Environment-sensitive hydrogels for drug delivery

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Abstract

Environment-sensitive hydrogels have enormous potential in various applications. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature-sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. Light-sensitive, pressure-responsive and electro-sensitive hydrogels also have the potential to be used in drug delivery and bioseparation. While the concepts of these environment-sensitive hydrogels are sound, the practical applications require significant improvements in the hydrogel properties. The most significant weakness of all these external stimuli-sensitive hydrogels is that their response time is too slow. Thus, fast-acting hydrogels are necessary, and the easiest way of achieving that goal is to make thinner and smaller hydrogels. This usually makes the hydrogel systems too fragile and they do not have mechanical strength necessary in many applications. Environmentally sensitive hydrogels for drug delivery applications also require biocompatibility. Synthesis of new polymers and crosslinkers with more biocompatibility and better biodegradability would be essential for successful applications. Development of environmentally sensitive hydrogels with such properties is a formidable challenge. If the achievements of the past can be extrapolated into the future, however, it is highly likely that responsive hydrogels with a wide array of desirable properties can be made.

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Abbreviations: IPN, interpenetrating polymer network; LCST, lower critical solution temperature; PAAm, poly(acrylamide); BMA, butyl methacrylate; PNiAAm, poly(N-isopropylacrylamide); PDEAAM, poly(N,N-diethylacrylamide); PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PPO, poly(propylene oxide); poly(acrylic acid), poly(acrylic acid); PMA, poly(methacrylic acid); PLA, poly(l-lactic acid); PDEAEM, poly(N,N-diethyldiaminoethyl methacrylate); DMAEM, N,N'-dimethylaminooethyl methacrylate; PVD, poly(vinylaceteldiethylaminoacetate); PVA, poly(vinylalcohol); Con A, concanavalin A.

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1. Introduction

Controlled drug delivery systems, which are intended to deliver drugs at predetermined rates for predefined periods of time, have been used to overcome the shortcomings of conventional drug formulations. Although significant progress has been made in the controlled drug delivery area, more advances are yet to be made for treating many clinical disorders, such as diabetes and rhythmic heart disorders. In these cases, the drug has to be delivered in response to fluctuating metabolic requirements or the presence of certain biomolecules in the body. In fact, it would be most desirable if the drugs could be administered in a manner that precisely matches physiological needs at proper times (temporal modulation) and/or at the proper site (site-specific targeting). In addition, the controlled drug delivery area needs further development of techniques for delivery of peptide and protein drugs. In the body, the appearance of numerous bioactive peptides is tightly controlled to maintain a normal metabolic balance via a feedback system called ‘homeostasis’ [1]. It would be highly beneficial if the active agents were delivered by a system that sensed the signal caused by disease, judged the magnitude of signal, and then acted to release the right amount of drug in response. Such a system would require coupling of the drug delivery rate with the physiological need by means of some feedback mechanism.

Hydrogels have been used extensively in the development of the smart drug delivery systems. A hydrogel is a network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure. A three-dimensional network is formed by crosslinking polymer chains. Crosslinking can be provided by covalent bonds, hydrogen bonding, van der Waals interactions, or physical entanglements [2,3]. Hydrogels can protect the drug from hostile environments, e.g. the presence of enzymes and low pH in the stomach. Hydrogels can also control drug release by changing the gel structure in response to environmental stimuli. Hydrogels containing such ‘sensor’ properties can undergo reversible volume phase transitions or gel–sol phase transitions upon only minute changes in the environmental condition. The types of environment-sensitive hydrogels are also called ‘intelligent’ or ‘smart’ hydrogels [4]. Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. The physical stimuli include temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields, while the chemical or biochemical stimuli include pH, ions and specific molecular recognition events [5,6]. Smart hydrogels have been used in diverse applications, such as in making artificial muscles [7–11], chemical valves [12], immobilization of enzymes and cells [13–21], and concentrating dilute solutions in bioseparation [22–27]. Environment-sensitive hydrogels are ideal candidates for developing self-regulated drug delivery systems. For convenience, environment-sensitive hydrogels are classified based on the type of stimuli in this chapter.

2. Temperature-sensitive hydrogels

2.1. Polymer structures

Temperature-sensitive hydrogels are probably the most commonly studied class of environmentally sensitive polymer systems in drug delivery research [28]. Many polymers exhibit a temperature-responsive phase transition property. The structures of some of those polymers are shown in Fig. 1. The common characteristic of temperature-sensitive polymers is the presence of hydrophobic groups, such as methyl, ethyl and propyl groups. Of the many temperature-sensitive polymers, poly(N–isopropylacrylamide) (PNIPAAm) is probably the most extensively used. Poly(N,N-diethylacrylamide) (PDEAAm) is also widely used because of its lower critical solution temperature (LCST) in the range of 25–32 °C, close to the body temperature. Copolymers of NIPAAm can also be made using other monomers, e.g. butyl methacrylate (BMA), to alter the LCST.

Certain types of block copolymers made of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) also possess an inverse temperature-sensitive property. Because of their LCST at around the body temperature, they have been used widely in the development of controlled drug delivery systems based on the sol–gel phase conversion at the body temperature. A large number of PEO–PPO block copolymers are commercially available under the names of Pluronics® (or Poloxamers®) and Tetronics®. Their structures are shown in Fig. 2.

2.2. Properties of temperature-sensitive hydrogels

Most polymers increase their water-solubility as the temperature increases. Polymers with LCST, however, decrease their water-solubility as the temperature increases. Hydrogels made of LCST polymers shrink as the temperature increases above the LCST. This type of swelling behavior is known as inverse (or negative) temperature-dependence. The inverse temperature-dependent hydrogels are made of polymer chains that either possess moderately hydrophobic groups (if too hydrophobic, the polymer chains would not dissolve in water at all) or contain a mixture of hydrophilic and hydrophobic segments. At lower temperatures, hydrogen bonding between hydrophilic segments of the polymer chain and water molecules are dominates, leading to enhanced dissolution in water. As the temperature increases, however, hydrophobic
interactions among hydrophobic segments become strengthened, while hydrogen bonding becomes weaker. The net result is shrinking of the hydrogels due to inter-polymer chain association through hydrophobic interactions. In general, as the polymer chain contains more hydrophobic constituent, LCST becomes lower [29]. The LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segment of the polymer. One way is to make copolymers of hydrophobic (e.g. NIPAAm) and hydrophilic (e.g. acrylic acid) monomers [29–32]. The continuous phase transition of PNIPAAm is known to be changed to a discontinuous one by incorporating a small amount of ionizable groups into the gel network [33,34] or by changing solvent composition [35]. Copolymerization of NIPAAm with different types of monomers results in hydrogels with more versatile properties, such as faster rates of shrinking when heated through the LCST [36], and sensitivity to additional stimuli.

If the polymer chains in hydrogels are not covalently crosslinked, temperature-sensitive hydrogels may undergo sol–gel phase transitions, instead of swelling–shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Polymers that show this type of behavior are block copolymers of PEO and PPO as shown in Fig. 2. The hydrophobic PPO block can be replaced with other hydrophobic polymers. For example, PEO-containing block copolymers with poly(lactic acid) show the same thermo-reversible behavior. In this case, the poly(lactic acid) segment provides a biodegradable property.

Temperature-sensitive hydrogels can also be made using temperature-sensitive crosslinking agents. A hybrid hydrogel system was assembled from water-soluble synthetic polymers and a well-defined protein-folding motif, the coiled coil [37]. The hydrogel underwent temperature-induced collapse due to the cooperative conformational transition. Using temperature-sensitive crosslinking agents adds a new dimension in designing temperature-sensitive hydrogels.

2.3. Applications of temperature-sensitive hydrogels

Temperature-sensitive hydrogels have been studied most extensively and their unique applications have been reviewed in depth before [1,15,28,29,31,32]. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels.

2.3.1. Negatively thermosensitive drug release systems

Thermosensitive monolithic hydrogels were used to obtain an on–off drug release profile in response to a stepwise temperature change [38–40]. The hydrogels used in these studies include crosslinked P(NIPAAm–co-BMA) hydrogels [40–42], and interpenetrating polymer networks (IPNs) of P(NIPAAm) and poly(tetramethyleneether glycol) (PTMEG). Hydrophobic comonomer BMA was introduced into NIPAAm gels to increase their mechanical strength. The on–off release profile of indomethacin from these matrices was achieved with on at low temperature and off at high temperature. It was explained by the formation of a dense, less permeable surface layer of gel, described as a skin-type barrier. The skin barrier was formed upon a sudden temperature change due to the faster collapse of the gel surface than the interior. This surface shrinking process was found to be regulated by the length of the methacrylate alkyl side-chain, i.e. the hydrophobicity of the comonomer [43,44]. The results also suggested that the drug in the polymeric matrices diffused

![Fig. 1. Structures of some temperature-sensitive polymers.](image1)

![Fig. 2. Polymer structures of Pluronic®, Pluronic® R, Tetronic® and Tetronic® R.](image2)
from the inside to the surface during the off state even when no drug release was seen.

Temperature-sensitive hydrogels can also be placed inside a rigid capsule containing holes or apertures. As shown in Fig. 3, the on–off release is achieved by the reversible volume change of temperature-sensitive hydrogels [45,46]. Such a device is called a squeezing hydrogel device because the drug release is affected by the hydrogel dimension. In addition to temperature, hydrogels can be made to respond to other stimuli, such as pH. In this type of system, the drug release rate was found to be proportional to the rate of squeezing of the drug-loaded polymer.

Temperature-sensitive hydrogels can be secured by placing them inside a rigid matrix or by grafting them to the surface of rigid membranes. A composite membrane was prepared by dispersing PNIPAAm hydrogel microparticles into a crosslinked gelatin matrix [47]. The release of a model drug, 4-acetamidophen, was dependent on the temperature which determined the swelling status of the PNIPAAm hydrogel microparticles in the microchannels of the membrane. A similar approach was used to develop a reservoir type microcapsule drug delivery system by encapsulating the drug core with ethylcellulose containing nano-sized PNIPAAm hydrogel particles [48]. For making stable thermally controlled on–off devices, PNIPAAm hydrogel can be grafted onto the entire surface of a rigid porous polymer membrane [49].

### 2.3.2. Positively thermosensitive drug release systems

Certain hydrogels formed by IPNs show positive thermosensitivity, i.e. swelling at high temperature and shrinking at low temperature. IPNs of poly(acrylic acid) and polyacrylamide (PAAm) or P(AAm–co-BMA) have positive temperature dependence of swelling [50]. Increasing the BMA content shifted the transition temperature to higher temperature. The swelling of those hydrogels was reversible, responding to stepwise temperature changes. This resulted in reversible changes in the release rate of a model drug, ketoprofen, from a monolithic device.

### 2.3.3. Thermoreversible gels

The most commonly used thermoreversible gels are Pluronics® and Tetrinics®. Some of them have been approved by FDA and EPA for applications in food additives, pharmaceutical ingredients and agricultural products. A review on the properties and applications of Pluronics® in drug delivery is available [28]. For parenteral application of thermoreversible gels, it is most desirable that they are biodegradable. To add biodegradable capacity, the PPO segment of PEO–PPO–PEO block copolymers is often replaced by a biodegradable poly(γ-lactic acid) segment [51–53]. The molecular architecture was not limited to the A–B–A type block copolymer, but expanded into three-dimensional, hyperbranched structures, such as a star-shaped structure. Proper combinations of molecular weight and polymer architecture resulted in gels with different LCST values. When the hydrogel was formed by injecting the polymer solution loaded with model drugs into a 37 °C aqueous environment, the release of a hydrophilic model drug (ketoprofen) and a hydrophobic model drug (spironolactone) were first-order and S-shaped, respectively.

### 2.4. Limitations and improvements

Clinical applications of thermosensitive hydrogels based on NIPAAm and its derivatives have limitations. The monomers and crosslinkers used in the synthesis of the hydrogels are not known to be biocompatible, i.e. they may be toxic, carcinogenic or teratogenic. In addition, the polymers of NIPAAm and its derivatives are not biodegradable. The observation that acrylamide-based polymers activate platelets upon contact with blood, together with the unclear metabolism of poly(NIPAAm), requires extensive toxicity studies before clinical applications can emerge [28]. Further development of new, biocompatible and biodegradable thermoreversible gels, such as PEO–PLA block copolymers, is necessary to exploit the useful properties of thermoreversible hydrogels.

### 3. pH-sensitive hydrogels

#### 3.1. Polymer structures

All the pH-sensitive polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Fig. 4 shows structures of examples of anionic and cationic polyelectrolytes and their pH-dependent ionization. Poly(acrylic acid) (PAA) becomes ionized at high pH, while poly(N,N-diethylaminoethyl methacrylate) (PDEAEM) becomes ionized at low pH. As shown in Fig. 4, cationic polyelectrolytes, such as PDEAEM, dissolve more, or swell more if crosslinked, at low pH due to ionization. On the other hand, polyamions, such as PAA, dissolve more at high pH.

#### 3.2. Properties of pH-sensitive hydrogels

Hydrogels made of crosslinked polyelectrolytes display big differences in swelling properties depending on the pH of the environment. The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. Ionization on polyelectrolytes, however, is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This tends to make the apparent dissociation constant ($K_a$) different from that of the corresponding monoacid or monobase. The presence of ionizable groups on polymer chains results in swelling of the hydrogels much beyond that can be achievable by nonelectrolyte polymer hydrogels. Since the swelling of polyelectrolyte hydrogels is mainly due to the electrostatic repulsion among charges present on the polymer chain, the extent of swelling is influenced by any condition that

![Fig. 3. Schematic illustration of on–off release from a squeezing hydrogel device for drug delivery (from Ref. [46]).](image)

![Fig. 4. pH-dependent ionization of polyelectrolytes. Poly(acrylic acid) (top) and poly(N,N-diethylaminoethyl methacrylate) (bottom).](image)
reduce electrostatic repulsion, such as pH, ionic strength, and type of counterners [54]. The swelling and pH-responsiveness of polyelectrolyte hydrogels can be adjusted by using neutral comonomers, such as 2-hydroxyethyl methacrylate, methyl methacrylate and maleic anhydride [55–58]. Different comonomers provide different hydrophobicity to the polymer chain, leading to different pH-sensitive behavior.

Hydrogels made of poly(methacrylic acid) (PMA) grafted with poly(ethylene glycol) (PEG) have unique pH-sensitive properties [59]. At low pH, the acidic protons of the carboxyl groups of PMA interact with the ether oxygen of PEG through hydrogen bonding, and such complexation results in shrinkage of the hydrogels. As the carboxyl groups of PMA become ionized at high pH, the resulting decomposition leads to swelling of the hydrogels. The same principle can be applied to IPN systems where two different types of polymer chain interact through pH-dependent hydrogen bonding.

### 3.3. Applications of pH-sensitive hydrogels

#### 3.3.1. Controlled drug delivery

pH-sensitive hydrogels have been most frequently used to develop controlled release formulations for oral administration. The pH in the stomach (<3) is quite different from the neutral pH in the intestine, and such a difference is large enough to elicit pH-dependent behavior of polyelectrolyte hydrogels. For polyacationic hydrogels, the swelling is minimal at neutral pH, thus minimizing drug release from the hydrogels. This property has been used to prevent release of foul-tasting drugs into the neutral pH environment of the mouth. When caffeine was loaded into hydrogels made of copolymers of methacrylate and N,N′-dimethylaminoethylmethacrylate (DMAEM), it was not released at neutral pH, but released at zero-order at pH 3–5 where DMAEM became ionized [60]. Polyacationic hydrogels in the form of semi-IPN have also been used for drug delivery in the stomach. Semi-IPN of crosslinked chitosan and PEO showed more swelling under acidic conditions (as in the stomach). This type of hydrogels would be ideal for localized delivery of antibiotics, such as amoxicillin and metronidazole, in the stomach for the treatment of *Helicobacter pylori* [61].

Hydrogels made of PAA or PMA can be used to develop formulations that release drugs in a neutral pH environment [57,58]. Hydrogels made of polyanions (e.g. PAA) crosslinked with azoaromatic crosslinkers were developed for colon-specific drug delivery. Swelling of such hydrogels in the stomach is minimal and thus, the drug release is also minimal. The extent of swelling increases as the hydrogel passes down the intestinal tract due to increase in pH leading to ionization of the carboxylic groups. But, only in the colon, can the azoaromatic cross-links of the hydrogels be degraded by azoreductase produced by the microbial flora of the colon [62,63], as shown in Fig. 5. The degradation kinetics and degradation pattern (e.g. surface erosion or bulk erosion) can be controlled by the crosslinking density [62]. The kinetics of hydrogel swelling can be controlled by changing the polymer composition [63]. The polymer composition can be changed as the pH of the environment changes. Some pendant groups, such as N-alkanoyl (e.g. propionyl, hexanoyl and lauroyl) and O-acylhydroxylyamine moieties, can be hydrolyzed as the pH changes from acidic to neutral values, and the rate of side-chain hydrolysis is dependent on the length of the alkyl moiety.

pH-sensitive hydrogels were placed inside capsules [46] or silicone matrices [64,65] to modulate the drug release. In the squeezing hydrogel system [46], drug release was controlled by a mechanism similar to that shown in Fig. 3. The only difference is that the swelling—shrinking of hydrogels is controlled by changing pH, instead of temperature. In the silicone matrix system [64,65], medicated pH-dependent hydrogel particles made of semi-IPN of PAA and PEO were used. The release patterns of several model drugs having different aqueous solubilities and partitioning properties (including salicylamide, nicotinamide, clonidine HCl and prednisolone) were correlated with the pH-dependent swelling pattern of the semi-IPN. At pH 1.2, the network swelling was low and the release was limited to an initial burst. At pH 6.8, the network became ionized and higher swelling resulted in increased release. Poly(vinylacetaldiethylaminoacetate) (PVD) has pH-dependent aqueous solubility. Both the turbidity and SEM results showed that PVD formed a hydrogel upon increase in pH from 4 to 7.4 [66]. The release of a model drug, chlorpheniramine maleate, was fast right after the PVD solution was introduced into a pH 7.4 buffer solution, but became very slow after the PVD hydrogel was formed [66]. The pH-dependent sol-to-gel transformation of AEA was used to develop nasal spray dosage forms for treating allergic rhinitis and sinusitis [67]. The in vivo rat study showed that the apparent disappearance rate constant of chlorpheniramine maleate decreased with increase in the PVD concentration. The hydrogel formation on the mucous membranes in the rat nasal cavity was visually confirmed. If the time for sol-to-gel transition is shortened and the mucoadhesive property is added, the PVD system could be an ideal system for nasal delivery.

Hydrogels that are responsive to both temperature and pH can be made by simply incorporating ionizable and hydrophobic (inverse thermosensitive) functional groups to the same hydrogels. When a small amount of anionic monomer, such as acrylic acid, is incorporated in a thermoreversible polymer, the LCST of the hydrogel depends on the ionization of the pendant carboxyl groups, i.e. the pH of the medium. As the pH of the medium increases above the pK of the carboxyl groups of polyanions, LCST shifts to higher temperatures due to the increased hydrophilicity and charge repulsion. Terpolymer hydrogels made of NIPAAm, vinyl terminated polydimethylsiloxane macromer and acrylic acid were used for the delivery of indomethacin and amylase [36,68]. Other terpolymer hydrogels containing NIPAAm, acrylic acid and 2-hydroxyethyl methacrylate were prepared for the pulsatile delivery of streptokinase and heparin as a function of stepwise pH and temperature changes [69,70].

#### 3.3.2. Other applications

pH-sensitive hydrogels have also been used in making biosensors and permeation switches [5]. The pH-dependent hydrogels for these applications are usually loaded with enzymes that change the pH of the local microenvironment inside the hydrogels. One of the common enzymes used in pH-sensitive hydrogels is glucose oxidase which transforms glucose to gluconic acid. The formation of gluconic acid lowers the local pH, thus affecting the swelling of pH-dependent hydrogels.
3.4. Limitations and improvements

One of the inherent limitations of synthetic pH-sensitive polymers is their non-biodegradability. For this reason, hydrogels made of non-biodegradable polymers have to be removed from the body after use. The non-biodegradability is not a problem in certain applications, such as in oral drug delivery, but it becomes a serious limitation in other applications, such as the development of implantable drug delivery agents or implantable biosensors. Thus, attention has been focused on the development of biodegradable, pH-sensitive hydrogels based on polypeptides, proteins and polysaccharides [71,72]. Dextran was activated with 4-aminobutyric acid for crosslinking with 1,10-diaminodecane, and also grafted with carboxylic groups [71]. The modified dextran hydrogels showed a faster and higher degree of swelling at high pH conditions, and changing the pH between 7.4 and 2.0 resulted in cyclic swelling–deswelling. It is noted that dextran hydrogels may not be exactly biodegradable, since the body or certain sites in the body may not have the enzyme to degrade dextran molecules. Natural polysaccharides are not necessarily biodegradable in the human body.

Synthetic polypeptides were also used in synthesis of biodegradable hydrogels because of their more regular arrangement and less versatile amino acid residues than those derived from natural proteins. Examples of such synthetic polypeptide hydrogels include poly(hydroxyl-L-glutamate), poly(L-ornithine), poly(aspartic acid), poly(L-lysine) and poly(L-glutamic acid) [72]. In addition to normal electrostatic effects associated with most pH-sensitive synthetic polymer hydrogels, secondary structures of the polypeptide backbone may also contribute to the pH-sensitive swelling behavior [72]. The overall extent of pH-responsive swelling could be engineered by modification of the polypeptide by changing its hydrophobicity and degree of ionization.

4. Glucose-sensitive hydrogels

One of the most challenging problems in controlled drug delivery area is the development of self-regulated (modulated) insulin delivery systems. Delivery of insulin is different from delivery of other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Thus, self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for modulating insulin delivery, and all of them have a glucose sensor built into the system.

4.1. pH-sensitive membrane systems

Glucose oxidase is probably the most widely used enzyme in glucose sensing. It oxidizes glucose to gluconic acid, resulting in a pH change of the environment. This makes it possible to use different types of pH-sensitive hydrogels for modulated insulin delivery. For hydrogel membranes made of polycations, such as PDEAEM, the lowering of pH leads to hydrogel membrane swelling due to the ionization of PDEAEM. When a membrane swells, it tends to release more drugs, including insulin, than the membrane in the less-swollen state [73,74].

If the hydrogel membranes are made of polyanions, self-regulated insulin release is controlled by different mechanisms. A glucose-sensitive hydraulic flow controller can be designed using a porous membrane system consisting of a porous filter grafted with polyanions, e.g. poly(methacrylic acid–co-butyl methacrylate), and immobilized glucose oxidase. The grafted polyanion chains are expanded at pH 7 due to electrostatic repulsion among the charges on the polymer chains. When glucose oxidase converts glucose to gluconic acid, however, the chains collapse due to the protonation of the carboxyl groups of the polymer. Thus, the pores are open for the diffusion of insulin [75]. In another formulation, insulin can be loaded inside a hydrogel matrix which can be collapsed (or shrunken) as a result of lowering the pH. In this case, insulin release is enhanced due to the ‘squeezing’ action of the collapsing hydrogel [76]. In a system where a glucose oxidase-containing hydrogel covers a pH-sensitive erodible polymer that contains insulin, the polymer erosion, and thus insulin release, is controlled by the lowering of the local pH [77].

4.2. Con A-immobilized systems

Concanavalin A (Con A) has also been frequently used in modulated insulin delivery. Con A is a glucose-binding protein obtained from the jack bean plant, Canavalia ensiformis. In this type of system, insulin molecules are attached to a support or carrier through specific interactions which can be interrupted by glucose itself. This generally requires the introduction of functional groups onto insulin molecules. In one approach, insulin was chemically modified to introduce glucose, which itself binds especially to Con A [78]. The glycosylated insulin–Con A system exploits the complementary and competitive binding behavior of Con A with glucose and glycosylated insulin. The free glucose molecules compete with glucose–insulin conjugates bound to Con A and thus, the glycosylated insulin is desorbed from the Con A host in the presence of free glucose. The desorbed glucose–insulin conjugates are released within the surrounding tissue, where studies have shown that they are bioactive. Various glycosylated insulins having different binding affinities to Con A have been synthesized in an effort to manipulate the displacement of immobilized insulin from Con A at different glucose levels [79–84].

4.3. Sol–gel phase reversible hydrogel systems

Hydrogels can be made to undergo sol–gel phase transformations depending on the glucose concentration in the environment. Reversible sol–gel phase transformations require glucose-responsive crosslinking. A highly specific interaction between glucose and Con A was used to form crosslinks between glucose-containing polymer chains. Since Con A exists as a tetramer at physiological pH and each subunit has a glucose binding site, Con A can function as a crosslinking agent for glucose-containing polymer chains. Because of the non-covalent interaction between glucose and Con A, the formed crosslinks are reversible, as shown in Fig. 6 [85–89]. As the external glucose molecules diffuse into the hydrogel, individual free glucose molecules can compete with the polymer-attached glucose molecules and exchange with them. The concentrations of Con A and glucose-containing polymers can be adjusted to make hydrogels that respond (i.e. undergo gel-to-sol transformation) at specific free glucose concentrations. It has been shown that diffusion of insulin through the solution (Sol) phase is an order of magnitude faster than that through the hydrogel (gel) phase, and that insulin release can be controlled as a function of the glucose concentration in the environment. Other similar systems utilized poly(glucosyloxyethylmethacrylate)–Con A complexes [90,91] and polysaccharide (e.g. polysucrose, dextran, glycogen)–Con A gel membranes [92–94].

Glucose-sensitive phase-reversible hydrogels can also be prepared without using Con A. Polymers having phenylboronic groups (e.g. poly [3-(acylamido)phenylboronic acid] and its copolymers) and polyl polymers (e.g. PVA) form a gel through complex formation between the pendant phenylborate and hydroxyl groups, as shown in Fig. 7 [95–97]. Glucose, having pendant hydroxyl groups, competes with polyol polymers for the borate cross-linkages. Since glucose is monofunctional (i.e. has only one binding site for the borate group), it cannot function as a crosslinking agent as polyol polymer does. Thus, as the glucose concentration increases, the crosslinking density of the gel decreases and the gel swells/erodes to release more insulin. With higher glucose concentrations, the gel becomes a sol. The glucose exchange reaction is reversible and borate-polyol crosslinking is reformed at a lower glucose concentration. Instead of long chain polyol polymers, shorter molecules, such as diglucosylnexanediamine, can be used as a
crosslinking agent. Since the phenylboronic acid gel is sensitive to glucose only at alkaline conditions (pH 9), various copolymers containing phenylboronic acid were synthesized to provide glucose sensitivity at physiological pH. The main problem of this system is the low specificity of PBA-containing polymers to glucose.

4.4. Limitations and improvements

Although all of the glucose-sensitive insulin delivery systems are elegant and highly promising, many improvements need to be made for them to become clinically useful. First of all, the response of these hydrogels upon changes in the environmental glucose concentration occurs too slowly. Furthermore, hydrogels do not go back to their original states fast enough after responding to the changing glucose concentration. Reducing the hydrogel dimensions may be one way of shortening the response time. The current hydrogel systems also need improved reproducibility. In clinical situations, the hydrogels need to respond to ever changing glucose concentrations all the time, requiring hydrogels that can respond reproducibly and with rapid response onset times on a long-term basis. An additional constraint is that all the components used in the glucose-sensitive hydrogels should be biocompatible (e.g. Con A, the crosslinker most frequently used in modulated insulin delivery, is known to induce undesirable immune response [98,99]). Successful clinical applications of glucose-sensitive hydrogels for modulated insulin delivery demand new, biocompatible glucose-binding molecules.

5. Electric signal-sensitive hydrogels

5.1. Properties of electro-sensitive hydrogels

Electric current can also be used as an environmental signal to induce responses of hydrogels. Hydrogels sensitive to electric current are usually made of polyelectrolytes, as are pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. Sometimes, the hydrogels show swelling on one side and deswelling on the other side, resulting in bending of the hydrogels. The hydrogel shape change (including swelling, shrinking and bending) depends on a number of conditions. If the surface of hydrogel is in contact with the electrode, the result of applying electric field to the hydrogel may be different from systems where the hydrogel is placed in water (or acetone–water mixture) without touching the electrode. The result will be different yet if the aqueous phase contains electrolytes.

Partially hydrolyzed polyacrylamide hydrogels which are in contact with both the anode and cathode electrodes undergo volume collapse by an infinitesimal change in electric potential across the gel. It should be noted that the hydrogels do not contain any salts. When the potential is applied, hydrated H⁺ ions migrate toward the cathode resulting in loss of water at the anode side. At the same time, electrostatic attraction of negatively charged acrylic acid groups toward the anode surface creates a uniaxial stress along the gel axis, mostly at the anode side. These two simultaneous events lead to shrinking of the hydrogel at the anode side [100,101].

![Fig. 6. Sol–gel phase-transition of a glucose-sensitive hydrogel. Large circles represent Con A, a glucose-binding protein. Small open and closed hexagons represent polymer-attached glucose and free glucose, respectively.](image)

![Fig. 7. Sol–gel phase-transition of a phenylborate polymer. At alkaline pH, phenylborate polymer interacts with poly(vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to induce a transition from the gel to the sol phase.](image)
When a hydrogel made of sodium acrylic acid–acrylamide copolymer is placed in aqueous solution (acetone–water mixture) under electric field without touching the electrodes, the type of hydrogel deformation depends on the concentration of the electrolytes. In the absence of electrolytes or in the presence of very low concentration of electrolytes, application of an electric field causes the hydrogel to shrink. This is due to the migration of Na\(^+\) to the cathode electrode resulting in changes in the carboxyl groups of the polymer chains from –COOH to –COO\(^-\) [102]. In the presence of high concentration of electrolytes in solution, however, more Na\(^+\) enters the hydrogel than migrates from the hydrogel to the cathode [102]. The swelling is more prominent at the hydrogel side facing the anode and this results in bending of the hydrogels. If a cationic surfactant, such as n-dodecylpyridinium chloride, is added to the aqueous solution, the swelling occurs at the cathode side of the hydrogel [10]. This is due to the movement of positively charged surfactant molecules toward the cathode to form a complex with the negatively charged polymer chains on the side of the hydrogel facing the anode.

When microspherical hydrogel particles are placed in water without any salts, application of an electric field results in the shrinkage of the hydrogels due to electroosmosis (migration of water) and electrophoresis (migration of charged ions) from the hydrogel to the cathode [103]. This property has been used for modulated drug delivery by ‘on–off’ of the electric field. As described above, the response of electro-sensitive hydrogels depends on the experimental conditions and thus, any generalization on the swelling/collapse behavior cannot be made.

5.2. Applications of electro-sensitive hydrogels

5.2.1. Applications in drug delivery

Electro-sensitive hydrogels have been applied in controlled drug delivery [1,103]. Hydrogels made of poly(2-acrylamido-2-methylpropane sulfonic acid–co-n-butyldimethacrylate) were able to release edrophonium chloride and hydrocortisone in a pulsatile manner using electric current [104]. Control of ‘on–off’ drug release was achieved by varying the intensity of electric stimulation in distilled–deionized water. For edrophonium, a positively charged drug, the release pattern was explained as an ion exchange between the positively-charged solute and hydrogen ion produced by electrolysis of water.

Chemomechanical shrinking and swelling of PMA hydrogels under an electric field was used for the pulsatile delivery of pilocarpine and rafinose. Microparticles of PAA hydrogel which showed rapid and sharp shrinkage with the application of electric current, recovered their original size when the electric field was turned off. The electric field-induced changes in the size of the microparticles resulted in ‘on–off’ release profiles. The electric field-induced volume changes of poly(dimethylaminopropyl acrylamide) hydrogels were used for pulsatile release of insulin [103]. The monolithic device composed of sodium alginate and PAA was also used to release hydrocortisone in a pulsatile manner using an electric stimulus [105].

In addition to hydrogel swelling and contraction, electric fields have also been used to control the erosion of hydrogels made of poly(ethylenezoxazine)–PMA complex in a saline solution [106]. The two polymers form a hydrogel via intermolecular hydrogen bonding between carboxylic and oxazoline groups. When the gel matrix was facing a cathode surface, application of electric current caused disintegration of the complex into water-soluble polymers at the gel surface facing the cathode. The surface erosion of this polymer system was controlled either in a stepwise or continuous fashion by controlling the applied electrical stimulus. Pulsatile insulin release was achieved by applying a step function of electric current.

5.2.2. Applications in other areas

Electro-sensitive hydrogels, which are basically pH-sensitive hydrogels, are able to convert chemical energy to mechanical energy [9]. Those systems can serve as actuators or artificial muscles in many applications. All living organisms move by the isothermal conversion of chemical energy into mechanical work, e.g. muscular contraction, and flagellar and ciliary movement. Electrically driven motility has been demonstrated using weakly crosslinked poly(2-acrylamido-2-methylpropanesulfonic acid) hydrogels. In the presence of positively charged surfactant molecules, the surface of the polyanionic hydrogel facing the cathode is covered with surfactant molecules reducing the overall negative charge. This results in local shrinkage of the hydrogel leading to bending of the hydrogel. Application of an oscillating electrode polarity could lead the hydrogel to quickly repeat its oscillatory motion, leading to a worm-like motion [10].

5.2.3. Limitations and improvements

One of the advantages of electro-sensitive hydrogels in drug delivery is that the drug release rate can be easily controlled simply by modulating the electric field. At present, controlled drug delivery based on electro-sensitive hydrogels is still in its infancy. Aside from the problem common to all hydrogels, i.e. slow response of the hydrogel itself, the use of electro-sensitive hydrogels requires a controllable voltage source. In addition, most of the electro-sensitive hydrogels work in the absence of electrolytes. It may not be easy to develop drug delivery modules based on electro-sensitive hydrogels that work under physiological conditions.

6. Light-sensitive hydrogels

6.1. Properties of light-sensitive hydrogels

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others. For example, the sensitivity of temperature-sensitive hydrogels is rate limited by thermal diffusion, while pH-sensitive hydrogels can be limited by hydrogen ion diffusion. The capacity for instantaneous delivery of the sol–gel stimulus makes the development of light-sensitive hydrogels important for various applications in both engineering and biochemical fields. Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. Unlike UV light, visible light is readily available, inexpensive, safe, clean and easily manipulated.

The UV-sensitive hydrogels were synthesized by introducing a leuco derivative molecule, bis(4-dimethylamino)phenylmethyl leucocyanide, into the polymer network [107]. Triphenylmethane leuco derivatives are normally neutral but dissociate into ion pairs under ultraviolet irradiation producing triphenylmethylanions. As shown in Fig. 8, the leuco derivative molecule can be ionized upon ultraviolet irradiation. At a fixed temperature, the hydrogels discontinuously swelled in response to UV irradiation but shrank when the UV light was removed. The UV-induced discontinuous volume phase transition is different from a continuous volume phase transition in the absence of UV-irradiation. The UV light-induced swelling was due to an increase in osmotic pressure within the gel due to the appearance of cyanide ions formed by UV irradiation.

Visible light-sensitive hydrogels were prepared by introducing a light-sensitive chromophore (e.g. trisodium salt of copper chlorophyllin) into the polymer network [108]. Triphenylmethane leuco derivatives are normally neutral but dissociate into ion pairs under ultraviolet irradiation producing triphenylmethylanions. As shown in Fig. 8, the leuco derivative molecule can be ionized upon ultraviolet irradiation. At a fixed temperature, the hydrogels discontinuously swelled in response to UV irradiation but shrank when the UV light was removed. The UV-induced discontinuous volume phase transition is different from a continuous volume phase transition in the absence of UV-irradiation. The UV light-induced swelling was due to an increase in osmotic pressure within the gel due to the appearance of cyanide ions formed by UV irradiation.
to shrink) by visible light and can be deactivated (i.e. induced to swell) by increasing pH.

Since the mechanism of the visible light-induced volume change of these hydrogels is based on the induction of temperature changes via the incorporated photosensitive molecules, infrared light can also be used to elicit hydrogel response in the absence of the chromophores. This method is useful due to the high infrared light absorbency of water. When poly(N-isopropylacrylamide) hydrogels without any chromophores are irradiated by a CO₂ laser infrared, the volume phase transition, together with a gel bending toward the laser beam was observed during irradiation [110]. The degree of bending, due to the formation of a temperature gradient, depended on the CO₂ laser power, while the relaxation of the gel to its original shape after irradiation followed an exponential form.

6.2. Applications

Light-sensitive hydrogels can be used in the development of photoresponsive artificial muscles, switches and memory devices [108]. The potential application of visible light-responsive hydrogels for temporal drug delivery was also proposed, based on the response of crosslinked hyaluronic acid hydrogels that undergo photosensitized degradation in the presence of methylene blue [111].

6.3. Limitations and improvements

While the action of stimulus (light) is instantaneous, the reaction of hydrogels in response to such action is still slow. In most cases, the conversion of light into thermal energy must precede the restructuring of polymer chains upon temperature change. In addition, unless chromophores are covalently linked to the polymer backbone, they can be leached out during swelling–deswelling cycles.

7. Other stimuli sensitive hydrogels

In addition to the widely used stimuli discussed above, other stimuli have also been used for making environmentally sensitive hydrogels. Other stimuli include pressure [112], specific ions [113], thrombin [114–116] and antigen [117].

7.1. Pressure-sensitive hydrogels

The concept that hydrogels may undergo pressure-induced volume phase transition came from thermodynamic calculations based on uncharged hydrogel theory. According to the theory, hydrogels which are collapsed at low pressure would expand at higher pressure. Experiments with poly(N-isopropylacrylamide) hydrogels confirmed this prediction [112]. The degree of swelling of poly(N-isopropylacrylamide) hydrogels increased under hydrostatic pressure when the temperature is close to its LCST. Other hydrogels, such as poly(N-n-propylacrylamide), poly(N,N-diethylacrylamide) and poly(N-isopropylacrylamide), all showed the pressure sensitivity near their LCSTs. The pressure sensitivity appeared to be a common characteristic of temperature-sensitive gels. It was concluded that the pressure sensitivity of the temperature-sensitive gels was due to an increase in their LCST value with pressure [113].

7.2. Specific ion-sensitive hydrogels

Little or no effect of salt concentration on swelling behavior is expected for neutral hydrogels. A nonionic poly(N-isopropylacrylamide) hydrogel, however, showed a sharp volume phase transition at a critical concentration of sodium chloride in aqueous solution [118]. Below the LCST, the water content of the hydrogel is a strong function of the sodium chloride concentration. The gel collapses sharply at a critical sodium chloride concentration; this concentration was also found to be temperature dependent. Increasing temperatures leads to a corresponding decrease in the critical concentration of sodium chloride. Other salts tested show no such behavior outside the salting-out regime. Sodium ions were common to all of the salts tested, suggesting that chloride ions played a major role in this phase transition. Although the mechanism for this unique ion-sensitivity remained unknown, the LCST of the hydrogel appeared to be lowered by increasing the chloride concentration. This unique phase transition behavior could be applicable to making chloride ion-sensitive biosensors.

The phase transition behavior of positively charged poly(diallyldimethylammonium chloride) hydrogels is sensitive to the concentration of sodium iodide [119]. At the critical concentration, sodium iodide could induce a hydrogel to collapsed state phase transition, however, a wide hysteresis accompanies this transition. Since other salts tested did not initiate the network collapse in the investigated concentration ranges, an ion pair and multiplet (ionomer effect) theory was proposed to explain these interesting experimental results.

7.3. Specific antigen-responsive hydrogels

For some biomedical applications, it is highly desirable and useful to develop a material or device, which can respond to specific proteins. Sol–gel phase-reversible hydrogels were prepared based on antigen–antibody interactions. The concept is the same as that used in glucose-sensitive phase-reversible hydrogels. A semi-interpenetrating network hydrogel was prepared by grafting an antigen and a corresponding antibody to different polymer networks [117]. The gel is formed by crosslinking interactions that occur upon antigen–antibody binding. Hydrogel swelling is triggered in the presence of free antigens that compete with the polymer-bound antigen, leading to a reduction in the crosslinking density (Fig. 9).

7.4. Thrombin-induced infection-responsive hydrogels

For release of antibiotics at the site and time of infection, PVA hydrogels loaded with grafted gentamycin were made. Gentamycin was chemically attached to the polymer backbone through peptide linkers that can be enzymatically degraded by thrombin [114]. This approach was based on the observation that exudates from the dorsal pouch of rats infected by Pseudomonas aeruginosa showed significantly higher thrombin-like enzymatic activity toward a certain peptide sequence than exudates from non-infected wounds. This is the same approach as the polymeric prodrugs that release attached drug molecules slowly, except that in this case, the release is accelerated by infection. This type of approach can be applied to occlusive wound...
dressings and infection-prone catheters, drainage bags and prostheses [114]. This type of system in general has sufficient specificity and excellent potential as a stimulus-responsive, controlled drug release system [116].

8. Summary

Environmentally-sensitive hydrogels have enormous potential in various applications. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as bisensors as well as delivery systems. Light-sensitive, pressure-responsive and electro-sensitive hydrogels also have potential to be used in drug delivery and bioseparation. While the concepts of these environmentally-sensitive hydrogels are sound, the practical applications require significant improvements in the hydrogel properties. The most significant weakness of all these external stimuli-sensitive hydrogels is that their cant improvements in the hydrogel properties. The most significant weakness of all these external stimuli-sensitive hydrogels is that their response time is too slow. Thus, fast-acting hydrogels are necessary and the easiest way of achieving this goal is to make thinner and smaller hydrogels. This usually makes the hydrogel system too fragile and they do not have the mechanical strength necessary in many applications. Environmentally-sensitive hydrogels for drug delivery applications also require biocompatibility. Synthesis of new polymers and crosslinkers with more biocompatibility and better biodegradability would be essential for successful applications. Development of environmentally-sensitive hydrogels with such properties is a formidable challenge. If the achievements of the past can be extrapolated into the future, however, it is highly likely that responsive hydrogels with a wide array of desirable properties can be made.

References

R.D. Dinarvand, A. Emanuele, Use of thermoresponsive hydrogels for on


