HYDROGELS

1. Introduction

Hydrogels are hydrophilic polymer networks that are able to swell and retain large amounts of water and maintain three-dimension (3D) swollen structures. These hydrogels but do not dissolve in water. Upon swelling, hydrogels increase in volume, but keep their shape. In general, the amount of water absorbed by the hydrogel is at least 20% of the total weight, and for superabsorbent hydrogel it is usually >95% of the total weight. Due to the high water content, the mechanical strength of the swollen hydrogels is usually poor. The ability of hydrogel to imbibe water is determined by the hydrophilic groups in the hydrogel network chains and the degree of cross-linking. In general, hydrogels can be cross-linked chemically or physically. Chemically cross-linked hydrogels are cross-linked by covalent bonds and do not dissolve in water in any condition, while physically cross-linked hydrogels can be reversible in shape because they are cross-linked

through noncovalent bonds such as van der Waals interactions, ionic interactions, hydrogen bonding, or hydrophobic interactions. These physical hydrogels can show sol–gel reversibility. Because of the 3D network structures, the molecular weight of hydrogels is considered to be infinite. Responsive hydrogels can reversibly change volume in response to slight changes in the properties of the medium including pH, temperature, electric field, ionic strength, salt type, solvent, external stress, or light. In the past four decades, hydrogels have been a topic of extensive research because of their unique bulk and surface properties. The first hydrogel study for biomedical use of poly(2-hydroxyethyl methacrylate) was reported by Wichterle and Lim (1). Since then, various hydrogels have been synthesized by using a variety of monomers and methods.

2. The Common Monomers Used for Synthesizing Hydrogels

Table 1 shows common monomers for preparing hydrogels. Each monomer contains a carbon double bond through which polymerization propagates to produce polymer chains. A cross-linker that contains two double bonds is added to the monomers to obtain a 3D cross-linked structure. The polymerization usually is carried out using heat (with thermal-initiators), light (with photoinitiators), γ radiation, or an electron beam. Radiation polymerization does not require initiators and can be used with almost any monomer. Initiators provide free radicals that initiate a chain reaction among the monomer and cross-linker molecules. Thermal initiators include peroxides and azo compounds that undergo cleavage at a rate that is markedly temperature dependent, and redox systems comprised of reducing agents such as ferrous salts, sodium metabisulfite, or tetramethylenediamine (TEMED), plus oxidizing agents ammonium persulfate or hydrogen peroxide. Radiation sources include Co-60, Ce-137, or electron beams.

Table 1. **Common Monomers Used for Hydrogel Production**[a]

Monomer	Abbreviation	Chemical structure
hydroxyethyl methacrylate	HEMA	$CH_2=C(CH_3)COOCH_2CH_2OH$
hydroxyethoxyethyl methacrylate	HEEMA	$CH_2=C(CH_3)COOCH_2CH_2OCH_2CH_2OH$
ethylene glycol dimethacrylate	EGDMA	$CH_2=C(CH_3)COOCH_2CH_2OCOC(CH_3)=CH_2$
acrylic acid	AA	$CH_2=CHCOOH$
methacrylic acid	MAA	$CH_3CH=CHCOOH$
N-vinyl-2-pyrrolidone	NVP	$CH_2=CHNCOCH_2CH_2CH_2$
vinyl acetate	VAC	$CH_2=CHCOOCH_3$
N-substituted acrylamide	*n*-AM	$CHR_3=CHCONR_1R_2$
hydroxydiethoxyethyl methacrylate	HDEEMA	$CH_2=(CH_3)COOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$
2-acrylamido-2-methylpropanesulfonic acid	AMPS	$CH_2=CHCONH(CH_3)CH_2SO_3H$
acrylonitrile	AN	$CH_2=CH-CN$

[a] See Refs. 2 and 3.

3. General Methods of Preparation

3.1. Polymerization Methods. The techniques used for the production of hydrogels include bulk, solution, suspension, and emulsion polymerizations (Table 2). Emulsion and suspension polymerizations provide a good control over the shape and particle size distribution of the hydrogel.

3.2. Hydrogels Prepared Using Radiation. Ionizing radiation has long been recognized as a very useful tool for the synthesis of hydrogels. A major advantage is the ability to carry out a hydrogel synthesis and sterilization all in one step without the use of any initiator or cross-linker. A hydrogel can be obtained by irradiation of a solid polymer, monomer (bulk or solution), or aqueous solution of polymer (4). Upon irradiation of the polymer solution, reactive macromolecular intermediates are formed due to the direct action of radiation on the polymer chains or from the reaction of the intermediates generated in water with the polymer molecules. Irradiation of hydrophilic polymers in a dry form requires special sample preparation such as pressing or melting (5). It is difficult to obtain homogeneous hydrogels. The monomer irradiation method in which polymerization is followed by cross-linking is the most frequent. Because many monomers are harmful or even toxic, special care should be taken when using this method for the formation of hydrogels for biomedical uses. During irradiation of the monomer, multiple consecutive and parallel reactions occur. Typical hydrogels prepared by irradiation include poly(vinyl alcohol) (PVA) (6,7), poly(*N*-vinyl-2-pyrrolidone) (PVP) (8), poly(ethylene oxide) (PEO) (9),

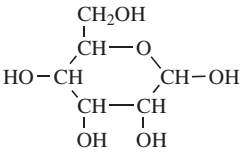
Table 2. **The Common Polymerization Methods for Preparing Hydrogels**[a]

Polymerization method	Important featuers	Problems related to polymer preparation and purity
bulk (mass)	initiator and monomer needed, cross-linking agent can be added	high viscosity, difficult agitation lead to non-uniformity of products; residual monomers
solution	Initiator, solvent, and monomer needed; easy agitation: controlled heat transfer; polymer soluble or insoluble in solvent	chain transfer frequently gives broad molecular weight distribution products; difficulty in removing solvent
suspension	initiator, solvent, monomer, and suspending agent needed; cross-linking agent can be added; polymer production in spherical or irregular particles depending on monomer–suspending agent interfacial tension	
emulsion	initiator, solvent, monomer, suspending agent, and emulsifier needed	residual emulsifier, etc
gaseous	reaction in gaseous phase; high pressure; unknown kinetics	pure polymers; technique not applied to many systems
plasma	glow discharge; unknown kinetics	new technique; ultrapure polymers, high cost of manufacture

[a]See Ref. 3

polyacrylamide (PAM) (10,11), poly(acrylic acid) (PAA) (12) and poly(methyl vinyl ether) (PMVE) (13) and poly(acrylamide/maleic acid) [P(AM–MA)] (14). Cross-linking agents and monomers can be added to increase the extent of cross-linking, modify the gel structure, or initiate grafting reactions.

The presence of oxygen plays an important role in the irradiation process. The initially generated carbon-centered macroradicals react with oxygen to form corresponding peroxyl radicals (15) that can cause chain scissions. In the initial period, the degradation is dominant, cross-linking or gel formation occurs only after the oxygen is used up. Many polymers that can be expected to form cross-linked structures degrade if irradiated in air under slow dose rates, due to the formation of weak peroxidic bonds in the main polymeric chain. These bonds decompose and cause oxidative degradation of the main chain.



Six-member hexose repeat unit

4. Properties and Preparation

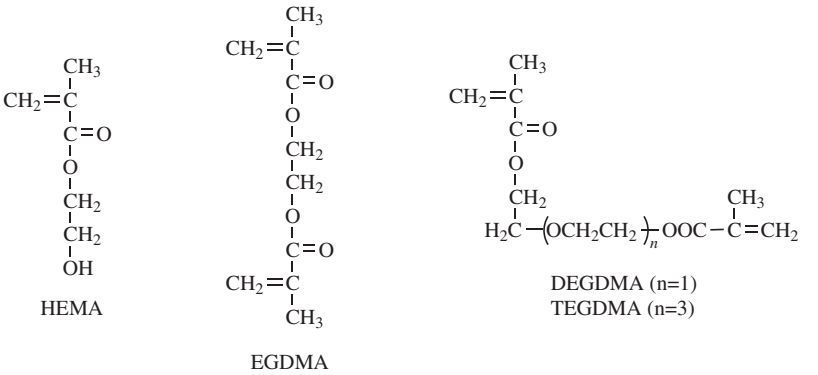
4.1. Hydrogels Based on Natural Polymers. The natural polymers that can be cross-linked include the macromolecules extracted from animal collagen, plants, and seaweed. Polysaccharides are classified on the basis of their main monosaccharide components and the sequences and linkages between them, as well as the anomeric configuration of linkages, the ring size (furanose or pyranose), the absolute configuration (D- or L-), and any other substituents present. Certain structural characteristics such as chain conformation and intermolecular associations will influence the physicochemical properties of polysaccharides. Polysaccharides are composed of glycosidic repeat units shown above (2). Polysaccharides copolymerized with acrylic acid or acrylamide form superabsorbent hydrogels, with water absorption as high as 420 times its weight (16). Alginate is a linear polysaccharide that is extracted from red-brown seaweed. It contains the repeat units of 1,4-linked α-L-guluronic acid and β-D-mannuronic acid. Upon mixing with divalent cations such as calcium, alginate can spontaneously form hydrogel by cross-linking through the gluronic acid residues. The ionically cross-linked alginate hydrogels have been used in control release of several proteins (17–19).

Gelatin is a natural physical hydrogel that is prepared by partial hydrolysis of water-insoluble collagen fibers from connective tissues. Gel is formed when gelatin solution (1–20% conc) is cooled below the gelation temperature; and degelation occurs upon heating above the gelation point (20). Ionic polysaccharides are also capable of being gelled *in situ*, by mixing an ionic ploysaccharide, a film-forming polymer, water, and a counterion that can form gel with the ionic polysaccharide. The gelation occurs by interaction between the ionic polysaccharide

and the film-forming polymer, or by counterion induced cross-linking of the ionic polysaccharide.

A semi-IPN (interpenetrating polymer network) hydrogel can be obtained by cross-linking chitosan with glutaraldehyde (21,22). The hydrolysis stability can be improved by increasing the extent of cross-linking, but the swelling ability decreases. Semi-IPN hydrogels of β-chitin and poly(ethylene glycol) (PEG) macromer have been synthesized for biomedical applications (23) with a high tensile strength (1.3–2.4 MPa) in the swollen state. Semi-IPN hydrogels of β-chitosan and PEG diacrylate macromer were prepared (24) by dissolving the mixture of PEGM and β-chitosan in aqueous acetic acid, and then the mixture was cast to a film, followed by subsequent cross-linking after ultraviolet (uv) irradiation with 2,2-dimethoxy-2-phenylacetophenone.

4.2. Poly(2-hydroxy ethyl methacrylate) Hydrogels (PHEMA). PHEMA hydrogel was first prepared and described for bioapplications by Wichterle and Lim (1). Advantages include hydrolysis stability, nonantigenicity, and nonirritability (2,25). Drawbacks include inertness to cell adhesion, low swelling in water, poor mechanical strength, and nondegradablity.



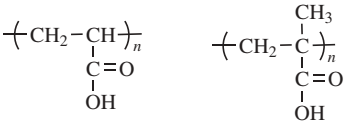
PHEMA hydrogels are usually prepared by free-radical solution polymerization of HEMA in the presence of a divinyl cross-linking agent. The solution polymerization is preferred as it facilitates the gel formation in a desired shape. The ratio of solvent to monomer plays an important role in determining the physical properties of the final product. If HEMA monomer containing cross-linking agent is polymerized in the presence of a good solvent for both monomer and polymer, an optically transparent hydrogel polymer is formed. The most widely used cross-linking agents are the dimethacrylate esters: EGDMA, diethylene glycol dimethacrylate (DEGDMA), and tetraethylene glycol dimethacrylate (TEGDMA) Azoisobutyionitrile (AIBN) is the most common initiator used; other initiators include ammonium persulfate, benzoyl peroxide, and isopropyl percarbonate (25).

The stereochemistry of a PHEMA hydrogel influences the swelling behavior, eg, isotactic PHEMA exhibited greater swelling $<30^{\circ}C$ than the syndiotactic PHEMA (26).

When HEMA is copolymerized with hydrophobic compositions, hydrogels with superior mechanical and tensile strength can be obtained. For example, hydroxypropyl methacrylates (HPMA) can be incorporated into HEMA to

increase the mechanical strength. EGDMA, being rather hydrophobic, controls the mechanical behavior of the hydrogel, whereas DEGDMA and TEGDMA, containing long ethoxy sequences, act both as hydrophilic and hydrophobic comonomers and are suitable with HEMA for contact lenses (27).

4.3. Poly(acrylic/methacrylic acid) Hydrogels



PAA PMAA

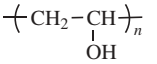
Acrylic/methacrylic acid hydrogels exhibit extremely high swelling capacities, eg, poly(acrylic acid) hydrogels can have water content as high as 99%, and hence are used as a superabsorbing material. The commercially important superabsorbent polymers are cross-linked polymers of partially neutralized acrylic acid or terpolymers of acrylic acid, sodium acrylate, and a cross-linker, or graft terpolymers with starch or poly(vinyl alcohol) (PVA). The swelling and elasticity of these polymers depend on the precise structure of the polymer network and the cross-link density (28,29).

Acrylic acid can form IPN hydrogels with other natural or synthetic polymers. Chitosan/PAA hydrogels prepared by uv irradiation (30) show pH sensitivity. The amino groups in the chitosan and carboxyl groups in PAA form a polyelectrolyte complex, improving the mechanical strength of the swollen hydrogel. The PAA/PVA IPN hydrogels are prepared by first cross-linking acrylic acid monomer inside PVA solution, then forming the second network by using cycles of the freeze–thaw process. The swelling behavior of the hydrogel depends on the solution pH, and the permeation depends on the ionic property of the solutes. In the case of nonionic solutes, the permeability follows the variation in hydrogel swelling.

Poly(methyacrylic acid-*g*-ethylene glycol) networks have been prepared by the copolymerization of methacrylic acid and oligomeric ethylene glycol monomethacrylate in the presence of tetraethylene glycol dimethacrylate (31). The hydrogel obtained has PMAA as its backbone and ethylene glycol as its pendant chains. The swelling depends on the solution pH, temperature, copolymer composition, and network structure. The copolymer hydrogels show lower swelling in acidic solutions as compared to the poly(methacrylic acid) hydrogel, due to the complexation between the PEG and PMAA segments.

Hydrogels with a high swelling ability are prepared, with a monomer conversion as high as 100% when acrylamide, acrylic acid mixtures with cross-linkers are irradiated in a ^{60}Co-γ source. This hydrogel has been tested for the removal of some textile dyes from aqueous solutions (32).

4.4. PVA Hydrogels



PVA

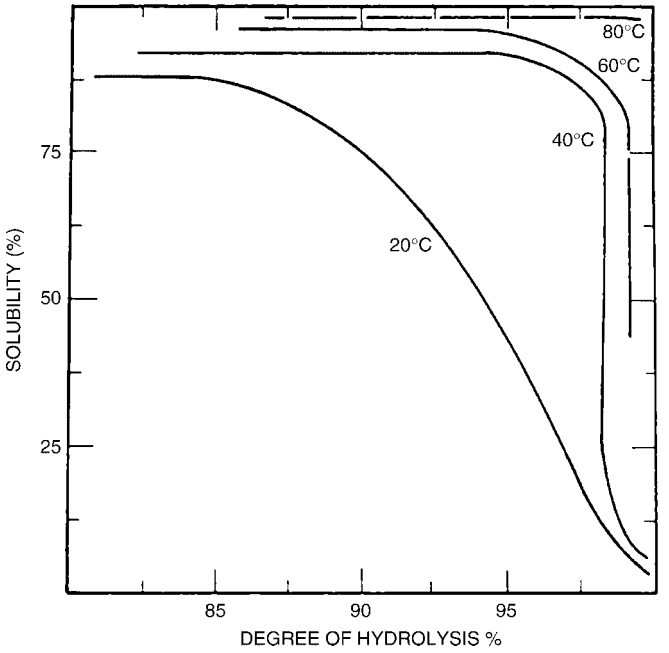


Fig. 1. Aqueous solubility of PVA as a function of hydrolysis. Reprinted with permission from Ref. 33.

PVA was first prepared in 1924 by Herrmann and Haehnel (33). The monomer, vinyl alcohol, usually exists in its rearranged form as the tautomer acetaldehyde. Thus, PVA is produced in industry by polymerization of vinyl acetate to form poly(vinyl acetate) (PVAC) followed by hydrolysis. Usually the hydrolysis does not go to completion, leaving some residual acetate groups in the polymer.

The solubility of PVA in water depends on both the degree of hydrolysis and the degree of polymerization. Figure 1 shows the solubility of PVA (number average molecular weight, 77,000) as a function of the degree of hydrolysis at 20–80°C. It is shown that highly hydrolyzed PVA does not easily dissolve in water at low temperatures, which is due to the residual acetate groups affecting the intra- and intermolecualr hydrogen bonding of adjoining hydroxyl groups. PVA with high hydrolysis degree is soluble in water 80°C. In many applications, it has been reported that temperature must be raised to 70°C for dissolution of highly hydrolyzed PVA. The PVA with a high degrees of hydrolysis is also more difficult to crystallize (33).

PVA is usually cross-linked for several applications, especially for medical and pharmaceutical uses. PVA can be cross-linked by a difunctional agent that condenses with the organic hydroxyl groups including formaldehyde, glutaradehyde, acetadehyde, or maleic acid (33), in which acetal bridges form between the pendant hydroxyl groups of the PVA chains. PVA can also be crosslinked by uv light with photoinitiators, electron-beam or γ-radiation. These methods have advantages over the chemical cross-linking as they do not leave behind toxic agents. Irradiation of dry PVA powder with γ rays leads to scission of the main chain and chain-branching (34).

Chemical cross-linking of PVA often leaves the residual cross-linking agent that is often toxic, so a physical method of gelation of PVA has been developed (35). In this method, aqueous PVA solution is first frozen and then thawed back to room temperature resulting in the formation of crystallites. The structure of the formed PVA hydrogel is described as one consisting of three phases: a water phase of low PVA concentration, an amorphous phase, and crystalline phase that restricts some of the motion of the amorphous PVA chains (36). The crystalline regions serve as the physical crosslinks. The PVA hydrogel produced by freeze–thaw method has a large pore size, a high tensile strength, a high water content, and a high light transmittance (37). High light transmittance makes the formed PVA hydrogel suitable for contact lenses. Large pores of PVA hydrogels make it suitable for drug release application. This PVA hydrogel also show thermosensitivity (38).

The PVA hydrogels have been used for a number of biomedical and pharmaceutical applications, due to its advantages such as: nontoxic, noncarcinogenic, and bioadhesive characteristics with the ease of processing. In addition to blood contact, artificial kidney, and drug delivery applications (39–41), PVA show potential applications for soft tissue replacements (42), articular cartilage (43), artificial organs (44) and membranes (45).

4.5. PEG Hydrogels

$$HO\left[CH_2-CH_2-O\right]_nH$$

The chemistry and biological application of PEG have been the subject of intense study both in academia and industry. PEG is a nontoxic, water soluble polymer that resists recognition by the immune system. Traditionally, PEG has been used in biological research as a precipitating agent for proteins. It has been approved for a wide range of biomedical applications, as they are biocompatible, nontoxic, and nonimmunogenic (46).

Hydrogels based on PEG derivatives have been widely used in covalent attachment to proteins to reduce immunogenicity, proteolysis and kidney clearance (47), attachement to low molecular weight drugs for enhanced solubility, reduces toxicity and alter biodistribution (48).

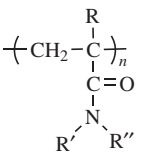
PEG hydrogels are usually prepared by radiation cross-linking of high molecular weight PEO or by chemical cross-linking by reaction of hydroxyl groups on the ends of PEG. The radiation dose needed to cross-link PEG chains is dependent not only on the molecular weight, but also on the concentration of PEG in the solution. Because cross-linking occurs randomly between PEG chains, a large number of hydroxyl groups are left available for biological reaction. There are mainly two types of PEG hydrogels (49). The first type is prepared by reaction of PEG carboxylic acids with PEG alcohols, the nearly formed ester cross-linkage between PEG molecular chains make the PEG hydrogel hydrolytically degradable. The gel made in this way will show a high swelling in water. The second type is prepared by first synthesizing a double-ester PEG, then reacting this intermediate with a PEG amine. Varying the PEG carboxylic acid and the hydroxy acid used in preparing the double ester PEG controls the degradation rate.

The copolymer network of poly(methacrylic acid) grafted with poly(ethylene glycol) exhibit pH-dependent swelling behavior due to the reversible formation/dissociation of interpolymer complexes (50). In acid media, such systems are relatively unswollen due to the formation of the intermacromolecular complexes. In basic solutions, the pendant groups ionize and the complexes dissociate. Because of the complexation/decomplexation phenomena, these gels exhibit large changes in their structure and are able to deliver proteins at varying rates depending on the pH of the surrounding fluid. The PEG star polymer hydrogels have been also prepared using γ-irradiation for use in protein delivery (51). The PEG based macromers or oilgomeric blocks of a hydrolyzable α-hydroxyl acid were synthesized and photopolymerized to form degradable hydrogels to control the release of hydrophilic solutes including dextran, lysozyme, and bovine serum albumin (BSA) (52). Experimental results show that the solute release behavior from these hydrogels is strongly affected by the network mesh size and the hydrodynamic radius of the solute. When the hydrodynamic radius of the solute is much larger than the mesh size of the network, the solute release behavior is degradation controlled.

PEG can also be cross-linked with collagen materials for a variety of applications, mediated by carbamation of primary amines on collagen with *N*-hydroxysuccinimide ester end-groups on the PEG cross-linkers (53). Disuccinimidyl glutarate PEG(di-SG-PEG), contains internal ester linkages that are capable of hydrolyzing and hence produce biodegradable network. On the other hand, disuccinimidyl propionate PEG(di-SE-PEG) contain hydrolytically stable internal ether linkages and produce a more durable network.

Enzymes have long been used in the biomedical field as diagnostic tools or disease markers. Unfortunately, enzymes are quiet unstable biopolymers and denature quickly. To overcome its shortcoming, PEG hydrogels has been used to improve the life span of enzymes in the organism by immobilizing the enzyme in the matrix of PEG modified hydrogels. PEG-BSA hydrogels have interesting characteristics for enzyme immobilization useful in biomedical applications (54). Due to the presence of PEG in the structure, the biocompatibility of PEG-BSA hydrogel is improved. Because of the large hydrodynamic volume of the PEG, the surface coated with PEG has low thrombogenecity and protein adsorption.

4.6. Poly(acrylamide)-Based Hydrogels



Polyacrylamide (PAM) (R, R′, R″ = H)

A large number of polymers based on N-alkyl acrylamide and its copolymers with acidic and basic comonomers, have been synthesized that have a lower critical solution temperature (LCST). Poly(*N*-isopropylacrylamide) is the most widely studied thermosensitive acrylamide hydrogel that has an LCST at 33°C. This phenomenon has been attributed to a delicate hydrophobic–hydrophilic balance, which changes abruptly across a small temperature range. Water

Table 3. **Commonly Used N-Substituted Acrylamide Monomers for Synthesizing Thermosensitive Hydrogels**

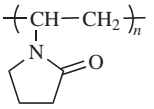
Monomer	Abbreviation	Chemical structure
N-isopropylacrylamide	NIPAm	CH_2=CHCONHCH(CH_3)
N,*N*-dimethylacrylamide	DMAm	CH_2=CHCON(CH_3)$_2$
N,*N*-diethylacrylamide	DEAm	CH_2=CHCON(CH_2CH_3)$_2$
N-tert-butylacrylamide	BAm	CH_2=CHCON(CH_2) $_2CH_3$
N-ethylacrylamide	EAAm	CH_2=CHCONHCH_2CH_3

behaves as a good solvent through hydrogen bonding with the amide groups at room temperature. This hydrogen bonding with water is increasingly disrupted on heating, rendering water to act as a poor solvent leading to gradual chain collapse. Inter- and intrapolymer hydrogen bonding and polymer–polymer hydrophobic interactions become dominant above the LCST. Commonly used N-substituted acrylamide thermosensitive polymers are listed in Table 3.

The introduction of ionic comonomers makes it possible to obtain hydrogels sensitive to changes in both temperature and pH. Macroporous gels with high rates of swelling and dehydration have been synthesized at temperatures below the LCST of PNIPAm (55). The PNIPAm gel in granulated form can be obtained by emulsion or suspension polymerization. The NIPAm hydrogels with AA, MAA and AMPS have been prepared by free-radical solution polymerization (56). When copolymerized with ionic monomers, the swelling ratio increase with the content of ionic comonomer, such as with AA and/or AMPS. But poly (NIPAm-*co*-MAA) hydrogels have entirely different characteristics: The swelling ratio is essentially independent of MAA content, at a given extent of cross-linker. Compared to poly(NIPAm-*co*-AA) and poly(NIPAm-*co*-AMPS) hydrogels, poly(NIPAm-*co*-MAA) show a significantly lower swelling due to weakly anionic MAA. By graft copolymerization of NIPAm and a photosensitive monomer triphenylmethane leucocyanide (LeCN) onto PVA, a thermo- and photosensitive hydrogel membrane can be prepared (57) exhibiting a reversible volume-phase transition at 33°C. In the dark, the permeation rate of PEGs through the membrane decreases monotonously with increasing temperature due to the shrinkage of the membranes. The permeation rates increase significantly after uv irradiation of the PGN–LeCN membranes at 32°C, but the change is small for uv irradiation at 25 and 35°C.

Various powdery hydrogels based on acrylamide, methacrylamide, and their N-substituted derivatives have been prepared by precipitation polymerization (58), mostly for use in silicon rubber–hydrogel composite materials. By employing different N-alkyl-substituted polyacrylamides, it is possible to synthesize thermoresponsive hydrogels with a LCST ranging from 5.5°C for the poly-*N*-acryloylpiperidine gel to 72°C for the poly-*N*-ethylacrylamide gel. The DMAm is a versatile hydrophilic comonomer but its homopolymers does not show LCST in water. Many reports on DMAM hydrogels have been published (59). By increasing the DMAm content, the swelling ratio of DMAm/nBMAAm copolymer hydrogel increases, and the swelling is faster.

4.7. Poly(*N*-vinyl 2-pyrrolidone) Hydrogels



Hydrogel based on NVP can be synthesized by free-radical polymerization, though homogeneously cross-linked PNVP is difficult to prepare and has a low mechanical strength. NVP is probably the most effective comonomer used to increase the water uptake ability of HEMA hydrogel as contact lens. The graft copolymer of NVP onto silicone rubber exhibits hydrophilicity, high oxygen permeability, and improved wettability (60). NVP polymers are also known to have excellent biocompatibility that is designed for controlled nonburst degradation in the vitreous body. Cross-linked PNVP has the potential to be use as vitreous substitute (61). Because of its hydrophility, NVP is copolymerized with hydrophobic comonomers to improve the mechanical strength (62–64). NVP copolymerized with methyl methacrylate (MMA) using 1,1,1-trimethylol propane trimethacrylate (TPTA) as cross-linker, is highly permeable and transparent (65).

4.8. Polyurethane Hydrogels. Polyurethane hydrogels are widely used in soft contact lenses, controlled release devices, semipermeable membranes and hydrophilic coatings (66). The properties of polyurethane hydrogels can be varied by variation of their components, such as the polyols, diisocyanate, chain extender, or cross-linker (67–69). Because of the excellent mechanical and physical properties, polyurethanes are widely used in medical applications such as coating for medical devices for preventing protein adsorption (70,71).

4.9. Biodegradable Hydrogels. Biodegradable hydrogels are of interest in pharmaceutical, veterinary, agricultural, and environmental applications. The use of biodegradable hydrogels is desirable because the dosage forms is degraded and eliminated from the body after drug delivery. These are specially advantageous as delivery systems for large molecular weight drugs, such as peptides and proteins, which are not easily delivered using general polymers.

The biodegradable hydrogels are usually classified into three categories: (*1*) hydrogels with degradable polymer backbone; (*2*) hydrogel with degradable cross-linking agents; and (*3*) hydrogels with degradable pendant groups (72). These can also be classified into either natural degradable and synthetic degradable hydrogels, or cross-linked and noncross-linked hydrogels. Figure 2 shows the scheme of hydrogel degradation mechanism by backbone, cross-linking agents, and pedant groups.

Hydrogels with Degradable Polymer Backbone. The degradation of polymer backbone takes place by hydrolysis or enzymatic action (72). Polymer backbone can be hydrolyzed and the low molecular weight by-products produced can be handled easily. Natural polymers, protein, and polysaccharides can be degraded by various enzymes as well as by hydrolysis. Hydrogels made of natural polymers undergo degradation by cleavage in the backbone chains. Due to biodegradability, albumin, gelatin, and dextran have been used widely for the preparation of biodegradable drug delivery system.

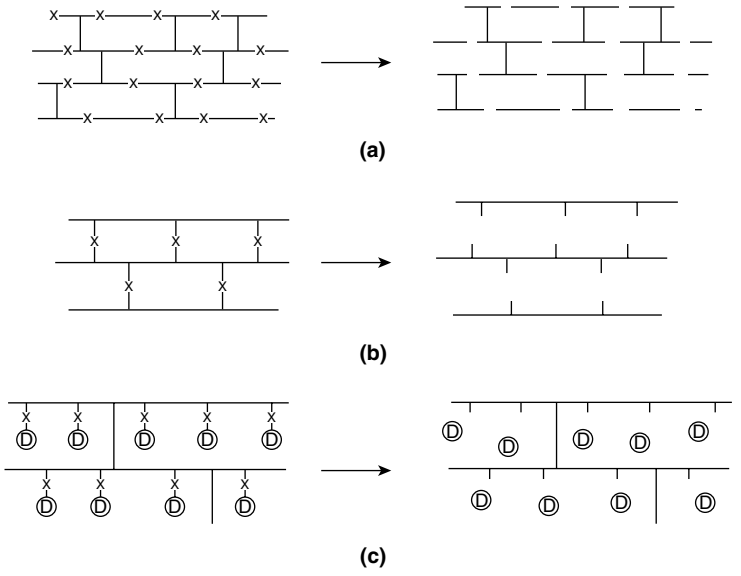


Fig. 2. Hydrogels degradation by cleavage of (**a**) polymer backbone, (**b**) cross-linking agent, and (**c**) pendant group (73). Reprinted with permission from Ref. 73.

Polysaccharides containing carboxyl groups, such as chondroitin sulfate and hyaluronic acid, are derivatized with cysteine methyl ester by substituting carboxyl groups of polysaccharides and subsequently cross-linked by mild oxidation to form hydrogels. IPNs and semi-IPNs can also be degraded from backbone.

Ester and ester derivative polymers are biodegradable polymers, and there are a large number of biodegradable hydrogels made of ester prepolymers by cross-linking with monomers such as AM and VP. The ester prepolymers are prepared via condensation reactions between an unsaturated diacid like fumaric acid, itaconic acid, or allylmalonic acid and a diol such as low molecualr weight PEG.

Hydrogels with Degradable Cross-Linking Agents. The cross-linking agents can also be degraded. In this case, after degradation, the final products are high molecular weight, water-soluble polymers. The hydrogels swell in water and the space between the hydrogel becomes large, making the hydrogels suitable for release of the drug. These types of hydrogels are useful in the delivery of poorly water soluble drugs or high molecular weight drugs such as peptides or proteins.

Methylene groups in *N*,*N*′-methylenebisacrylamide (BIS) can undergo degradation by hydrolysis to produce formaldehyde when the concentration of the cross-linking agent is low (74). Usually, when concentration of BIS is $>1\%$, there is no obviously degradation in reasonable timescales. Enzymes can reduce the degradation of the BIS-cross-linked hydrogels by entangling in the hydrogel or chemically bonding to the polymer backbone.

For hydrogels cross-linked by agents containing aromatic azo groups, the azo bond can be cleaved by enzyme azoreductase that are present predominantly

in the colon. Hence, this technique has been adapted to develop colon-specific drug delivery systems. In addition, other small and large molecules such as sucrose, oligopeptides, insulin, albumin, and polysaccharides are also used as cross-linking agent for hydrogels, as these cross-linking agents are all degradable by enzymes.

Hydrogels with Degradable Pendant Chains. In a drug delivery polymeric matrix, the small drug is easily released by diffusion. To avoid the early release of drug from the polymer, the small molecule drug is designed to attach to the easily degradable bond. The drug will be released only after the degradation of the pendant chains. Several systems involving poly(L-glutamic acid), poly-(hydroxyalkyllglutamines), and the copolymer of HPMA with the *p*-nitrophenyl esters of *N*-methacryloylated oligopeptides have been studied for attaching small molecular weight drugs.

Typical Biodegradable Hydrogels. Typical synthetic biodegradable polymers include polylactide (PLA) hydrogel (75), poly(lactide-*co*-glycolide) (PLGA) (76–78), poly(ϵ-caprolactone), polydioxanone, polyanhydride, trimethylene carbonate, poly(β-hydroxybutyrate), poly(γ-ethyl glutamate), poly(DTH iminocarbonate), poly(bisphenol A iminocarbonate), poly(ortho ester), polycyanoacrylate, and polyphosphazene. There are also a number of biodegradable polymers derived from natural sources such as modified polysaccharides (eg, cellulose, chitin, starch, and dextran), and modified proteins (eg, fibrin, and casein).

To date, the compounds that have been employed most widely in commercial applications are PLGA, PLA, poly(ϵ-caprolactone), polydioxanone, trimethylene carbonate, and polyanhydriden (79). Some of the common PLA products include tissue screws, tacks, and suture anchors, as well as systems for meniscus and cartilage repair. The use of PLGA copolymers for control release of proteins and peptides has been widely studied. PLGA copolymers can be fabricated into films, rods, microspheres, and nanospheres. The first FDA approved PLGA product was the Lupron Depot drug-delivery system (TAP Pharmaceutical Products, Inc.), which is a controlled release device for the treatment of advanced prostate cancer that used biodegradable microspheres of 75:25 lactide/glycolide to administer leuprolide acetate over period as long as 4 months (replacing daily injections). Another drug-delivery device, the GLIADEL Wafer (Guilford Pharmaceuticals, Inc.), is used to prolong the life of patients suffering from a particular deadly form of brain cancer, glioblastoma multiforme (GMB). In this case, dime-sized wafers of a biodegradable poly[anhydride-*co*-bis(*p*-carboxyphenoxy) propane]/sebacic acid in a 20:80 molar ratio are implanted directly into the brain to deliver a powerful cancer chemotherapeutic drug, carmustine, or BCNU, the wafers slowly dissolve over a period of weeks, delivering BCNU directly to the tumor site in high concentrations.

The commonly used polymer for preparing degradable hydrogels are PVA, PEG, PVP, puronic polyol, and some natural polymers including cellulose and alginate (80).

Puronic polyols are block copolymers of PEG and poly(propylene oxide). Pluronic copolymers with 70% ethylene oxide and 30% propylene oxide, with an average molecular weight of 11,500, exhibits a reversible thermal gelation in aqueous solution at >20%concentration. The polymer solution at room

temperature is liquid, but turns to a gel in the body. This gel has been used as a delivery system for several proteins (80).

The biodegradable *in situ* gelling poly[ethylene glycol-*b*-(DL-lactic acid)-*b*-ethylene glycol], PEG–PLGA–PEG triblock copolymers (81) and poly[(DL-lactic acid-*co*-glycolic acid)-γ-ethylene glycol], PLGA-*g*-PEG copolymers (82) with hydrophobic PLGA backbones show promising properties as injectable drug delivery systems. *In vivo* studies in rats show that the copolymer gels retain in the rat body for >1 month. A PEG-*g*-PLGA copolymer aqueous solution flows freely at room temperature but form gels at higher temperatures. The gel form can be maintained for 1 week, providing a promising material for short-term drug delivery.

Starch is used in a wide range of food products with different water content, either as a raw material or as a food additive. Starch granules are composed of two polysaccharides, amylose, and amylopectin, forming a semicrystalline entity (83). Cross-linked high amylose starch (HASCL) has been shown to control the release over 18–24 h (84), the cross-linking high amylose starch with epichlorohydrin with ionic or neutral groups can be used as novel matrices for the controlled release of drugs from high loading dosages with several types of pharmaceutical tracers (acetaminophen, acetylsalicylic acid, and metformin) (85). Some other applications of starch- based hydrogel are also described in literature (86–88).

4.10. Smart Hydrogels. Polymers that respond to external stimuli are termed as smart, intelligent, stimuli-responsive, or environmentally sensitive. Among water-soluble polymers and hydrogels, the term "smart" may be applied to systems that respond reversibly to slight changes in the properties of the medium. The properties can be pH, temperature, ionic strength, illumination, or electric field. The response is readily observed optically because of new phase formation in a hitherto homogeneous solution, by sudden swelling or contraction of the hydrogel.

The history of the creation of the first "smart" polymeric system dates back to the works of Kuhn and Katchalsky (89,90). They demonstrated that collagen fibers changed dimension reversibly on transition from cyclic helices to random coils when immersed cyclically between salt solution and water. This was referred to as a mechano–chemical system capable of transforming chemical energy to mechanical work.

For a polymer system to be capable of responding strongly to slight changes in the external medium, a first-order phase transition accompanied by a sharp decrease in the specific volume of the macromolecule should occur. The theoretical foundation of such process was laid by Flory. One of the main conditions for the manifestation of critical phenomena in swollen polymer networks or linear macromolecules is the presence of a "poor" solvent. In such a solvent, the forces of attraction between the segments of the polymer chain may overcome the repulsive forces associated with the excluded volume, leading to the collapse of the polymer chain.

The structure of macromolecules is governed by four fundamental interactions, viz, van der Waals, hydrophobic, hydrogen bonding, and electrostatic interactions. The electrostatic interactions between charges of polymer chain constitute the most effective repulsion. The osmotic pressure within a hydrogel,

Table 4. **The Monomers Used in pH-Sensitive Hydrogels**

Acidic		Basic	
Monomer	pH-sensitive group	Monomer	pH-sensitive group
methacrylic acid	$-COOH$	aminoethyl methacrylate	$-NH_2$
acrylic acid	$-COOH$	*N*,*N*-dimethylamino-ethyl methacrylate	$-N(CH_3)_2$
maleic acid	$-COOH$	*N*,*N*-diethylamino-ethyl methacrylate	$-N(CH_2CH_3)_2$
styrenesulfonate	$-SO_3Na$	vinylpyridine	$-NC_5H_4$
sulfonyloxyethyl methacrylate	$-SO_3H$	vinylbenzyltrimethylammonium chloride	$-N(CH_3)_3^+Cl^-$

arising due to low molecular mass counterions, also promotes the swelling of hydrogels. van der Waals forces, hydrogen bonds, and the interaction of ions of opposite charges constitute attraction forces and give rise to the collapse of hydrogels. If van der Waals forces or hydrogen bonds are responsible for the collapse of the hydrogel, the hydrogel swells upon heating and contracts upon cooling. On the other hand, if hydrophobic interactions or the interaction of ions of opposite charges induces the collapse of the gel, the gel swells upon cooling and contracts upon heating. In certain hydrophilic gels, such as sodium acrylamide vinylsulfonate copolymer, there is a possibility of having two phase transitions.

Thermosensitive Hydrogels. Temperature-sensitive polymers have been studied extensively and many of these exhibit the LCST in aqueous solution. The volume–phase transition of a thermosensitive hydrogel was first reported for PNIPAm hydrogel in water (91). After that, a large number of hydrogels based on NIPAm has been prepared and the phase transition upon temperature change have been studied.

pH-Sensitive Hydrogels. Table 4 presents the monomers used in the synthesis of pH-sensitive hydrogels. Monomers containing both weak acidic or basic groups and strong acidic or basic groups are used to synthesize such hydrogels. By varying the composition of the monomers and the content of the cross-linking agent, it is possible to obtain hydrogels with varing degrees of swelling. The degree of swelling depends mainly on the charge of the monomer in the polymer network, the degree of cross-linking, the pH and the ionic strength of the medium.

Hydrogels containing acidic groups swell in a weakly alkaline medium but collapse in an acidic medium. On the other hand, hydrogels containing basic groups swell in an acid medium but collapse in alkaline. Polyampholytic hydrogels, with both acidic and basic groups, swell to the maximum extent at neutral pH, and shrink in acidic or alkaline medium.

4.11. Microgels. A microgel is a cross-linked latex micoparticle that is swollen by a good solvent, and has a globular structure (Fig. 3). Staudinger, and Husemann were the first to prepare microgel particles (92), by polymerizing divinylbenzene (DVB) in a good solvent to get swollen cross-linked polymer particles. The average diameters of microgel particles range from nanometers to

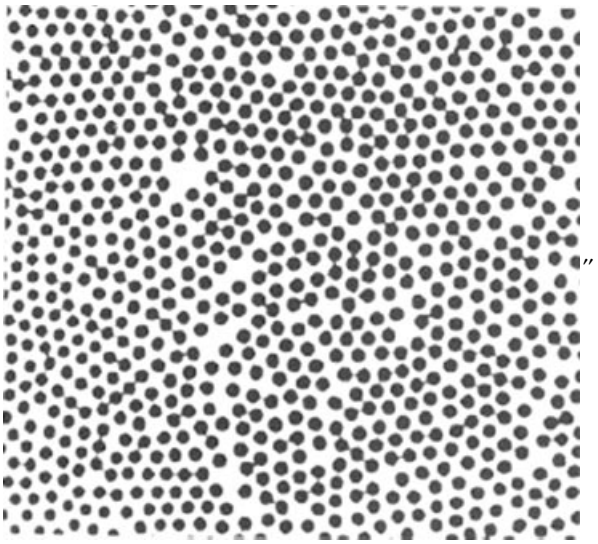


Fig. 3. The structure of PNIPAm microgel particles. Reprinted from B. Saunders and B. Vincent, "Microgel particles as model colloids", *Colloid and interface science*, **80**(1), 1 (1999). Copyright © 1999 with permission from Elsevier Science.

micrometers. Since beginning of 1970s, the research on microgels increased steadily due to the growing industrial and commercial importance.

Synthesis Methods. Usually microgels are prepared by emulsion polymerization, anionic copolymerization, cross-linking of neighboring polymer chains or inverse micro-emulsion polymerization (93). Emulsion polymerization can produce microgel particles with a narrow size distribution. When emulsion polymerization is carried out in the absence of the surfactant (surfactant free polymerization, SFEP), the continuous phase in the solution need to have a high dielectric constant and ionic initiators ($K_2S_2O_8$) are employed. The charged polymer chains formed during polymerization act as surfactant and stabilize the growing particles. SFEP has been widely used for the preparation of PNIPAm, in the presence of persulfate and cross-linking monomer at 70°C. Figures 3 and 4 show the PNIPAm microgel particles and scheme of synthesis by SFEP, respectively. It is difficult to prepare small microgels by surfactant-free methods because there is usually not enough available charge to stabilize the high concentrations of small particles. Adding a small amount of surfactant like sodium dodecyl sulfate (SDS) in the polymerization solution can reduce the microgel size greatly, but SDS can bind to poly(NIPAm) microgel, which is difficult to remove from the product.

Common Monomers for Microgel Synthesis. The common monomers used for synthesis of microgels are listed in Table 5.

Properties of Microgels. Due to a compact structure, the intrinsic viscosities of the microgels [h] are much lower than those of corresponding linear or branched polymers. When collapsed microgel particles swell in a good solvent, previously buried segment become accessible to the continuous phase. Because of the high interfacial area per unit mass, microgel particles show a rapid

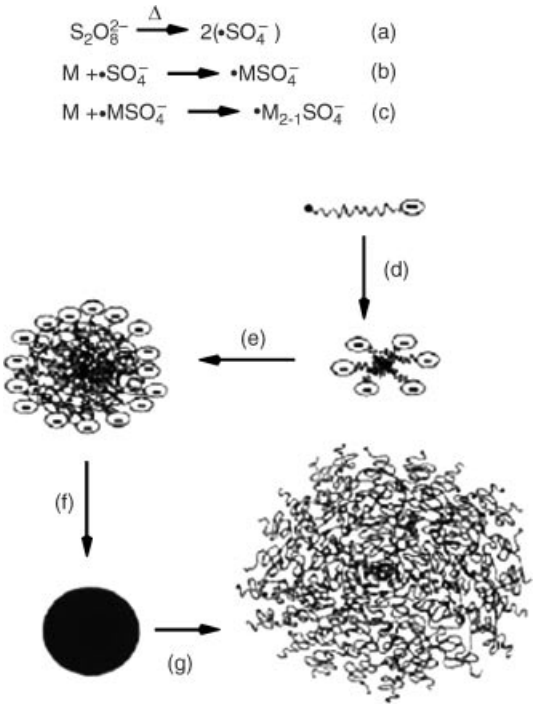


Fig. 4. The process of microgel forming. Reprinted from B. Saunders and B. Vincent, "Microgel particles as model colloids," *Colloid and surface science*, 80(1), 1 (1999). Copyright © with permission from elsevier Science.

swelling/de-swelling kinetics in comparison to bulk hydrogels. Microgels achieve steady-state swelling in <1 when the temperature is changed whereas bulk hydrogel can take days to weeks because the shrinking of the exterior layer can prevent transport from the interior. It is estimated that, for swelling, a microgel particle with diameter of 100 nm is eight orders of magnitude faster than a bulk hydrogel with diameter of 0.5 mm (93).

The deformable nature of microgel particles has important implications for the rheological properties. Dilute microgel dispersions exhibit Newtonian flow; whereas concentrated dispersions are highly shear thinning. Compared to

Table 5. **The Common Monomers for Synthesizing Microgels**

Monomer	Structure	Abbreviation	Reference
acrylic acid	CH_2=CHCOOH	AC	94
acrylamide	CH_2=$CHCONH_2$	AM	95
2-acrylamido-2-methylpropanesulfonic acid	CH_2=CHCONH(CH_3) CH_2SO_3H	AMPS	96
acrylonitrile	CH_2=CH-CN	AN	97
N-isopropylacrylamide	H_2C=CHCONHCH(CH_3)$_2$	NIPA	98
ethylacrylamide	CH_2=$CHCONHCH_2CH_3$	DEAm	99

hard sphere particles, swollen microgel particles have much higher dispersion viscosity, which is due to the large effective hydrodynamic diameter of the swollen particles. The microgel particles have applications in the surface coating and as filler materials.

One important property of microgel particles is the osmotic de-swelling behavior (100). For example, in the polystyrene (microgel)/toluene/ polystyrene (free polymer) system, an "exclusion shell" for PS free polymer is produced around the microgel particles. Also, in the poly(acrylate) microgel system, the added sodium salt of PAA cause de-swelling of the microgel particles that is believed to be due to the osmotic pressure of the mobile phase. If charge groups are incorporated (on the surface or in the interior) into the microgel particles during polymerization, then electrostatic interactions play an important role in determining stabilization. Small free polymer chains may diffuse through the microgel particle pores into the microgel particle interior with a uniform pore size distribution, thus may cause the swelling of the microgel particles. When the polymer chains are too large to diffuse into the microgel particles interior, the de-swelling results in the collapse of the network.

Responsive Micorgels. Thermoresponsive aqueous microgels have properties in common with water-soluble polymers and water swollen hydrogels. The properties of microgels depend on the subtle balance of polymer–polymer versus polymer–water interactions. Microgel can be characterized by standard colloidal techniques including dynamic light scattering, rheology, and electron microscopy.

Poly(NIPAm) microgels cross-linked with *N*,*N*′-methylenebisacrylamide rapidly swell and de-swell upon warming and subsequent cooling, in aqueous media (101). At temperatures below the LCST (33°C), poly(NIPAm) microgel become expanded, with "sponge-like" structure having water in the interstitial spaces, due to colloidal stabilization because the interparticle van der Waals attractive forces are negligibly small. On warming >33°C, the water in the interparticle spaces squeezes out leading to an increase in the interparticle attraction. In contrast to the discontinuous volume change in PNIPAm bulk hydrogels, the PNIPAm microgel particles has continuous volume change (98).

N-ethylacrylamide microgels are temperature sensitive with a phase transition at 78°C, but less abrupt than that of PNIPAm micorgel (102).

An interpenetrating network of microgel particles prepared by PAAc microgel in the presence of PAAm microgel exhibits an upper critical solution temperature, and a sharp swelling transition as compared to poly(acrylic acid-*co*-acrylamide) microgel particles (95).

pH-sensitive microgels can be prepared by copolymerizing acidic and basic groups into the polymer network. Variation in the solution pH induces a change in the network ionization and a corresponding change in swelling capacity.

The main applications involving microgel particles have been in the surface coating industry. Microgel particle dispersions are shear thinning and provide rheological control for automotive surface coatings (103). The particles also have good film-forming properties and favor the alignment of added metallic flakes parallel to the substrate surface. Microgel particles also show promise in the printing and pharmaceutical industries. The high surface area and good surface-coating characteristics have allowed functionalized microgel particles to be

coated on offset plates with impressive results. Alternatively, microgel particles have potential applications as drug delivery systems with the design to swell in the vicinity of the target sites inside the body. Ideally, this microencapsulation should possess a sensitive trigger mechanism, whereby the specific sites in target cells (eg, cancer cells) triggers microgel swelling, releasing the entrapped drug molecules.

5. Applications

5.1. Molecular Separation. Temperature sensitive hydrogels have been used to separate large molecules (eg proteins) from small molecules (eg, water) (104–107). In the separation, collapsed hydrogel (ie, below LCST) is added to the aqueous solution that is to be concentrated. Hydrogel swells by absorbing water, and small molecular solutes, leaving larger molecules behind. After equilibrium swelling is reached, the solid hydrogel is physically removed from the solution. The hydrogel is re-activated for another de-swelling use by raising the temperature a little over the LCST. Figure 5 (108) illustrated the separation process. Adjusting the cross-linking density can control the pore size of the hydrogels. The technology has been studied for the separation of soy proteins, enzymes (109), cellulases (110) nonionic surfactants (111), lignin (112), and bacteria dispersions (113). Since most thermosensitive hydrogels have LCST $<50^{\circ}$C, they require low energy to operate.

Although smart hydrogels have several advantages in the separation of biomoleucles over conventional methods, a number of properties (swelling rate, mechanical strength, and surface adsorption) of hydrogels need to be considered or improved before large scale use.

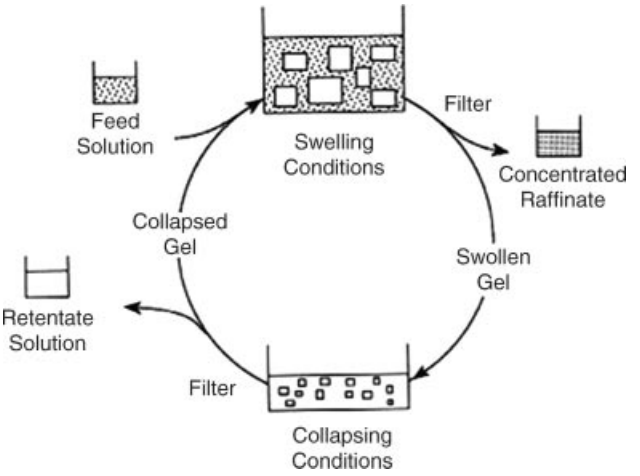


Fig. 5. Separation process by thermoreversible hydrogels. Reprinted with permission from K. L. Wang, J. H. Burban, and E. L. Cussler, K.Dusek, ed., *Advances in Polymer Science*, Springer Verlag, Berlin, Heidelberg, New York, 1993, P. 68.

The swelling rate of the hydrogels determines the speed of separation. Attempts have been made to improve the swelling rate of the hydrogels by having a porous structure (microporous, macroporous, and superporous). The temperature sensitive superporous hydrogels made of poly(*N*-isopropyl acrylamide-*co*-acrylamide) can swell to equilibrium in a matter of minutes (114).

The mechanical strength of hydrogels is important for proper handing, especially when the hydrogel is to be used in a large number of cycles. The hydrogel materials must have enough rigidity to retain mechanical integrity during the operation. Several methods have been used to improve the mechanical strength of the hydrogels (98,115–117).

When applying a hydrogel in the separation of proteins, the adsorption of proteins on the hydrogel surface results in a poor separation efficiency. For example, enzymes and BSA are found to adsorb onto a PNIPAm hydrogel surface resulting in a low separation efficiency. Grafting hydrophilic, flexible polymer chains, or incorporating reverse ionic charge on the hydrogel surface can reduce the adsorption of the proteins (118).

5.2. Proteins Isolation by Conjugating. The ability of responsive polymers in aqueous solutions to form a separate phase after a slight change in conditions has been used to isolate and purify proteins. A responsive polymer can be conjugated with a ligand that has affinity to the target protein (119). When the polymer is added to the mixture containing the protein and the conditions are changed (eg, pH, temperature, ionic strength, or a specific complex-forming agent), the polymeric conjugate together with the target protein segregates as a separate phase, while the impurities remain in the solution. The polymer-rich phase is filtered from the supernatant. Now, the target protein is either eluted from the polymeric phase, or is redissolved altering the conditions in such a way that the complex dissociates. The polymeric conjugate is reprecipitated but this time without the target protein, which remains in the solution. Instead of precipitation, reversible flocculation may also be used for the purification of biomolecules.

5.3. Hydrogel-Based Drug Delivery. Over the past few decades, there has been increasing attention devoted to the development of controlled release system using polymeric carriers. For example, drug embedded in a polymer matrix is surgically planted into the body. The drug is released directly into an affected site by diffusion or surface erosion. An ideal mechanism for release of the drug should be at zero order or at a constant rate. The polymer used for drug delivery must be biocompatible and degradable, the degradation products of the polymer must be nontoxic and not create any inflammatory response (120); and the degradation of the polymer should occur within a reasonable period of time.

In biodegradable hydrogels, drugs are usually in contact with water and thus the drug solubility is an important factor in drug release. The release of drugs with a high water solubility is rapid and independent of the matrix degradation rate. Thus, in general, the hydrogels are suitable for the controlled release of most low molecular weight, water-soluble drugs. In addition, the biodegradable hydrogel systems are useful for the delivery of macromolecular drugs, such as peptides and proteins, which are entrapped in the hydrogel network until the hydrogel is degraded (80).

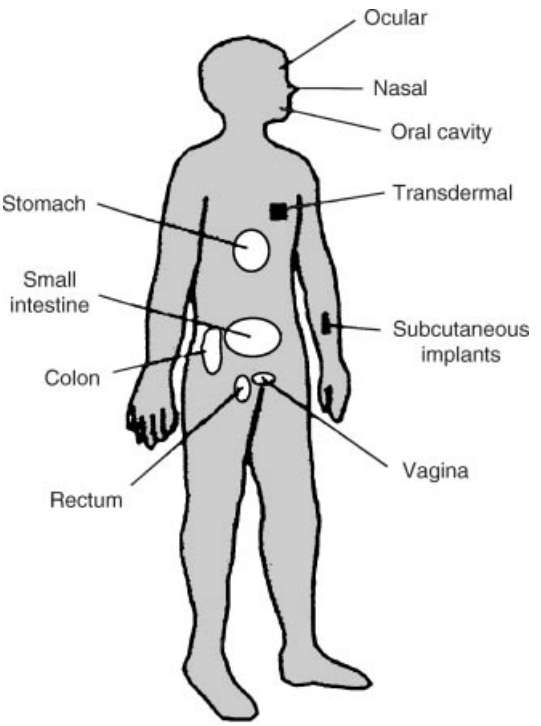


Fig. 6. Tissue locations applicable for hydrogel-based drug delivery (with permission from Ref. 121).

Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal, and subcutaneous application (121). Figure 6 illustrated various sites that are available for the application of hydrogels for drug delivery.

Drug delivery through the oral route has been the most common method in the pharmaceutical application of the hydrogels. Drug delivered to the oral cavity has been for the diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. The hydrogels need to have a high bioadhesion if copious salivery flow is present in the development of controlled release system for contraceptive application.

Rod-shaped monolithic hydrogel devices with progesterine have been studied in the development of controlled release system for contraceptive application. It was found that progesterine release depends on the initial drug load, the degree of cross-linking, and the water content of the hydrogel. The first-order release was observed.

Several hydrogel formulations for the subcutaneous delivery of anticancer drugs have been proposed. PHEMA with a good biocompatibility has been used for the release of cystabine (Ara-C) and methotrexate (122). A biodegradable hydrogel based on a semi-IPN structure composed of a poly(ε-caprolactone) and PEG macromer terminated with acrylate groups was used for the controlled release of clonazepam; a long-term constant release was successfully observed $>$45 days (123).

In addition, hydrogels have been investigated for rectal (124), ocular (125), transdermal (126), and subcutaneous (127) deliveries. Progesterone (128), nitroglycerin (129), and insulin (130) are a few of the drugs that are currently delivered to the body using polymer-based drug delivery systems. Microencapsulation is also a growing application of polymer-based controlled drug delivery (131,132).

For controlled release of insulin, the hydrogel system features an insulin-containing reservoir within a membrane of poly(methacrylic acid)-graft-poly-(ethylene glycol) copolymer in which the glucose oxidase is immobilized. The surface of the porous membrane contains a series of molecular "gates", which release insulin when the hydrogel shrinks at a low pH due to the interaction of glucose with glucose oxidase. The cross-linked PEG has the ability to adhere to a specific region in the upper intestine preferred for the delivery of insulin.

5.4. Hydrogels as Artificial Organs. Physical properties of hydrogels resemble living tissue more than any other kind of synthetic biomaterials. In particular, the high water content and the soft, rubbery consistency give them a strong, superficial resemblance to living soft tissue. PHEMA and its copolymers have been used as hemodialysis membranes that act as an artificial kidney (39). The membranes include poly(glycerol methacrylate-*co*-MMA), poly(hydroxypropyl methacrylate-*co*-MMA), and PHEMA hydrogels. The artificial kidney works like a hemodialysis machine, which cleanses the blood of people with kidney failure outside the body. Some artificial kidneys incorporate living kidney cells into its design, so that it can produce important hormones, process metabolites, and provide immune functions that dialysis cannot.

Recently, hydrogel membranes have been used for cell microencapsulation in biohybrid artificial organs. A high water-content (83%) and highly permeable polyelectrolyte hydrogel was developed, which was selective for albumin (67 kD) and IgG (150 kD) over IgA (170 kD) and IgM (900 kD) (133). The hydrogel has highly favorable properties for the encapsulation of hepatocytes, is biocompatible, and has the ability to maintain hepatocytes in a functional state for prolonged periods (survival rate of 85% for 45 days). Hydrogel can also be used as an alternative to ultrafiltration membranes for macroencapsulation. Microfiltration membranes (0.5-μm pore size) with neutral PAM hydrogels (134) have been used for the separation of ribonuclease A (RNAse, 13.5 kD) and BSA (67 kD).

A hybrid artificial liver support system was developed by using hepatocytes entrapped within a calcium alginate hydrogel (135). The module was designed in imitation of the gas–liquid contactor that uses the same principle. Forty disks with film-shaped hydrogel were mounted to a horizontal rotating axis and were kept in contact with blood. The concentration of hepatocytes in the gel varied from 1.9×10^9 to 1.7×10^{10} cells/L of gel. The results of *ex vivo* perfusion experiments using cats with acute hepatic insufficiency indicated that this module has the ability to replace liver function.

5.5. Porous Hydrogels for Tissue Engineering. The use of biocompatible hydrogels for tissue engineering is one area of intense research activity. The candidate materials include both natural polymers (such as fibrin, collagen, and gelatin) and synthetic polymers (PLA and PLGA). The use of hydrogel matrices for tissue repair and regeneration in the central nervous system (CNS) is based on two complementary aspects (136). The first is concerned with the healing process in the injured CNS as a potential mechanism for tissue

repair and axonal regeneration in mammals as observed in the lamprey, amphibians, and fish. The second is concerned with the process of organ repair and regeneration. Restoration of organ continuity and some degree of tissue repair in the CNS can be achieved using collagen gels or hydrogel matrices. The advantage is the nontoxicity of the collagen, the simplicity of the method, and the possibility to form a gel that exactly moulds the lesion. Porous matrices prepared from synthetic hydrogels are more stable, allowing it to sustain tissue growth and organization over long periods. But the potential toxicity with biological tissue of the synthetic hydrogel is a concern for tissue repairing.

The freeze–drying technique has been used to prepare porous gelatin hydrogels for tissue engineering. Gelatin is cross-linked with glutaraldehyde in aqueous solution, followed by rinsing and washing. The swollen hydrogel is frozen, and then the ice formed within the hydrogel network is sublimed by freeze–drying. Different porous structure can be obtained by varying the freezing temperature. The porosity of dried hydrogels can be controlled by the size of ice crystals formed during freezing. This method provides a promising way to prepare the porous scaffolds for cell growth, extra cellular matrix production (137,138), and for regeneration of damaged or lost tissues. Basic proteins, bFGF and TGF-β1, markedly absorb over time in the acidic-gelatin hydrogels, while less sorption takes place in the basic-gelatin hydrogels, because of the electrostatic interaction between the basic growth factors and the acidic gelatin. Animal experiments have proven that the biological performance of growth factors is enhanced by their sustained release, in marked contrast to the growth factors administered in the solution form.

5.6. Wound Dressings. Throughout the healing process, wounds produce a variety of fluids, generally known as wound exudate. The exudate contents may vary consisting primarily of blood and serum fluids to highly concentrated protein solutions. The amount of wound exudates must be controlled because overproduction can provide a media for bacterial proliferation or lead to maceration of the surrounding healthy tissue. Wound dressing can help control the wound. There are two types of dressings: dry and wet. It has been reported that healing with a wet environment is faster than that with the dry environment (139), due to the fact that renewed skin, without the formation of eschar, forms during healing in a wet environment. Hydrogel dressings were originally invented as wound burn dressings (140). Hydrogel wound dressings have many interesting properties including immediate pain control, easy replacement, transparency to allow healing follow up, absorption and loss prevention of body fluids, barrier against bacteria, good adhesion, good handling, oxygen permeability, and control of drug release. Hydrogel produced by radiation polymerization are fully sterile. The hydrogel allows permeation of drug and oxygen to the wound being healed and sticks to healthy skin surrounding the wound but not to the newly forming dermis. Hydrogel wound dressings are made in sheets with an impermeable polymeric backing sheet. The backing sheet prevents the partially hydrated hydrogel from dehydrating and drying onto the wound bed. Hydrogel based on collagen (141), PVA (142), PVP (143), PVA/PVP (144), and PEO/PVA (145) have been investigated for wound dressings. Collagen hydrogels have a high tensile strength, low extensibility, controllable cross-linking, and a low antigenicity. These hydrogels can be produced in a variety

of forms such as sheets, tubes, sponges, and powder (141). *In vivo* studies showed that the use of a collagen-based hydrogel sponge allowed cell migration, inhibited wound contraction, and accelerated wound repair. PVA/PVP hydrogel is promising for use as a burn wound covering. It shows some properties that can meet the requirements of an ideal wound dressing, eg, effective fluid absorption, pleasant in touch and painless on removal, exhibit a high elasticity but also good mechanical strength, good transparency, and can act as an efficient barrier against the microbes.

5.7. Fire Protection. It is well known that moist fire protection materials have good fire resistance characteristics. Due to its high water content, hydrogels can be used as burn free materials for fire protection (146,147). A commercial fire protection product Burnfree Fire/Trauma Blankets (www.saftycentral.com) is made of pure virgin wool, woven with a unique interlinking cell construction. The special construction, in conjunction with the wool fiber, allows the blanket to hold up to 14 times its weight of the hydrogel Burnfree solution. Burnfree blankets reduces physiological and psychological trauma by providing immediate cooling, soothing, and moistening of the burn. It also reduces the pain and trauma of wounds from fires, flames, scalds, chemical, and electrical injuries. Hydrogels are also used as dry fire extinguishing agent or mixed with water as aqueous extinguishing agent (148).

5.8. Hydrogel as Superabsorbent Materials. In the past 20 years, superabsorbent polymers (SAPs) have achieved a worldwide market. Figure 7 shows the swelling mechanism of superabsorbent polymers (149). In contact with water, the hydrophilic backbone interacts through hydration and hydrogen bonding with the solvent, accompanied by an energy decrease and entropy increase. Hydration leads to a high number of allowed configurations of the

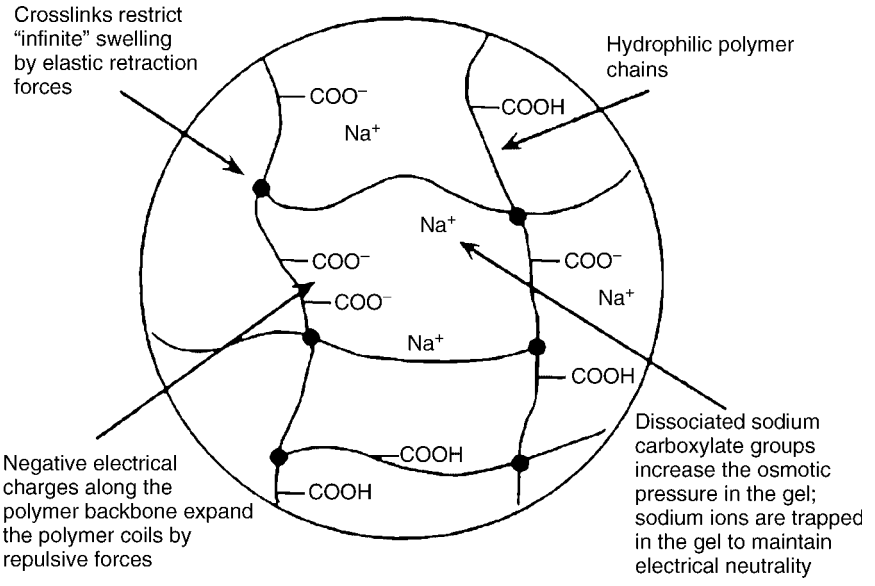


Fig. 7. The swelling mechanism of superabsorbent hydrogels. Reprinted from Ref. 149 by permission of the Dow Chemical Company.

system, which is equivalent to a higher degree of entropy. Because of the cross-linking, there is a balance between the trend toward infinite dilution of the chains and the restrictive forces. Higher cross-linking densities give networks with stronger restrictive forces and SAPs with lower degrees of swelling.

5.9. Diapers. The first commercial production of superabsorbent polymer was began in Japan in 1978, as feminine napkins, using cross-linked starch-grafted polyacryalte. In 1980, superabsorbent polymer was used in baby diapers in Germany and France (150). At first, the diapers used only a small amount of superabsorbent polymer as a supplement to fluff pulp that furnished most of the absorbency. Gradually, the superabsorbent polymers become the major component of the diapers. The commercial diaper products are packed with poly(acrylic acid) resins. Superabsorbent polymers are added to baby diapers in basically two ways: layered or blended. In the layered application, powered polymer first is scattered onto a layer of fluff pulp, then the fluff is folded, making the polymer located in a centralized layer in the absorbent structure. This structure is covered with a nonwoven fabric layer. In the blended application, the superabsorbent polymer first is mixed homogeneously with the fluff pulp. Then the mixture is covered with a nonwoven fabric, a method usually is adopted by American diaper makers.

5.10. Water-Sealing Construction Materials. Superabsorbent polymer can be used as a water-blocking construction filler with cement and asphalt emulsion (151). The main benefit of the fill material is its high ductility compared to conventional construction backfills such as gravel or sand. These fillers can be delivered in low viscosity, which aids in the complete filling of the space. Similar principles are employed in making and using sealing compounds for electrical and optical cables.

5.11. Agricultural Applications. Superabsorbent polymers have also found limited utility as additives to soil to improve the water-holding ability. The hydogel absorbs the water and controls its release back into the soil as conditions become drier. Poly(ammonium acrylate) and poly(acrylamide) hydrogels have been studied for spray application to the soil and plants. The gels are prepared for spraying by adding water to provide a readily deformable polymer that will pass through a spray apparatus. (152). Such hydrogels may be sprayed into the soil by use of a plow with special attachments for spraying below the surface of the soil that allows the gel to be placed at a definite depth and concentration. Modified PAM hydrogels are also used as conditioners for sandy soils (153). The hydrogel use reduces water consumption and increases both water and fertilizer use efficiency, hence the product can be used for conserving irrigation water and increasing the agricultural potentialities of sandy soils.

Biodegradable hydrogels based on polysaccharide or polyester–polyurea–polyurethane are used as an artificial soil for plant material capable of growth (eg, embedding plant materials in biodegradable hydrogels for use as an artificial seed, (154). The cross-linked PEO has been shown to substantially reduce the sensitivity of plants to water shortage, to promote their growth under condition of water shortage, and to improve the seeding survival and final crop. Beside a direct addition to growth media, polymer hydrogels can also been used as coatings for seeds and bare roots (155).

6. Safety and Health Aspects

Although most monomers and organic solvent involved in the hydrogel synthesis are harmful or toxic by direct touch, the polymerization and cross-linking suppresses the toxicity. Cumulative evidence shows that hydrogels are highly biocompatible and have extremely low toxicity to the human body. Most hydrogel products such as contact lenses, medicines, surgical dressings, and foods can be used directly. Biodegradable hydrogels can degrade into harmless small molecules within the human body. Some hydrogel breast implants have been removed from the market due to the lack of long-term toxicity data or clinical follow-up. The long-term risks of implants are not always obvious during the first few years of use (156). The studies of the risks of long-term use are essential to establish the safety of the implants. Acrylate, acrylamide monomers are eye and skin irritants, substituted acrylamides are less toxic. Acrylonitrile monomer is a neurotoxin and especially inhalation and ingestion should be avoided.

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