equilibrium degree of cross-linked polymers postulated that the degree to which a polymer network swelled was governed by the elastic retractive forces of the polymer chains and the thermodynamic compatibility of the polymer and the solvent molecules. In terms of the free energy of the system, the total free energy change upon swelling was written as:

$$\Delta G = \Delta G_{\text{elastic}} + \Delta G_{\text{mix}} \quad (1)$$

Here, $\Delta G_{\text{elastic}}$ is the contribution due to the elastic retractive forces and ΔG_{mix} represents the thermodynamic compatibility of the polymer and the swelling agent (water).

Upon differentiation of Eq. 1 with respect to the water molecules in the system, an expression can be derived for the chemical potential change of water in terms of the elastic and mixing contributions due to swelling.

$$\mu_1 - \mu_{1,0} = \Delta\mu_{\text{elastic}} + \Delta\mu_{\text{mix}} \quad (2)$$

Here, μ_1 is the chemical potential of water within the gel and $\mu_{1,0}$ is the chemical potential of pure water.

At equilibrium, the chemical potentials of water inside and outside of the gel must be equal. Therefore, the elastic and mixing contributions to the chemical potential will balance one another at equilibrium. The chemical potential change upon mixing can be determined from the heat of mixing and the entropy of mixing. Using the Flory-Huggins theory, the

chemical potential of mixing can be expressed as:

$$\Delta\mu_{\text{mix}} = RT \left(\ln(1 - 2v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}^2 \right) \quad (3)$$

where χ_1 is the polymer-water interaction parameter, $v_{2,s}$ is the polymer volume fraction of the gel, T is absolute temperature, and R is the gas constant.

This thermodynamic swelling contribution is counterbalanced by the retractive elastic contribution of the cross-linked structure. The latter is usually described by the rubber elasticity theory and its variations (Peppas, 1987). Equilibrium is attained in a particular solvent at a particular temperature when the two forces become equal. The volume degree of swelling, Q (i.e., the ratio of the actual volume of a sample in the swollen state divided by its volume in the dry state), can then be determined from Eq. 4.

$$v_{2,s} = \frac{\text{Volume of polymer}}{\text{Volume of swollen gel}} = \frac{V_p}{V_{\text{gel}}} = 1/Q \quad (4)$$

Researchers working with hydrogels for biomedical applications prefer to use other parameters in order to define the equilibrium-swelling behavior. For example, Yasuda *et al.* (1969) introduced the use of the so-called hydration ratio, H , which has been accepted by those researchers who use hydrogels for contact lens applications (Peppas and Yang, 1981). Another definition is that of the weight degree of swelling, q , which is the ratio of the weight of the swollen sample to that of the dry sample.

In general, highly swollen hydrogels include those of cellulose derivatives, poly(vinyl alcohol), poly(*N*-vinyl-2-pyrrolidone) (PNVP), and poly(ethylene glycol), among others. Moderately and poorly swollen hydrogels are those of poly(hydroxyethyl methacrylate) (PHEMA) and many of its derivatives. In general, a basic hydrophilic monomer can be copolymerized with other more or less hydrophilic monomers to achieve desired swelling properties. Such processes have led to a wide range of swellable hydrogels, as Gregonis *et al.* (1976), Peppas (1987, 1997), and others have pointed out. Knowledge of the swelling characteristics of a polymer is of utmost importance in biomedical and pharmaceutical applications since the equilibrium degree of swelling influences (i) the solute diffusion coefficient through these hydrogels, (ii) the surface properties and surface mobility, (iii) the optical properties,

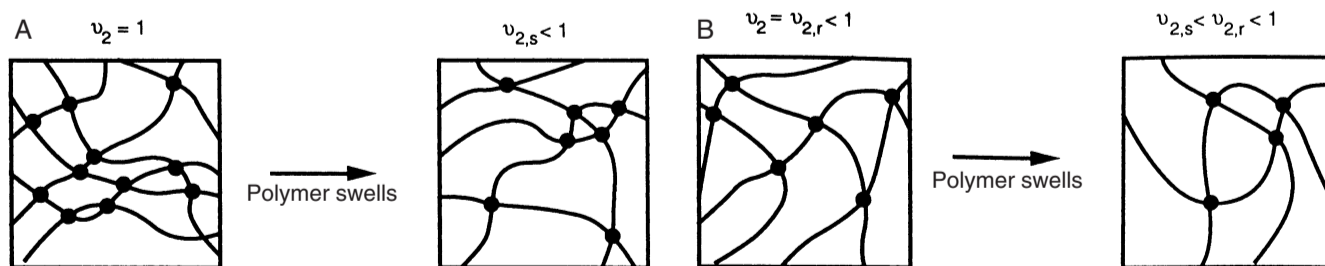


FIG. 2. (A) Swelling of a network prepared by cross-linking in dry state. (B) Swelling of a network prepared by cross-linking in solution.

especially in relation to contact lens applications, and (iv) the mechanical properties.

DETERMINATION OF STRUCTURAL CHARACTERISTICS

The parameter that describes the basic structure of the hydrogel is the molecular weight between cross-links, \bar{M}_c (as shown in Fig. 1a). This parameter defines the average molecular size between two consecutive junctions regardless of the nature of those junctions and can be calculated by Eq. 5.

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_c} - \frac{(v/V_1) [\ln(1 - v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}^2]}{(v_{2,s}^{1/3} - v_{2,s}/2)} \quad (5)$$

An additional parameter of importance in structural analysis of hydrogels is the cross-linking density, ρ_x , which is defined by Eq. 6.

$$\rho_x = \frac{1}{\bar{v}\bar{M}_c} \quad (6)$$

In these equations, v is the specific volume of the polymer (i.e., the reciprocal of the amorphous density of the polymer), and \bar{M}_n is the initial molecular weight of the un-cross-linked polymer.

PROPERTIES OF IMPORTANT BIOMEDICAL HYDROGELS

The multitude of hydrogels available leaves numerous choices for polymeric formulations. The best approach for developing a hydrogel with the desired characteristics for biomedical application is to correlate the macromolecular structures of the polymers available with the swelling and mechanical characteristics desired (Peppas *et al.*, 2000; Peppas, 2001).

The most widely used hydrogel is water-swollen, cross-linked PHEMA, which was introduced as a biological material by Wichterle and Lim (1960). The hydrogel is inert to normal biological processes, shows resistance to degradation, is permeable to metabolites, is not absorbed by the body, is biocompatible, withstands heat sterilization without damage, and can be prepared in a variety of shapes and forms.

The swelling, mechanical, diffusional, and biomedical characteristics of PHEMA gels have been studied extensively. The properties of these hydrogels are dependent upon their method of preparation, polymer volume fraction, degree of cross-linking, temperature, and swelling agent.

Other hydrogels of biomedical interest include polyacrylamides. Tanaka (1979) has done extensive studies on the abrupt swelling and deswelling of partially hydrolyzed acrylamide gels with changes in swelling agent composition, curing time, degree of cross-linking, degree of hydrolysis, and temperature. These studies have shown that the ionic groups produced in an acrylamide gel upon hydrolysis give the gel

a structure that shows a discrete transition in equilibrium-swollen volume with environmental changes.

Discontinuous swelling in partially hydrolyzed polyacrylamide gels has been studied by Gehrke *et al.* (1986). Besides HEMA and acrylamides, *N*-vinyl-2-pyrrolidone (NVP), methacrylic acid (MAA), methyl methacrylate (MMA), and maleic anhydride (MAH) have all been proven useful as monomers for hydrogels in biomedical applications. For instance, cross-linked PNVP is used in soft contact lenses. Small amounts of MAA as a comonomer have been shown to dramatically increase the swelling of PHEMA polymers. Owing to the hydrophobic nature of MMA, copolymers of MMA and HEMA have a lower degree of swelling than pure PHEMA (Brannon-Peppas and Peppas, 1991). All of these materials have potential use in advanced technology applications, including biomedical separations, and biomedical and pharmaceutical devices.

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INTELLIGENT OR SMART HYDROGELS

Hydrogels may exhibit swelling behavior dependent on the external environment. Over the past 30 years there has been a significant interest in the development and analysis of environmentally or physiologically responsive hydrogels (Peppas, 1991). Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, enzymatic or chemical reaction, and electrical or magnetic stimuli (Peppas, 1993). In most responsive networks, a critical point exists at which this transition occurs.

An interesting characteristic of numerous responsive gels is that the mechanism causing the network structural changes can be entirely reversible in nature. The ability of pH- or temperature-responsive gels to exhibit rapid changes in their swelling behavior and pore structure in response to changes in environmental conditions lend these materials favorable characteristics as carriers for bioactive agents, including peptides and proteins. This type of behavior may allow these materials to serve as self-regulated, pulsatile drug delivery systems.

pH-Sensitive Hydrogels

One of the most widely studied types of physiologically responsive hydrogels is pH-responsive hydrogels. These hydrogels are swollen ionic networks containing either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize developing fixed charges on the gel. All ionic materials exhibit a pH and ionic strength sensitivity. The swelling forces developed in these systems are increased over those of nonionic materials. This increase in swelling force is due to the localization of fixed charges on the pendant groups. As a result, the mesh size of the polymeric networks can change significantly with small pH changes.

Temperature Sensitive Hydrogels

Another class of environmentally sensitive gels exhibits temperature-sensitive swelling behavior due to a change in the polymer/swelling agent compatibility over the temperature range of interest. Temperature-sensitive polymers typically exhibit a lower critical solution temperature (LCST), below which the polymer is soluble. Above this temperature, the polymers are typically hydrophobic and do not swell significantly in water (Kim, 1996). However, below the LCST, the cross-linked gel swells to significantly higher degrees because of the increased compatibility with water.

Complexing Hydrogels

Some hydrogels may exhibit environmental sensitivity due to the formation of polymer complexes. Polymer complexes are insoluble, macromolecular structures formed by the non-covalent association of polymers with affinity for one another. The complexes form as a result of the association of repeating units on different chains (interpolymer complexes) or on separate regions of the same chain (intrapolymer complexes). Polymer complexes are classified by the nature of the association as stereocomplexes, polyelectrolyte complexes, or hydrogen-bonded complexes. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains.

In this type of gel, complex formation results in the formation of physical cross-links in the gel. As the degree of effective cross-linking is increased, the network mesh size and degree of swelling is significantly reduced. As a result, if hydrogels are used as drug carriers, the rate of drug release will decrease dramatically upon the formation of interpolymer complexes.

APPLICATIONS

Biomedical Applications

The physical properties of hydrogels make them attractive for a variety of biomedical and pharmaceutical applications. Their biocompatibility allows them to be considered for medical applications, whereas their hydrophilicity can impart desirable release characteristics to controlled and sustained release formulations.

Hydrogels exhibit properties that make them desirable candidates for biocompatible and blood-compatible biomaterials (Merrill *et al.*, 1987). Nonionic hydrogels for blood contact applications have been prepared from poly(vinyl alcohol), polyacrylamides, PNVP, PHEMA, and poly(ethylene oxide) (Peppas *et al.*, 1999). Heparinized polymer hydrogels also show promise as materials for blood-compatible applications (Sefton, 1987).

One of the earliest biomedical applications of hydrogels was in contact lenses (Tighe, 1976; Peppas and Yang, 1981) because of their relatively good mechanical stability, favorable refractive index, and high oxygen permeability.

Other potential applications of hydrogels include (Peppas, 1987) artificial tendon materials, wound-healing bioadhesives, artificial kidney membranes, articular cartilage, artificial skin, maxillofacial and sexual organ reconstruction materials, and vocal cord replacement materials (Byrne *et al.*, 2002).

Pharmaceutical Applications

Pharmaceutical hydrogel applications have become very popular in recent years. Pharmaceutical hydrogel systems include equilibrium-swollen hydrogels, i.e., matrices that have a drug incorporated in them and are swollen to equilibrium. The category of solvent-activated, matrix-type, controlled-release devices comprises two important types of systems: swellable and swelling-controlled devices. In general, a system prepared by incorporating a drug into a hydrophilic, glassy polymer can be swollen when brought in contact with water or a simulant of biological fluids. This swelling process may or may not be the controlling mechanism for diffusional release, depending on the relative rates of the macromolecular relaxation of the polymer and drug diffusion from the gel.

In swelling-controlled release systems, the bioactive agent is dispersed into the polymer to form nonporous films, disks, or spheres. Upon contact with an aqueous dissolution medium, a distinct front (interface) is observed that corresponds to the water penetration front into the polymer and separates the glassy from the rubbery (gel-like) state of the material. Under these conditions, the macromolecular relaxations of the polymer influence the diffusion mechanism of the drug through the rubbery state. This water uptake can lead to considerable swelling of the polymer with a thickness that depends on time. The swelling process proceeds toward equilibrium at a rate determined by the water activity in the system and the structure of the polymer. If the polymer is cross-linked or if it is of sufficiently high molecular weight (so that chain entanglements can maintain structural integrity), the equilibrium state is a water-swollen gel. The equilibrium water content of such hydrogels can vary from 30% to 90%. If the dry hydrogel contains a water-soluble drug, the drug is essentially immobile in the glassy matrix, but begins to diffuse out as the polymer swells with water. Drug release thus depends on two simultaneous rate processes: water migration into the device and drug diffusion outward through the swollen gel. Since some water uptake must occur before the drug can be released, the initial burst effect frequently observed in matrix devices is moderated, although it may still be present. The continued swelling of the matrix causes the drug to diffuse increasingly easily, ameliorating the slow tailing off of the release curve. The net effect of the swelling process is to prolong and linearize the release curve. Details of hydrogels for medical and pharmaceutical applications have been presented by Korsmeyer and Peppas (1987) for poly(vinyl alcohol) systems, and by Peppas (1981) for PHEMA systems and their copolymers. One of numerous examples of such swelling-controlled systems was reported by Franson and Peppas (1983), who prepared cross-linked copolymer gels of poly(HEMA-*co*-MAA) of varying compositions. Theophylline release was studied and it was found that near zero-order release could be achieved using copolymers containing 90% PHEMA.

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Poly(vinyl alcohol)

Another hydrophilic polymer that has received attention is poly(vinyl alcohol) (PVA). This material holds tremendous promise as a biological drug delivery device because it is nontoxic, is hydrophilic, and exhibits good mucoadhesive properties. Two methods exist for the preparation of PVA gels. In the first method, linear PVA chains are cross-linked using glyoxal, glutaraldehyde, or borate. In the second method, Peppas and Hassan (2000), semicrystalline gels were prepared by exposing aqueous solutions of PVA to repeating freezing and thawing. The freezing and thawing induced crystal formation in the materials and allowed for the formation of a network structure cross-linked with the quasi-permanent crystallites. The latter method is the preferred method for preparation as it allows for the formation of an “ultrapure” network without the use of toxic cross-linking agents. Ficek and Peppas (1993) used PVA gels for the release of bovine serum albumin using novel PVA microparticles.

Poly(ethylene glycol)

Hydrogels of poly(ethylene oxide) (PEO) and poly(ethylene glycol) (PEG) have received significant attention for biomedical applications in the past few years (Graham, 1992). Three major preparation techniques exist for the preparation of cross-linked PEG networks: (i) chemical cross-linking between PEG chains, (ii) radiation cross-linking of PEG chains, and (iii) chemical reaction of mono- and difunctional PEGs. The advantage of using radiation-cross-linked PEO networks is that no toxic cross-linking agents are required. However, it is difficult to control the network structure of these materials. Stringer and Peppas (1996) have prepared PEO hydrogels by radiation cross-linking. In this work, they analyzed the network structure in detail. Additionally, they investigated the diffusional behavior of smaller molecular weight drugs, such as theophylline, in these gels. Kofinas *et al.* (1996) have prepared PEO hydrogels by a similar technique. In this work, they studied the diffusional behavior of various macromolecules in these gels. They noted an interesting, yet previously unreported dependence between the cross-link density and protein diffusion coefficient and the initial molecular weight of the linear PEGs.

Lowman *et al.* (1997) have presented an exciting new method for the preparation of PEG gels with controllable structures. In this work, highly cross-linked and tethered PEG gels were prepared from PEG dimethacrylates and PEG monomethacrylates. The diffusional behavior of diltiazem and theophylline in these networks was studied. The technique presented in this work is promising for the development of a new class of functionalized PEG-containing gels that may be of use in a wide variety of drug delivery applications.

pH-Sensitive Hydrogels

Hydrogels that have the ability to respond to pH changes have been studied extensively over the years. These gels typically contain side ionizable side groups such as carboxylic acids or amine groups. The most commonly studied ionic polymers include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA),

poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA). The swelling and release characteristics of anionic copolymers of PMAA and PHEMA (PHEMA-*co*-MAA) have been investigated. In acidic media, the gels did not swell significantly; however, in neutral or basic media, the gels swelled to a high degree because of ionization of the pendant acid group. Brannon-Peppas and Peppas (1991) have also studied the oscillatory swelling behavior of these gels.

Temperature-Sensitive Hydrogels

Some of the earliest work with temperature-sensitive hydrogels was done by Hirotsu *et al.* (1987). They synthesized cross-linked poly(*N*-isopropyl acrylamide) (PNIPAAm) and determined that the LCST of the PNIPAAm gels was 34.3°C. Below this temperature, significant gel swelling occurred. The transition about this point was reversible. They discovered that the transition temperature was raised by copolymerizing PNIPAAm with small amounts of ionic monomers. Dong and Hoffman (1991) prepared heterogeneous gels containing PNIPAAm that collapsed at significantly faster rates than homopolymers of PNIPAAm. Yoshida *et al.* (1995) and Kaneko *et al.* (1996) developed an ingenious method to prepare comb-type graft hydrogels of PNIPAAm. The main chain of the cross-linked PNIPAAm contained small-molecular-weight grafts of PNIPAAm. Under conditions of gel collapse (above the LCST), hydrophobic regions were developed in the pores of the gel resulting in a rapid collapse. These materials had the ability to collapse from a fully swollen conformation in less than 20 minutes, whereas comparable gels that did not contain graft chains required up to a month to fully collapse. Such systems show major promise for rapid and abrupt or oscillatory release of drugs, peptides, or proteins.

Complexation Hydrogels

Another promising class of hydrogels that exhibit responsive behavior is complexing hydrogels. Bell and Peppas (1995) have discussed a class of graft copolymer gels of PMAA grafted with PEG, poly(MAA-*g*-EG). These gels exhibited pH-dependent swelling behavior due to the presence of acidic pendant groups and the formation of interpolymer complexes between the ether groups on the graft chains and protonated pendant groups. In these covalently cross-linked, complexing poly(MAA-*g*-EG) hydrogels, complexation resulted in the formation of temporary physical cross-links due to hydrogen bonding between the PEG grafts and the PMAA pendant groups. The physical cross-links were reversible in nature and dependent on the pH and ionic strength of the environment. As a result, these complexing hydrogels exhibit drastic changes in their mesh size in response to small changes of pH.

Promising new methods for the delivery of chemotherapeutic agents using hydrogels have been recently reported. Novel biorecognizable sugar-containing copolymers have been investigated for the use in targeted delivery of anti-cancer drugs. Peterson *et al.* (1996) have used poly(*N*-2-hydroxypropyl methacrylamide) carriers for the treatment of ovarian cancer.

Self-Assembled Structures

In the past few years there have been new, creative methods of preparation of novel hydrophilic polymers and hydrogels that may represent the future in drug delivery applications. The focus in these studies has been the development of polymeric structures with precise molecular architectures. Stupp *et al.* (1997) synthesized self-assembled triblock copolymer nanostructures that may have very promising biomedical applications.

Star Polymers

Dendrimers and star polymers (Dvornik and Tomalia, 1996) are exciting new materials because of the large number of functional groups available in a very small volume. Such systems could have tremendous promise in drug targeting applications. Merrill (1993) has offered an exceptional review of PEO star polymers and applications of such systems in the biomedical and pharmaceutical fields. Griffith and Lopina (1995) have prepared gels of controlled structure and large biological functionality by irradiation of PEO star polymers. Such new structures could have particularly promising drug delivery applications when combined with emerging new technologies such as molecular imprinting.

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2.6 APPLICATIONS OF “SMART POLYMERS” AS BIOMATERIALS

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INTRODUCTION

Stimulus-responsive, “intelligent” polymers are polymers that respond with sharp, large property changes to small changes in physical or chemical conditions. They are also known as “smart” or “environmentally sensitive” polymers. These polymers can take many forms; they may be dissolved in aqueous solution, adsorbed or grafted on aqueous–solid interfaces, or cross-linked in the form of hydrogels.

Many different stimuli have been investigated, and they are listed in Table 1. Typically, when the polymer’s critical response is stimulated, the behavior will be as follows (Fig. 1):

- The smart polymer that is dissolved in an aqueous solution will show a sudden onset of turbidity as its phase separates, and if its concentration is high enough, it will convert from a solution to a gel.

TABLE 1 Environmental Stimuli

Physical
Temperature
Ionic strength
Solvents
Radiation (UV, visible)
Electric fields
Mechanical stress
High pressure
Sonic radiation
Magnetic fields
Chemical
pH
Specific ions
Chemical agents
Biochemical
Enzyme substrates
Affinity ligands
Other biological agents

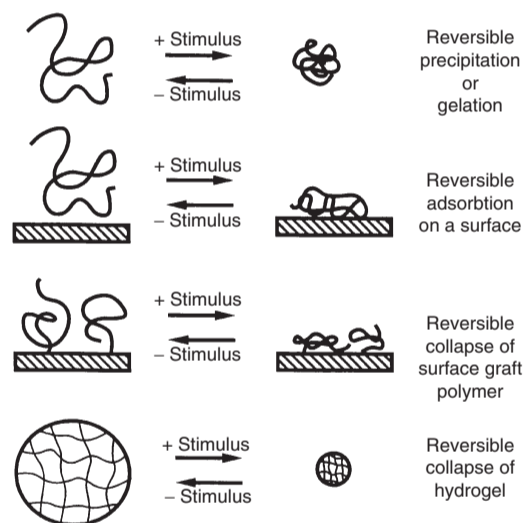


FIG. 1. Schematic illustration showing the different types of responses of “intelligent” polymer systems to environmental stimuli. Note that all systems are reversible when the stimulus is reversed (Hoffman *et al.*, 2000).

- The smart polymer that is chemically grafted to a surface and is stimulated to phase separate will collapse, converting that interface from a hydrophilic to a hydrophobic interface. If the smart polymer is in solution and it is stimulated to phase separate, it may physically adsorb to a hydrophobic surface whose composition has a balance of hydrophobic and polar groups that is similar to the phase-separated smart polymer.
- The smart polymer that is cross-linked in the form of a hydrogel will exhibit a sharp collapse, and release much of its swelling solution.

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