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RESEARCH PAPER

Stimulus-Responsive "Smart" Hydrogels as Novel Drug Delivery Systems*

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ABSTRACT

Recently, there has been a great deal of research activity in the development of stimulus-responsive polymeric hydrogels. These hydrogels are responsive to external or internal stimuli and the response can be observed through abrupt changes in the physical nature of the network. This property can be favorable in many drug delivery applications. The external stimuli can be temperature, pH, ionic strength, ultrasonic sound, electric current, etc. A majority of the literature related to the development of stimulus-responsive drug delivery systems deals with temperature-sensitive poly(N-isopropyl acrylamide)(pNIPAAm) and its various derivatives. However, acrylic-based pH-sensitive systems with weakly acidic/basic functional groups have also been widely studied. Quite recently, glucose-sensitive hydrogels that are responsive to glucose concentration have been developed to monitor the release of insulin. The present article provides a brief introduction and recent developments in the area of stimulus-responsive hydrogels, particularly those that respond to temperature and pH, and their applications in drug delivery.

Key Words: *Hydrogel; pH sensitive; Drug delivery; Poly(N-isopropylacrylamide)*

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INTRODUCTION

Hydrogels are crosslinked network polymeric materials that are not soluble but can absorb large quantities of water. These materials are soft and rubbery in nature, resembling living tissues in their physical properties.[1,2] In view of their biocompatibility and non-toxicity, they are excellent choices as biomaterials in drug delivery. Tanaka and coworkers[3–5] first suggested the existence of hydrogels in the late seventies while studying the water absorption properties of gels. When a clear polyacrylamide gel is cooled it clouds up and eventually becomes opaque, and any small change in solvent concentration or temperature could then cause the gel to swell abruptly to many times its original size or collapse into a compact mass. Since that time this phenomenon has opened up new and exciting avenues for polymeric hydrogels.

Hydrogels containing interactive functional groups along the main polymeric chains are usually called ''smart'' or ''stimuli-responsive'' polymers. In such systems, the polymer conformation in solution is dictated by both the polymer–solvent and polymer–polymer interactions. In a good solvent, polymer–solvent interactions dominate and the polymer chains are relaxed due to minimal inter-segmental interactions. When in contact with a poor solvent, the polymer will aggregate due to a restricted chain movement because of increased polymer–polymer interaction. Such a phase change leads to varying physical properties of the polymer solution. It is thus possible to alter the polymer–solvent interaction by changing the pH, temperature, and ionic strength of the solution in addition to other external stimuli. Recently, such materials are gaining tremendous applications in drug delivery research as stimuli-responsive polymers.

The present article addresses recent important research developments, which have occurred in the area of smart hydrogels, with particular emphasis on pH and temperature effects. While the literature on general aspects of hydrogels is exhaustive, we will only concentrate on the applications of hydrogels that are responsive to pH and temperature, with particular emphasis on the delivery of drugs. In the present article, our discussions will be restricted to the most important and latest findings on the use of hydrogels in drug delivery applications. At any rate, our review should not be regarded as exhaustive, and more interested readers may consult the original, cited papers.

POLYMERS USED AS STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Table 1 presents different drug delivery systems based on ''smart hydrogels'' and their release

Table 1

Effect of Different External Stimuli on the Release of Bioactive Molecules from Smart Hydrogels[6]

Stimulus	Hydrogel Type	Release Mechanism
pH	Acidic or basic hydrogel	Change in pH—swelling—release of drug
Ionic Strength	Ionic hydrogel	Change in ionic strength—change in concentration of ions inside the gel—change in swelling—release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds—formation of charge-transfer complexes—change in swelling—release of drug
Enzyme substrate	Hydrogel containing immobilized enzymes	Substrate present—enzymatic conversion—product changes swelling of gel—release of drug
Magnetic	Magnetic particles dispersed in microspheres	Applied magnetic field—change in pores in gel—change in swelling—release of drug
Thermal	Thermo-responsive hydrogel	Change in temperature—change in polymer–polymer and water–polymer interactions—change in swelling—release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric field—membrane charging—electrophoresis of charged drug—change in swelling—release of drug
Ultrasound irradiation	Ethylene–vinyl alcohol hydrogel	Ultrasound irradiation—temperature increase—release of drug

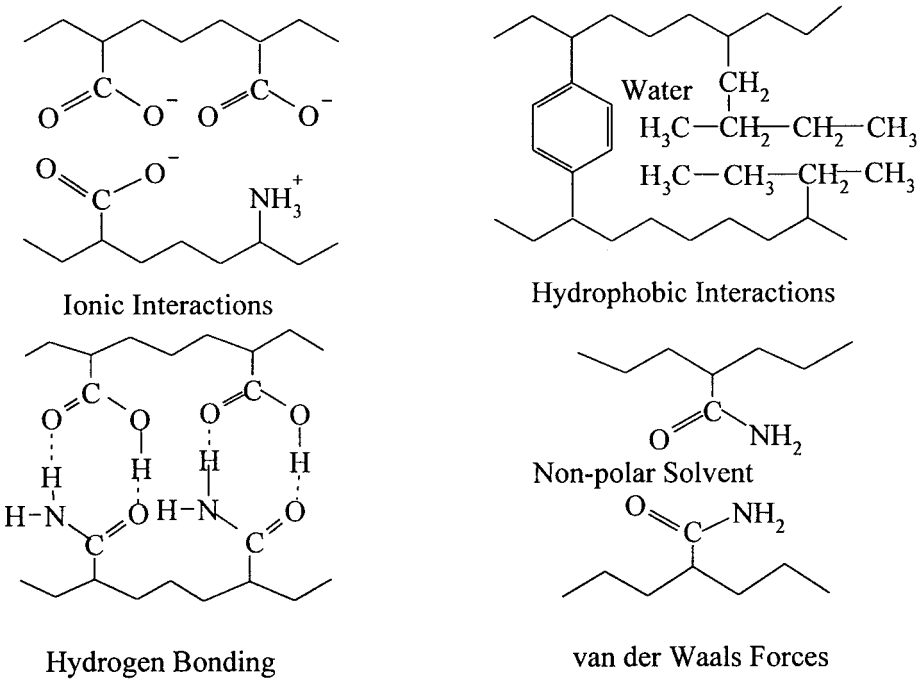


Figure 1. Four fundamental forces that control the behavior of stimuli-responsive hydrogels.

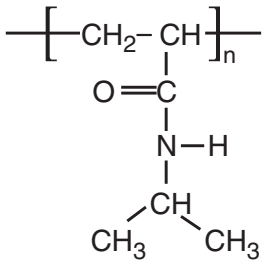
mechanism with an external stimulus.[6] In all these cases, phase transitions occur due to the change in external environment. The change may be gradual and smooth, or may be abrupt or discontinuous, depending upon the nature of the system. This leads to a change in the water uptake or swelling behavior of the polymer, which is dependent upon factors like pH, ionic strength, temperature, electric current, ultrasound velocity, etc.

Polymers that are used to develop stimulus-responsive systems are mainly hydrogels with ionizable groups. However, the magnitude of their response depends upon the type of functional group, basic polymer repeat unit, in the case of copolymers, the composition of such units, and the amount of ionizable functional groups present on the backbone. The behavior of most of the stimuli-responsive hydrogels can be understood in terms of four fundamental forces, summarized in Fig. 1. These are ionic, hydrophobic, hydrogen bonding, and van der Waals interactions. Any or all of these forces are responsible for the gel's ability to inter-convert between two phases. In one phase, the environmental conditions cause the attractive forces to be stronger and the gel collapses by expelling out the solvent. In the other phase, the environmental conditions cause the repulsive forces to be stronger, thus expanding the gel by absorbing solvent. The phase transition of such polymers with external stimuli leads to a change in the physico-chemical properties of the polymer. These effects are presented in Table 2, along with their possible applications in drug delivery.

The most extensively studied systems in the literature are the modified forms of weak polyacids consisting of acrylic acid, *n*-alkylacrylate, methacrylate, and 2-hydroxyethylmethacrylate.[7,8] However, the positively charged gels containing poly (*N*-isopropylacrylamide), *N*,*N*′-dimethylaminopropylmethacrylamide, and *N*,*N*′-diethylethylene diamine have also been used.[9,10] In the following sections, we shall discuss some of the most widely used systems with reference to different stimuli effects.

POLY(*N*-ISOPROPYLACRYLAMIDE) AND ITS DERIVATIVES

Among the many polymeric systems studied in the literature, poly(*N*-isopropylacrylamide) (pNIPAAm) (chemical structure shown below) has been widely exploited since it is sensitive to both pH and temperature.



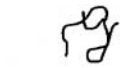
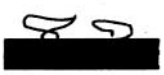
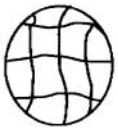
poly(*N*-isopropylacrylamide)
(pNIPAAm)

The polymer exhibits a lower critical solution temperature (LCST) at ~32°C[11] and is soluble below its LCST, but precipitates above the LCST. These properties can be attributed to the reversible formation (below LCST) and cleavage (above LCST) of the hydrogen bonds between –NH and C=O groups of pNIPAAm chains and the surrounding water molecules. This is attributed to the pentagonal water structure that is generated among the water molecules adjacent to the hydrophobic molecular groups of pNIPAAm.[12]

The hydrophilic hydrogels comprised of pNIPAAm or its copolymers have been used for the controlled release of drugs. They act by forming a reversible skin layer at the gel surface, which is sensitive to temperature. The skin layer prevents drug diffusion by the creation of an "on–off" pulsatile drug release pattern in response to temperature.[13,14] The normal-type pNIPAAm gels show very slow deswelling characteristics, i.e., they take more than one month to reach equilibrium. In contrast, Kaneko et al.[15,16] synthesized fast-responsive, comb-like, grafted polymeric gels of pNIPAAm. These gels, developed by grafting pNIPAAm (having a molar mass in the range of 9000–40,000) with its monomer, shrink very fast and equilibrium can be achieved within 50 min. These results indicate that normal-type gels "release-on" at lower temperature, but "release-off" at higher temperature, while the graft-type gels could achieve a pulsatile drug release pattern to temperature, i.e., diffusive release at low temperature and more rapid release at higher temperature via conventional transport (see Fig. 2). Similarly, Gutowska et al.[17] showed a temperature-sensitive, squeezing, controlled "on–off" release profile of pNIPAAm hydrogels in response to temperature changes between 35 and 40°C. Drug release profiles from pH or temperature-sensitive hydrogels were strongly affected by pH changes at 37°C, the human body temperature. The gel showed a minimal delayed release at pH 2 and zero-order release

Table 2

Changes in the Physical Properties of a Polymer with External Stimuli and Their Possible Applications

+Stimulus	−Stimulus	Physical Change	Application
		Reversible precipitation or gelation	Sol–gels for ophthalmic applications
		Reversible adsorption	Mucoadhesive and blocking anionic receptors
		Reversible collapse on a surface	On–Off release from surface-grafted microcapsules
		Reversible collapse	Oral delivery of proteins

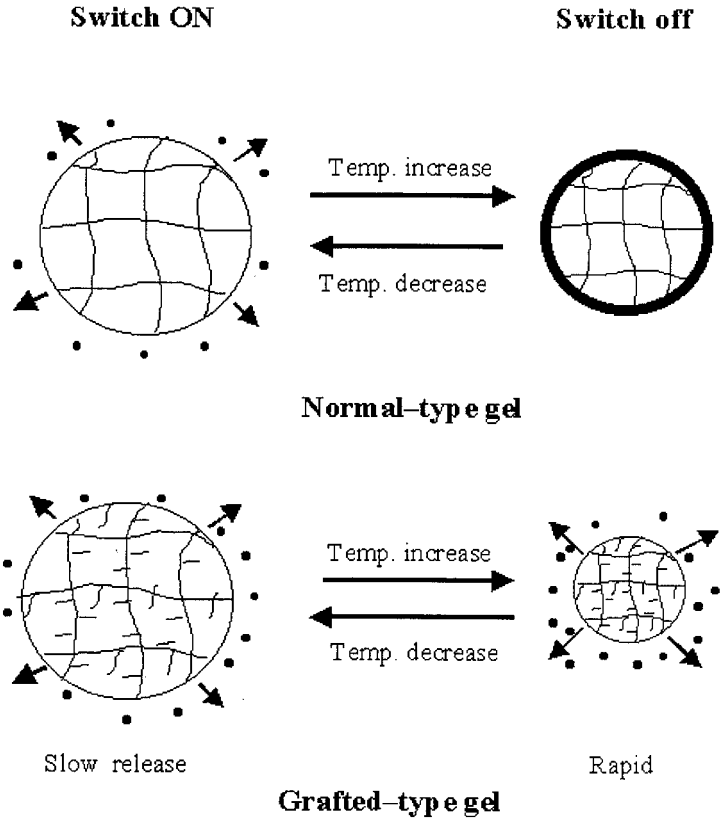


Figure 2. Comparison between normal and grafted pNIPAAm hydrogels.[61]

at pH 7.4 controlled by a mechanical squeezing mechanism determined by deswelling kinetics.

Copolymers of pNIPAAm have been developed to optimize its LCST. Hydrophilic comonomers like acrylamide increase the LCST, while hydrophobic comonomers tend to decrease the LCST.[18,19] The pNIPAAm polymers exhibit limited physical features and weak mechanical properties;[20] copolymerization helps to circumvent these problems. The use of copolymers of pNIPAAm containing ionic moieties will also be helpful in designing delivery systems which exhibit both pH and temperature-sensitive characteristics. Some of the research findings on copolymerization of pNIPAAm with various monomers will be presented in the ensuing part of this article. However, for more details, the readers may consult the original papers.

Thermoresponsive hydrogels are designed to release drugs at temperatures below the LCST. However, it may be desirable to design a system where the release of a drug occurs above a critical temperature. Such devices have applications in situations where the release of a substance is required at a critical temperature. In this pursuit, Dinarvand and D'Emanuele[21,22] have reported thermosensitive discs based on the copolymer of NIPAAm and acrylamide (AAm) exhibiting an LCST at ~37°C. These polymers were prepared by a free radical mechanism using methyl *bis*-acrylamide (MBAAm) as the crosslinking agent. The devices were prepared in the form of microspheres to achieve zero-order release (the most commonly occurring release in such systems) of indomethacin drug. It was found that the release of indomethacin below the phase transition temperature (i.e., 25, 30, and 35°C) was significantly higher than at temperatures above the phase transition temperature. However, drug release above the phase transition temperature did not completely cease, but was quite slow, probably because the hydrogels were not completely dehydrated at these temperatures. Similar findings were observed for the value-based devices in the delivery of bovine serum albumin.[22]

In order to design new synthetic hydrogels for controlled drug delivery, the interactions of various drugs with polymers are important. Polymer gels are excellent model systems for studying such molecular interactions because a polymer network can be regarded as a single giant molecule. Any small change in certain interactions of a local part of the network can trigger a noticeable change in the macroscopic size of the gel. To meet these criteria, hydrophobic functional groups were introduced into the hydrophilic pNIPAAm polymer using different hydrophobic comonomers like methyl methacrylate, hexylacrylate, hexafluoroisopropylmethacrylate, and hexafluorobutylpolymethacrylate.[23] The swelling of hydrogel below the LCST decreased with increasing hydrophobicity of the copolymer. Hydrogels were loaded with ibuprofen and ephedrine as model drugs and swelling was studied in the temperature interval 20–46°C. It was found that ephedrine did not show any effect on the swelling of non-ionic gels, but a decrease in swelling of the anionic gels was observed. This decrease could have been due to the interaction of weakly basic ephedrine with the acidic gel, thereby reducing the repulsion between negative charges of the polymer chain. On the other hand, ibuprofen-loaded hydrogels exhibit limited swelling because the drug is sparingly soluble in water, thus creating a pronounced hydrophobic interaction between the polymer and the drug. This might have led to highly aggregated polymer chain conformations, thereby preventing the diffusion of water into the gels.

Dong and Hoffman[24] reported a new rationale for preparing pH-sensitive hydrogels based on thermally reversible polymers. They developed a new class of hydrogels for the controlled release of indomethacin using poly(*N*-isopropylacrylamide-*co*-acrylic acid) and poly(*N*-isopropylacrylamide-*co*-vinyl-polydimethylsiloxane-*co*-acrylic acid) hydrogels. The in vitro experiments showed that only a negligible amount of indomethacin was released at pH 1.4 in 24 hr, while at pH 7.4 more than 90% of the total drug in the gels was gradually released for about 5 hr. The release rate at pH 7.4 increases with the fraction of non-freezing, free water in the gels, which is in parallel with the gel acrylic acid content. An anomalous release profile was observed for all the pH-sensitive hydrogels at this pH, suggesting a swelling-controlled release mechanism.

While proteins and peptides are now available in large quantities to provide new therapies for diseases, their use as therapeutic agents is still hampered by the lack of an effective route of administration. Recently, Ganorkar et al.[25–27] have reported the preparation of novel terpolymeric beads of poly(NIPAAm-*co*-butylmethylacrylate-*co*-acrylic acid) (NIPAAm–BMA–AA) and studied their efficiency in loading model polypetide/protein drugs such as angiotensin II, insulin, and cytochrome c. They have reported hydrophobic interactions as well as non-specific surface interactions and/or specific interactions between proteins and polymers; loading efficiency of the gels increased with the ionic strength. Any further increase in ionic strength led to deswelling of the beads, possibly due to hydrophobic interactions. The release of proteins was dependent upon pH and the release in acidic pH was less than 20%; but a pronounced release of proteins was observed at pH 7.4. The molar mass of the polymer had an effect on pH and temperature responses, and hence on the release of active ingredients from the copolymeric beads. The mechanisms of protein release in the systems studied under variable pH conditions are depicted in Fig. 3 for three different types of polymeric beads.[27]

In a study by Serres et al.[28] the (NIPAAm–BMA–AA) beads were loaded with calcitonin. The beads were optimized for higher loading efficiency and stability of calcitonin. It was observed that as the concentration of AA in the terpolymer was increased from 0 to 10 mol%, there was an increase in both the loading efficiency and stability. Furthermore, the biological activity of human calcitonin was preserved even after its release. Since the polymers are pH-responsive, they will also protect proteins from proteolysis and are thus useful in the delivery of proteins and peptides through the peroral route. In continuation of these studies, for the delivery of proteins and peptides, Kim et al.[29] reported five different bead formulations loaded with insulin. The release study was carried out at both pH 2 and 7.4, as well as at 40 and 50°C, and the beads were responsive to both pH and temperature.

Considering the effect of both temperature and pH in a single polymer, Peppas et al.[30] synthesized the tercopolymer of NIPAAm with AA and hydroxyethylmethacrylate (HEMA) (i.e., NIPAAm–AA– HEMA). The random copolymeric gels exhibited a better sensitivity toward pH than temperature. The temperature sensitivity of these polymers was retained even without increasing

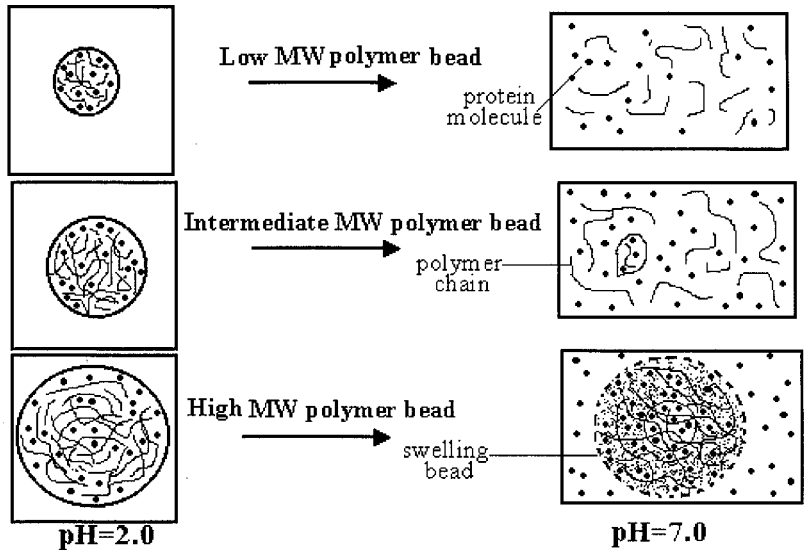


Figure 3. Mechanism of protein drug release from pH/thermo-sensitive beads made of polymers with increasing molecular weight (MW). (Top) Few physical crosslinks along polymer chains, bead dissolution results in fast release suited for duodenal delivery. (Center) Slightly greater number of physical crosslinks along the polymer chains, combination of swelling, diffusion, and dissolution mechanisms results in intermediate release suited for lower small intestine targeting. (Bottom) Large number of physical crosslinks along the polymer chains, swelling and drug diffusion-controlled mechanisms result in slow release suited for colon targeting.[27]

the concentration of NIPAAm while preparing the block copolymer.

Zhang and Peppas[31] further developed interpenetrating network (IPN) polymers of pNIPAAm and poly(methacrylic acid) (PMA) using tetraethylene glycol dimethacrylate (TGDMA) as a crosslinking agent. The swelling studies on these systems showed both temperature and pH sensitivity. Diffusion studies for oxoprenolol HCl, vitamin B_{12}, and insulin showed that the polymers were effective drug delivery devices.

Thermosensitive polymers have also been used in the preparation of particulate stimulus-responsive delivery systems, as well as in the surface modification of microspheres, micelles, and liposomes. The A–B type block copolymer of PIPAAm and a hydrophobic segment show thermo-responsive water solubility, and these can form heterogeneous microstructures, that is, micellar structures composed of hydrophilic microdomains of soluble PIPAAm segments together with hydrophobic aggregated microdomains of incorporated hydrophobic segments in aqueous solution below the LCST. The hydrophobic inner core of the micelle contains drug, while the PIPAAm outer shell plays a role in stabilization and temperature response. The outer shell hydrophilicity that prevents inner core interaction with drugs and other micelles can be suddenly switched to hydrophobicity.

To pursue the above-mentioned concepts, Chung et al.[32] reported temperature-responsive micelle formation using block copolymers of PIPAAm and poly(butyl methacrylate) (PBMA) to produce PIPAAm–PBMA micelles with an inner core formed by the self-aggregation of PBMA segments loaded with adriamycin drug. The outer shell hydrophilicity that prevents the inner core interaction with the biocomponents and other micelles was suddenly switched to hydrophobicity at a specific site by an increase in the local temperature beyond the LCST (32.5°C). In this study, a temperature-accelerated adriamycin release was observed, that was in agreement with the LCST values, i.e., the release was slower below the LCST of the polymer. The switch-off-and-on release from the micelle corresponds to reversible structural changes in the micelles due to temperature changes through the LCST. The interactions between PIPAAm–PBMA micelles and cells modulated by temperature control are depicted in Fig. 4.

Thermally sensitive block copolymers of poly(DL-lactide) (PLA) and pNIPAAm (pNIPAAm–PLA) were synthesized by ring-opening polymerization via

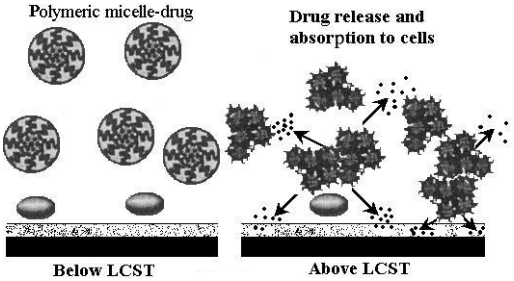


Figure 4. Interactions between PIPAAm–PBMA micelles and cells modulated by temperature control.[32]

the synthesis of hydroxy-terminated pNIPAAm using 2-hydroxyethanethiol as a chain-transfer agent.[33] These copolymers were used to prepare micelles that are expected to show LCST behavior at temperatures $<32^{\circ}$C because they are made up of hydrophobic PLA chains instead of hydrophilic terminal hydroxyl groups. The LCST measured for the micelles was 32°C because pNIPAAm segments of the micelle behaved similarly to those of pNIPAAm homopolymers. However, below the LCST of the polymer, the particle size of the micelle ranged between 43 and 50 nm, while at temperatures above 32°C a dramatic increase in size up to ~75 nm was observed. Above the LCST (≡LGCT in case of gel collapse as defined in Fig. 5), micelles aggregated by hydrophobic surface association and were found to be temperature-responsive without showing any hysteresis. Such micelles are promising targeted drug delivery systems, because of their small size as well as their potential to interact with the cell at specific sites heated locally above the LCST by hypothermia.[33]

Kono et al.[34] have reported the synthesis of liposomes bearing poly(NIPAAm). These liposomes were found to aggregate at 40°C, possibly due to the fact that liposomes at the phase transition temperature are hydrophobic, thus destabilizing the liposomal membrane. Okahata et al.[35] studied the permeation of NaCl and dyes from nylon capsules grafted with pNIPAAm. In the case of ungrafted hydrogel capsules, linear Arrhenius plots were observed for the temperature-dependent permeation of NaCl and dyes. On the contrary, permeability of the grafted capsules was remarkably reduced above ~35°C. The grafted pNIPAAm may be solubilized or repelled in water below the LCST. On the other hand, above the LCST, the grafted polymer was insoluble and the entangled polymer segments cover the porous capsule membrane, thus significantly reducing drug permeation depending upon the molecular size of the permeate.

Recently, novel thermosensitive controlled-release microcapsules of pNIPAAm, 100 μm in diameter, were prepared[36] by a two-phase polymerization technique. In brief, ethyl acrylate (EA) and methyl methacrylate (MMA) were emulsified in aqueous medium containing sodium lauryl sulfate and polymerized at 80°C. After 30 min of polymerization, an aqueous solution of NIPPAAm was added along with a small amount of methylene *bis*-acrylamide (crosslinking agent) for about 6 hr to harvest microcapsules of sizes between 357 and 72 nm at 11 and 58°C, respectively. At temperatures above 32°C, pNIPAAm chains in the membrane collapse fully, as indicated by a particle size reduction in water. Therefore, the enhanced release rates at higher temperatures above the LCST could be due to a thermally enhanced inherent diffusivity of the material in the core. The hydrogel particles in this study consisted of a composite latex, with a NIPAAm shell that could reversibly change the shell thickness in water with response to environmental changes in temperature. The ideal particle structure of the composite latex with the NIPAAm-rich shell, designed to be a nanosized thermosensitive hydrogel, is shown schematically in Fig. 5. At temperatures below the LCST, the NIPAAm hydrogel can hold a large amount of water by swelling, but releases a higher amount of drug. Wu and Lee[37] have also prepared nanospheres of poly(*N*-isopropylacrylamide-*co*-methacrylic acid) and loaded them with theophylline; these hydrogels were both thermal and pH-sensitive. The dispersion polymerization process resulted in particle sizes ranging from 114 to 413 nm. At temperatures above the LCST of the nanospheres, shrinkage in particle diameter with up to ninefold volume changes was observed. The isotherms for theophylline loading in these nanospheres showed a significant decrease in slope from 25 to 40°C. This is attributed to the loss of interstitial drug solution upon collapse of suspended nanoparticles above the transition temperature.

The pNIPAAm-based polymers are responsive to concentration as well as ionic strength of the species in solution. Hence, this behavior can be used to prepare tailor-made polymers for the delivery of bioactive materials that are responsive to the concentration of particular, immobile, ionic, functional groups. Recently, Lee and Hsu[38] have synthesized copolymers of pNIPAAm with 3-methyl-1-vinylimi-

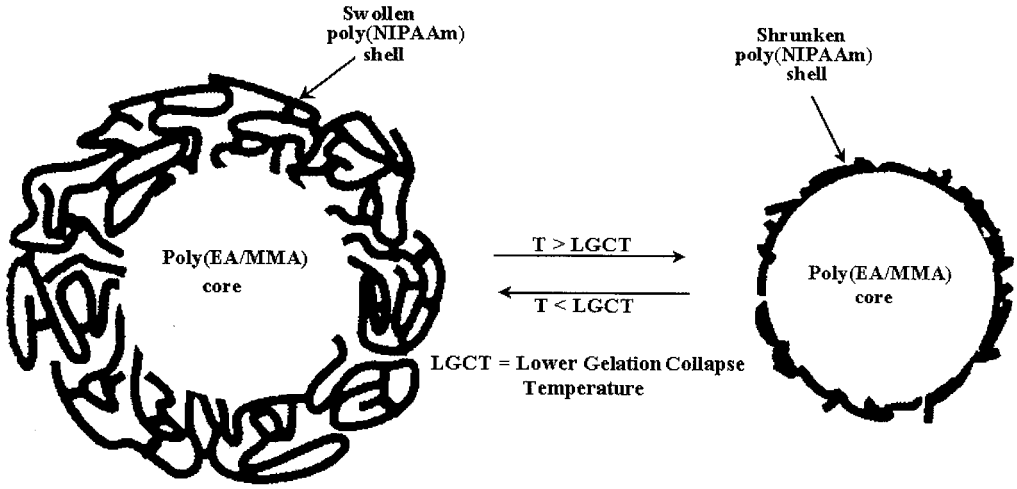


Figure 5. Schematic diagram showing ideal particle structure of composite latex with poly(NIPAAm) hydrogel shell.[36]

dazolium iodide (MVI), a cationic monomer. The volume phase transition temperature was found to increase with an increase in the amount of MVI. Swelling of the gels in the presence of different salt concentrations was studied, and it was found that divalent ions increased swelling more than monovalent ions.

From the foregoing discussion, we may conclude that most of the pNIPAAm-based hydrogels are responsive to temperature and hence they can be effectively used in designing temperature-sensitive "switch-on-off" drug delivery systems. It is also possible to synthesize "tailor-made" polymers with the required LCST and hydrophobicity by copolymerizing pNIPAAm. Research efforts by polymer scientists in this direction are still being actively pursued.

PLURONIC POLYOLS AND THEIR DERIVATIVES

The family of triblock copolymers containing poly(propylene oxide) (PPO) and poly(ethylene oxide) (PEO) in the sequence PEO–PPO–PEO have the trade name of pluronic polyols. The hydrophobic PPO segments of pluronic aggregates show a distinct gelation behavior at body temperature. Hoffman et al.[39–41] grafted pluronic side-chains in a well-defined manner onto the bioadhesive backbone of either PAA or chitosan. The hydrogels were formed from these graft copolymers a 37°C. The gelation behavior of these graft copolymers was critical to their performance in in vitro drug release. It has been found that gelation of the graft copolymer not only prolonged the rate at which an antiglaucoma drug diffused out of a polymer matrix, but also slowed down the dissolution rate of the matrix, another factor in controlling the rate of drug release.

Hoffman et al.[39–41] also studied the release of anti-inflammatory proteins from pluronic–chitosan hydrogels. The receptor proteins, intended for nasal administration, were designed to block the action of cytokines such as interleukin-1 and tumor necrosis factor, which can cause asthma and other diseases. Because the receptor proteins are anionic, they bind very strongly to the cationic chitosan backbone of the gel matrix. Nevertheless, when proteins are released from the gel in vitro, they are found to be totally active. Chitosan was preferred because, unlike PAA, it is biodegradable and has been shown to enhance the penetration of drugs through the nasal mucosa.

Temperature-sensitive materials based on α-amino acid,[42] poly(*N*,*N*-dimethylaminomethacrylate),[43] and some natural polymers like xyloglucan[44] have also been studied, but the literature evidence is very rare. At any rate, temperature-sensitive hydrogels with an α-amino acid group as a side-chain on a polymer are worth mentioning,[42] because the biological system has various sensory systems with responsive functions for external stimuli, in which α-amino acid plays an important role. For this reason, methacryloyl derivatives containing α-amino acid groups in their side-chains are important. Yoshida et al.[42] synthesized hydrogels by copoly-

merizing a variety of monomers with small amounts of crosslinking agents to increase the strength of the materials. These copolymeric gels deswell in aqueous media when the temperature is raised and also exhibit reversible swelling tendencies when cycled in solutions at different temperatures, i.e., in the range of 0 to 80°C. A schematic representation of drug release from such a thermoresponsive gel is shown in Fig. 6. Such a quick response of the gel surface to temperature changes is of great value as a smart material.

ANIONIC pH-SENSITIVE ACRYLIC-BASED POLYMERS

An understanding of the mechanism of drug release from pH-sensitive polymers represents one of the rapidly developing areas in the delivery of a variety of drugs.[45,46] These polymers contain weakly acidic and/or basic pendant groups. Water uptake by such polymers takes place mainly because of the ionization of the functional groups, which depends upon the pH and ionic strength of the external solution. With ionic hydrogels having weakly acidic (anionic) groups, water uptake increases as the external pH increases. However, swelling increases as the pH decreases in the case of weakly basic (cationic) groups. The pH-sensitive polymeric hydrogels release the drug due to the presence of specific charged species in the structure of the swelling network. However, these charges may interact in different ways with the dissolution medium than with the drug.

In the literature, anionic pH-sensitive polymers were designed by copolymerizing or blending polyacrylic acids. Peppas and coworkers[45,46] reported the syntheses of anionic copolymers of MMA with HEMA by bulk polymerization and by crosslinking with EGDMA. These polymers show a pH-dependent swelling. Since the copolymer of MMA has a dissociation constant, pK_a, ranging from 4.3 to 5.9, an increased water uptake can be observed above this pH range due to the ionization of the carboxylic group. The authors[45,46] further suggest

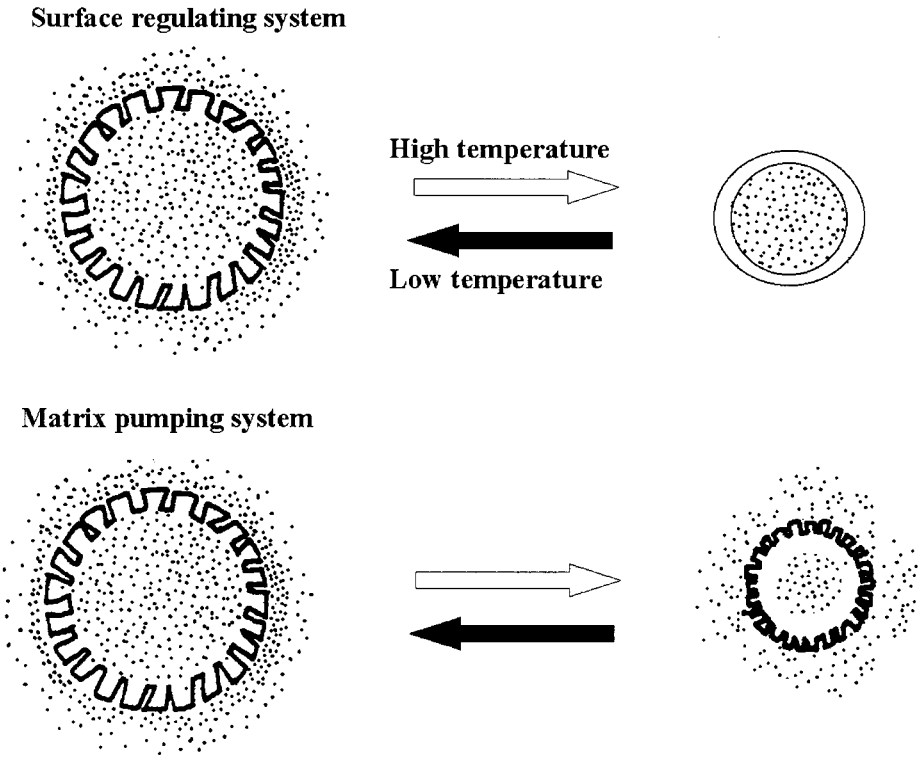


Figure 6. Mechanisms of drug release from thermo-responsive MA–(L)Pro-containing copolymer formulations. Dots in figure represent drug.[42]

that swelling-controlled release systems that are sensitive to pH changes function in a manner similar to those of other initially dry, swellable polymers. The drug release from such systems could be the result of macromolecular chain relaxation, since the swelling of glassy polymers is accompanied by chain relaxation processes. In some cases, the pH of the swelling solution affects the chain relaxation and swelling of the sample, thus leading to a modified drug-release behavior. In another study,[47] the copolymer of PAA with HEMA showed an increased release of oxoprenolol HCl drug with increasing pH of the dissolution medium. For instance, the diffusion coefficient at pH 2.9 was $0.3\times10^{-7}\,cm^2/sec$, but at pH 7.1, the diffusion coefficient increased to $4.3\times10^{-7}\,cm^2/sec$. It was also reported that the release of oxoprenolol HCl was relatively higher from acrylic acid copolymer than from methylacrylic acid polymer. The reason is that MAA-containing copolymers are more hydrophobic due to the presence of the α-methyl group.[48]

Ranjha and Doelker[49] reported the syntheses of copolymers of poly(methylacrylate-*co*-methacrylic acid), i.e., p(MA–MAA), and poly(ethylacrylate-*co*-methacrylic acid), i.e., p(EA–MAA). These polymers were loaded with both water-insoluble (i.e., betamethasone) and water-soluble (i.e., proxyphylline) drugs. It was found that those copolymers that combine the hydrophobic unit of MA or EA with MAA exhibited pH-responsive release. The betamethasone was released at pH 6.5 for p(EA–MAA), but for p(MA–MAA) the threshold pH was 5.5. It was further observed that by increasing the MAA component in the polymer, the threshold pH was shifted to lower values, probably due to a decrease in the apparent pK_a value at high concentration of MAA moiety.

Negishi et al.[50] synthesized novel gel-based amino acid copolymers consisting of a combination of thermo-sensitive acryloyl-L-proline ethyl ester (A–ProOEt) as well as thermo- and pH-sensitive methacryloyl–glycine (MA–Gly) or methacrylic acid (MA–Ac). The release of ketoprofen from copoly(A–ProOEt/MA–Gly) gel reached 100% in pH 7.4 phosphate buffer, while the same amount is released after 4 hr in pH 5.5 buffer. At pH 3.0, the cumulative amount of released drug was only 14%, even after 6 hr. These findings support the idea of pH-dependent swelling. The MA–Gly induced strong ionic repulsion with a rapid increase in swelling as well as drug release when compared with MA–Ac. The copolymer of polyacrylamide with acrylic acid produced a pH-sensitive polymer.[51] The release of fluorescein isothiocyanate-labeled bovine serum albumin (FITC–BSA) from this polymer was also pH-dependent; i.e., at pH 2, the release of FITC–BSA was 91 μg, whereas under basic conditions, the release was 1485 μg.

Yao and Sun[52] prepared a pH-sensitive poly[(ethylene glycol-*co*-propylene glycol)-*g*-acrylamide] IPN polymer crosslinked with poly(acrylic acid). The swelling of the gels formed from this polymer was studied under basic and acidic conditions. A pH-dependent swelling mechanism was proposed on the basis of intramolecular hydrogen bonding between the –COOH of AA and the $–CONH_2$/ether functional groups at a lower pH. Yuk et al.[53] reported the preparation of an anionic pH-sensitive drug delivery system based on the oil-in-water emulsion method. As shown in Fig. 7, the drug delivery system consisted of a core and a capsule. The core consists of oil and the dispersed drug. This novel semi-interpenetrating networks (semi-IPNs) system has been developed to provide a capsule network, which showed pH-dependent swelling behavior. This system consisted of two chemically independent polymers in which the proportions and properties of both polymers can be independently varied. The first network consisted of sodium alginate, which disintegrated in the intestinal fluid. The other is a polyacrylic acid (PAA), which provided pH-sensitive swelling capacity to the capsule network. The utilization of this system for oral drug delivery was demonstrated by varying the chemical composition of the capsule network and the pH of the release media. The semi-IPN beads of PAA and sodium alginate were loaded with hydrocortisone. It was found that at pH 1, swelling was minimal, while at pH 4 or above, a remarkable increase in swelling was observed. Similar pH effects were observed on the release of hydrocortisone, with an increase in the PAA ratio of the polymeric network beads that were sensitive to pH.

Kono et al.[54] developed polyelectrolyte capsules of PAA styrene copolymer with oppositely charged cationic poly(ethylenimine) in the size range 2–6 μm. The permeability of poly(ethylene glycol)(i.e., PEG) through these polyelectrolyte complex capsules was minimum between pH 3 and 7, at which the dissociation of polyelectrolyte complex was suppressed. When the ambient pH was decreased below 3 or

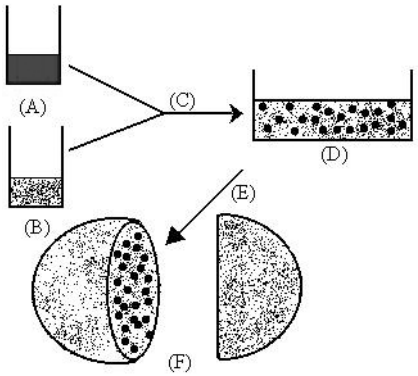


Figure 7. Schematic diagram for the preparation of drug delivery systems using O/W emulsion. (A) Drug in oil phase, (B) polymer aqueous solution for capsule network, (C) sonication under ice cooling, (D) O/W emulsion, (E) coagulation, and (F) emulsion bead.[53]

increased above 8, the dissociation of polyelectrolyte complex was rapid, resulting in a drastic increase of PEG permeability. A similar dependency of pH was observed for the release of polyethylene glycol from the capsules.

Grafted copolymers based on PMMA and PEG, i.e., p(MAA-*g*-EG), were synthesized.[55,56] These hydrogels exhibit pH-responsive swelling behavior due to the presence of ionic moieties on the PMMA backbone. In these systems, the formation of interpolymer complexes was stabilized by hydrogen bonding between –COOH protons and ether groups on the grafted chains. The complexes were sensitive to the nature of the swelling agent as well as copolymer composition. Initially, the polymers were swollen when placed in pH 6.6 solution because the carboxylic pendant groups were ionized and temporary crosslinks were broken. The characteristic mesh size of the gel was increased 100 times. When placed in a solution with a pH below the pK_a of the gels, there was a rapid collapse of the hydrogel network. The hydrogels containing higher molar mass PEG grafts exhibited the quickest syneresis. In such materials, the PEG grafts were the longest and were able to reach the carboxylic groups more rapidly and thereby collapse the network. These hydrogels exhibited an oscillatory release mechanism for proxyphylline as well as large solutes like FITC–dextran.[57] The grafted copolymer p(MMA-*g*-EG) developed in the above work was used for the delivery of proteins and peptides like insulin and calcitonin.[58,59] Insulin microspheres of p(MMA-*g*-EG) were prepared and evaluated for their in vivo performance in diabetes-induced Wistar rats. The insulin-loaded microspheres decreased the blood glucose level significantly for at least 8 hr. The p(MMA-*g*-EG) microspheres exhibited a better hypoglycemic activity than the insulin-loaded microspheres of hydrophobic acrylic polymer (Eudragit L-100), probably because the presence of the PEG chain helped to maintain the biological activity of insulin. Additionally, these hydrogels had mucoadhesive properties and exhibited strong adhesion to the mucosa of the intestine rather than that of the stomach.

Recently, microgels based on poly(methacrylic acid-*co*-nitrophenylacrylate) have been developed,[60,61] and these were chemically modified by introducing different chemical groups like carboxylic acid, glutamic acid, hydroxamic acid, sulfonic acid, and ethanol by post-polymerization reactions. The microgels were loaded with three cationic drugs, i.e., benzyl amine, dubucaine, and doxirubicin. The loading efficiency was dependent upon the proton binding ability of the polymer. A micromanipulation technique was used to observe the volume changes with change in the microgels. These have shown varying volume changes with a change in pH and ionic strength. The pH range was shifted by an amount proportional to the pK_a of the functional groups that were derivatized on the polymer backbone. In order to avoid the release of doxirubicin with the exchange of Na^+ when the microgels enter the blood stream, the microgels were coated with an ion-impermeable lipid bilayer after drug loading. An external electrical stimulus was then applied to rupture the lipid wall to release the drug. Thus, by applying the energy source through the skin, one could punch holes in the lipid coating and thereby release the drugs at a desired site.[61]

CATIONIC pH-SENSITIVE HYDROGELS AS GLUCOSE-SENSITIVE HYDROGELS

Hydrogels can be anionic or cationic. Cationic hydrogels have been studied extensively by Siegel and coworkers[62–65] and in these studies, hydrogels were derived from cationic monomers such as dimethylaminoethylmethacrylate (DMAEM) or diethylaminoethylmethacrylate (DEAEM). At pH values above the pK_a of the cationic group, the

copolymers are hydrophobic and thus exclude water. On the other hand, at a pH lower than the pK_a, the amine groups are protonated so that the gels become hydrophilic and absorb water. These studies explain the transport characteristics of cationic polymers in the presence of buffers of different pH and ionic strength. Transport through these gels in acidic media exhibit (i) transport of protons (co-ion) and counterions to the swelling front, (ii) ionization of acidic groups of the uncharged microgel at the swelling front, (iii) relaxation of the polymer in the vicinity of the ionic interface, and (iv) equilibration of rubbery polymer with the ions in the external media. These events are responsible for the rate-controlling steps during water transport into the ionic gels, and these determine the mechanism of water transport. The Donnan exclusion of hydrogen ions from the gel is the rate-limiting step in water transport, which can be brought about by incorporating slightly acidic buffering ions. It was concluded that the transport properties of these cationic polymers in the presence of acidic buffer deviates from Fickian transport.[65] However, the swelling and critical pH of the gels depend upon the molar ratio of MMA:DMAEM.[62] Chemical modification, such as increasing the side-chain length and using a crosslinking agent, decreased the pH and water uptake capacity of the hydrogels.[66]

Cationic polymers also find applications as glucose-sensitive polymeric systems for the delivery of insulin. When these polymers are loaded with insulin and also glucose oxidase (GOD), an enzyme which produces gluconic acid when it reacts with glucose in the presence of oxygen, it causes a lowering of the pH in the delivery system's microenvironment. This lowering of pH of the cationic polymer facilitates the syneresis of the gel and thereby squeezes out insulin from the polymeric gel as per the following reaction:

$$\text{Glucose} + O_2 + H_2O \rightarrow \underset{\downarrow}{\text{Glucose oxidase}} \quad \text{Gluconic acid} + H_2O_2$$

Albin et al.[67,68] developed glucose-sensitive cationic polymers based on polyacrylamide and poly(diethylaminoethylmethacrylate). The transport of ^{125}I-labeled insulin shows that microporous hydrogels have better glucose sensitivity than nonporous gels. Further, it was reported that the depletion of oxygen limited the response of these cationic gels to glucose. This oxygen depletion is strongly influenced by the extent of GOD loading and membrane thickness. However, Klumb and Horbett[69] developed a new geometry for the delivery devices to avoid the problem related with the depletion of oxygen.

Hariharan and Peppas[70] developed p(HEMA-*co*-DEAEM) cationic polymers and found that their swelling characteristics were a strong function of ionic strength and pH. Podual et al.[71,72] developed copolymers of DEAEM and poly(ethylene glycol) monomethacrylate loaded with GOD. Swelling studies of these cationic polymers showed a transition at pH 7.1, below which they were in the collapsed state. These gels show a pulsatile swelling behavior with changing environmental pH. Since the glucose response of GOD-loaded gels is limited by the depletion of oxygen, catalase was used to reduce hydrogen peroxide to water and oxygen, thus making the GOD continue to react in the presence of glucose to produce gluconic acid and making the delivery system practical under physiological conditions (as shown below):

$$2H_2O_2 \xrightarrow{\text{Catalase}} O_2 + 2H_2O$$

The above process can lead to an increase in the pore size (opening of molecular gates), thus allowing the release of insulin by diffusion ("molecular gate" principle as shown in Fig. 8). As the glucose level decreases by the action of insulin, the local pH increases the swelling of the gel and thereby closes the molecular gate, and the membrane becomes impermeable to insulin.[73]

In addition to the synthetic functional polymers, there are some natural polymers like chitosan,[74,75] alginate, pectin,[76] etc., which can perform the role of pH-responsive polymers. The advantage of such polymers is that they are biodegradable, but they may not possess required properties such as stability, mechanical strength, etc. These problems can be circumvented by copolymerizing and/or blending them with synthetic cousins. The functional groups can also be introduced on the natural polymers to make them stimulus-responsive.

Recently, we have developed[77,78] anionic microgels in the size range 300–600 μm. These microgels were produced by the controlled hydrolysis of crosslinked polyacrylamide-grafted guar gum (pAAm-*g*-GG). These microgels were responsive to both pH and ionic strength of the environment. The swelling

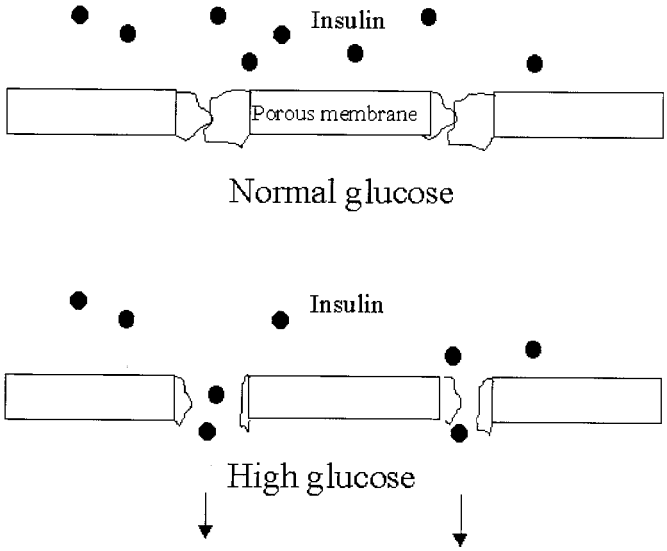


Figure 8. Mechanism of "molecular gate" systems.[79]

(calculated in terms of the diameter of the microgels) was reversible and pulsatile (see Fig. 9). The solvent front diffusion coefficients (D_v) (calculated by measuring the change in the volume of the microgels) have increased from 5.37×10^{-5} to $27.3\times10^{-3}\,cm^2/sec$. Similarly, the release of diltiazem hydrochloride depends upon the pH of the external media (see Fig. 10). Diffusion coefficients (D_r) calculated for the release increased from 4.83×10^{-8} to $6.77\times10^{-7}\,cm^2/sec$ when the pH of the external medium was increased to 7.4. Investigations are still underway in our laboratories to develop these microgels for applications in the delivery of drugs, proteins, and peptides.

CONCLUDING REMARKS

Advances in polymer science and technology resulted in accelerated research and developmental

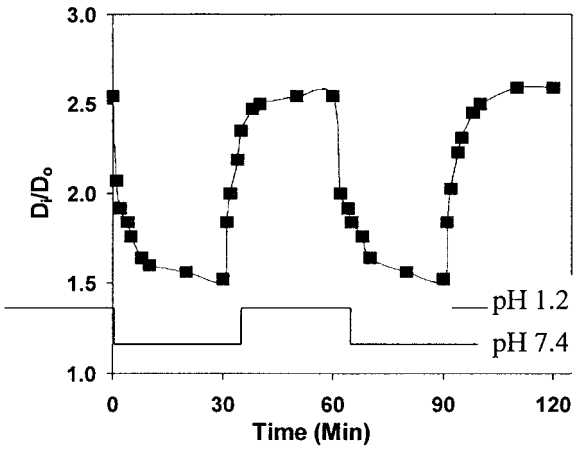


Figure 9. Pulsatile swelling of PAAm–GG ionic microgels.[78]

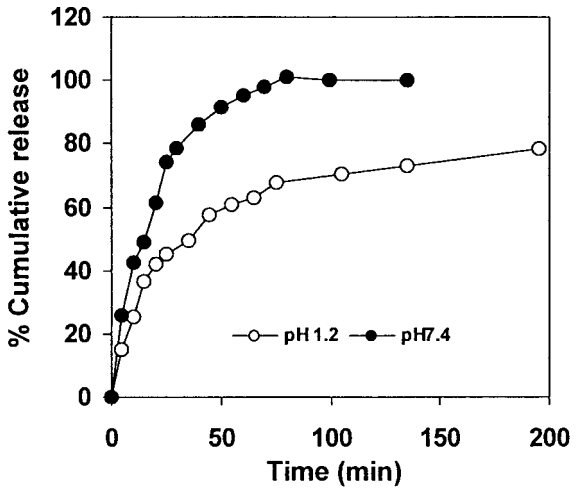


Figure 10. Release of diltiazem hydrochloride from PAAm-*g*-*GG*.[77]

activity in the design of innumerable drug delivery devices, particularly in the area of functional polymers that are pH or temperature-responsive. However, the extent and type of response of these polymers are based on polymer type and their functional groups. From the survey of literature in this area, it has been possible to develop an array of polymers with varying abilities by altering their hydrophobic and hydrophilic properties. Of the many polymers, the temperature-sensitive NIPAAm polymer has been most widely studied. Further modification of this basic structure by copolymerization, etc., has led to the production of suitable thermo-responsive smart materials that are useful in a variety of applications. On the other hand, pH-sensitive acrylic-based polymers seem to be better suited for protein/peptide delivery by an oral route. The cationic pH-sensitive polymers based on dimethylaminomethacrylate may be useful in the development of stimuli-responsive hydrogels that are sensitive to fluctuations of the blood glucose level, and hence such systems may be useful in monitoring the release of insulin as well as blood glucose level. There is still a need for more developmental work in this area. Different types of functional polymers are still to be tested in vivo for a series of drugs. Some of these areas are currently under active investigation by many research laboratories. However, this area requires a multidisciplinary approach and combined efforts between polymer scientists, medical doctors, and pharmacists.

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REFERENCES

1. Hoffman, A.S. In *Polymer Gels—Fundamentals and Biomedical Applications*; DeRossi, D., Kajiwara, K., Osad, Y., Yamauchi, A., Eds.; Plenum Press: New York, 1991.
2. Peppas, N.A.; Khare, A.R. Preparation and Diffusion Behavior of Hydrogels in Controlled Release. Adv. Drug Del. Rev. **1993**, *11*, 1–35.
3. Tanaka, T. Dynamics of Critical Concentration Fluctuations in Gels. Phys. Rev. **1978**, *A17*, 763–766.
4. Tanaka, T. Collapse of Gels and the Critical Endpoint. Phys. Rev. Lett. **1978**, *40*, 820–823.
5. Tanaka, T.; Fillmore, D.J. Kinetics of Swelling of Gels. J. Chem. Phys. **1979**, *70*, 1214–1218.
6. Kim, S.W. Temperature Sensitive Polymers for Delivery of Macromolecular Drugs. In *Advanced Biomaterials in Biomedical Engineering and Drug Delivery Systems*; Ogata, N., Kim, S.W., Feijen, J., Eds.; Springer: Tokyo, 1996; 126–133.
7. Philippova, O.E.; Hourdet, D.; Audebert, R.; Khokhlov, A.R. Macromolecules **1997**, *30*, 8278–8285.
8. Wen, S.; Stevenson, W.T.K. Colloid. Polym. Sci. **1993**, *271*, 38.
9. Park, T.G.; Hoffman, A.S. J. Appl. Polym. Sci. **1992**, *46*, 659.
10. Kataoka, K.; Koyo, H.; Tsuruta, T. Macromolecules **1995**, *28*, 333–336.
11. Heskins, M.; Guillet, J.E. Solution Properties of Poly(*N*-Isopropylacrylamide). J. Macromol. Sci. Chem. **1968**, *A2*, 1441–1455.
12. Feil, H.; Bae, Y.H.; Feijen, J.; Kim, S.W. Effect of Comonomer Hydrophilicity and Ionization on the Lower Critical Solution Temperature of *N*-Isopropylacrylamide Copolymer. Macromolecules **1995**, *36*, 125–133.
13. Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, T.; Bae, Y.H.; Kim, S.W. Surface-Modulated Skin Layers of Thermal Responsive Hydrogels as On–Off Switches: I. Drug Release. J. Biomater. Sci. Polym. Ed. **1991**, *3*, 155–162.
14. Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. J. Biomater. Sci. Polym. Ed. **1992**, *3*, 243.
15. Kaneko, Y.; Sakai, K.; Kikuchi, A.; Aoyagi, T.; Sakurai, Y.; Okano, T. Pulsed Drug Release Using Fast Responsive Comb-Type Grafted Polymeric Gel. Int. Symp. Contr. Rel. Bioact. Mater. **1996**, *23*, 223–324.
16. Kaneko, Y.; Sakai, K.; Kikuchi, A.; Aoyagi, T.; Sakurai, Y.; Okano, T. Oscillating Drug Release in the Deswelling Process of Temperature-Responsive Comb-Type Grafted Poly(*N*-Isopropylacrylamide) Hydrogel. Int. Symp. Contr. Rel. Bioact. Mater. **1997**, *24*, 543–544.
17. Gutowska, A.; Bark, J.K.; Kwon, I.C.; Bae, Y.H.; Kim, S.W. Squeezing Hydrogels for Controlled Drug Delivery. J. Contr. Rel. **1997**, *48*, 141–148.
18. Priest, J.H.; Murray, S.L.; Nelson, R.J.; Hoffman, A.S. LCST of Aqueous Copolymer of *N*-Isopropylacrylamide and Other *N*-Substituted Acrylamides. In *Reversible Polymer Gels and Related Systems*; Rosso, F., Ed.; ACS Press: Washington DC, 1987; 255–264.

19. Okano, T.; Bae, Y.H.; Kim, S.W. Insulin Permeation Through Temperature Sensitive Hydrogels. Proc. Am. Chem. Soc. Meeting, New York, 1986.
20. Bae, Y.H.; Okano, T.; Hsu, R.; Kim, S.W. Thermosensitive Polymers as On–Off Switches for Drug Release. Makromol. Chem. Rapid Commun. **1987**, *8*, 481–485.
21. Dinarvand, R.; D'Emanuele, A. A Comparison of Drug Release from Thermosensitive Microspheres and Discs. Int. Symp. Contr. Rel. Bioact. Mater. **1992**, *19*, 373–374.
22. Dinarvand, R.; D'Emanuele, A. The Use of Thermosensitive Hydrogels for On–Off Release of Molecules. J. Contr. Rel. **1995**, *36*, 221–227.
23. Lowe, T.L.; Virtanen, J.; Tenhu, H. Interactions of Drugs and Spin Probes with Hydrophobically Modified Polyelectrolyte Hydrogels Based on *N*-Isopropylacrylamide. Polymer **1999**, *40*, 2595–2603.
24. Dong, L.C.; Hoffman, A.S. Novel Approach for Preparation of pH-Sensitive Hydrogels for Enteric Drug Delivery. J. Contr. Rel. **1991**, *15*, 141–152.
25. Ganorkar, C.R.; Baudys, M.; Kim, S.W. J. Biomater. Sci. Polym. Ed. **2000**, *11*, 45–54.
26. Ganorkar, C.R.; Gutowska, A.; Liu, F.; Baudys, M.; Kim, S.W. Polymer Molecular Weight Alters Properties of pH-/Temperature-Sensitive Polymeric Beads. Pharm. Res. **1999**, *16*, 819–827.
27. Ganorkar, C.R.; Liu, F.; Baudys, M.; Kim, S.W. Modulating Insulin-Release Profiles from pH/Thermosensitive Polymeric Beads Through Polymer Molecular Weight. J. Contr. Rel. **1999**, *59*, 287–298.
28. Serres, A.; Baudys, M.; Kim, S.W. Temperature and pH-Sensitive Polymers for Human Calcitonin Delivery. Pharm. Res. **1996**, *13*, 196–201.
29. Kim, Y.H.; Bae, Y.H.; Kim, S.W. pH/Temperature Sensitive Polymers for Macromolecular Drug Loading and Release. J. Contr. Rel. **1994**, *28*, 143–152.
30. Peppas, N.A., Vakkalanka, S.K.; Brezil, C.S. Unique Swelling-Controlled Release Systems Based on Temperature Sensitive Terpolymer for Fiberinolytic Enzyme Delivery. Int. Symp. Contr. Rel. Bioact. Mater. **1996**, *23*, 267–268.
31. Zhang, J.; Peppas, N.A. Novel pNIPAAm/PMAA Interpenetrating Polymer Networks. Int. Symp. Contr. Rel. Bioact. Mater. **1998**, *25*, 870–871.
32. Chung, J.E.; Yokoyama, M.; Yamato, M.; Aoyagi, T.; Sakuri, Y.; Okano, T. Thermo-responsive Drug Delivery from Polymeric Micelles Constructed Using Block Copolymer of Poly(*N*-Isopropylacrylamide) and Poly-(Butylmethacrylate). J. Contr. Rel. **1999**, *62*, 115–127.
33. Kori, F.; Sakai, K.; Aoyagi, T.; Yokoyama, M.; Sakurai, Y.; Okano, T. Preparation and Characterization of Thermally Responsive Block copolymer Micelles Comprising Poly(*N*-Isopropylacrylamide-*b*-DL-Lactide). J. Contr. Rel. **1998**, *55*, 87–98.
34. Kono, K.; Hayashi, H.; Takagishi, T. Temperature-Controlled Release and Fusion of Liposomes Bearing Poly(*N*-Isopropylacrylamide). Int. Symp. Contr. Rel. Bioact. Mater. **1996**, *23*, 783–784.
35. Okahata, Y.; Noguchi, H.; Seki, T. Thermoselective Permeation from a Polymer-Grafted Capsules Membranes. Macromolecules **1986**, *19*, 493–494.
36. Ichikawa, H.; Fukumori, Y. A Novel Positive Thermosensitive Controlled-Release Microcapsule with Membrane of Nano-sized Poly(*N*-Isopropylacrylamide) Gel Dispersed in Ethyl Cellulose Matrices. J. Contr. Rel. **2000**, *63*, 107–109.
37. Wu, X.Y.; Lee, P.I. Preparation and Characterization of Thermal- and pH-Sensitive Nanospheres. Pharm. Res. **1993**, *10*, 1544–1547.
38. Lee, W.F.; Hsu, C.H. Thermoreversible Hydrogels. VII. Synthesis and Swelling Behavior of Poly(*N*-Isopropylacrylamide-*co*-3-Methyl-1-Vinylimidazolium Iodide) Hydrogels. J. Appl. Polym. Sci. **1999**, *74*, 3242–3253.
39. Hoffman, A.S.; Chen, G.; Wu, X.; Ding, Z.; Matsuura, J.E.; Gombotz, W.R. Stimuli Responsive Polymers Grafted onto Polyacrylic Acid and Chitosan Backbones as Bioadhesive Carriers for Mucosal Drug Delivery. In *Frontiers in Biomedical Polymer Applications*; Ottenbrite, R.M., Ed.; Technomic Publishing: Lancaster, PA, 1999; 17–29.
40. Hoffman, A.S.; Wu, X.; Ding, Z.; Schiller, M.; Ron, E. Novel Drug Carriers Based on Physical Gels of Pluronic® Polyethers Grafted to Chitosan Backbones: Syntheses and Solution Properties. Int. Symp. Contr. Rel. Bioact. Mater. **1997**, *24*, 563–564.
41. Hoffman, A.S.; Matsura, J.E.; Wu, X.; Gombotz, W.R. Release of Cytokine from Physical Hydrogels of Pluronic® Polyethers Grafted to Chitosan Backbones. Int. Symp. Contr. Rel. Bioact. Mater. **1997**, *24*, 126–127.
42. Yoshida, M.; Asano, M.; Kumakura, M. A New Temperature-Sensitive Hydrogel with α-Amino acid Groups as Side Chain of Polymer. Eur. Polym. J. **1989**, *12*, 1197–1202.
43. Yuk, S.H.; Cho, S.H. Thermocontrol of Solute Transport Using Temperature-Sensitive Polymer Membrane. Int. Symp. Contr. Rel. Bioact. Mater. **1997**, *24*, 521–522.
44. Miyazaki, S.; Suisha, F.; Kawasaki, N.; Shirakawa, M.; Yamatoya, K.; Attwood, D. Thermally Reversible Xyloglucan Gels as Vehicle for Rectal Drug Delivery. J. Contr. Rel. **1998**, *56*, 75–83.
45. Peppas, L.B.; Peppas, N.A. Solute and Penetrant Diffusion in Swellable Polymer. IX. The Mechanism of Drug Release from pH-Sensitive Swelling-Controlled Systems. J. Contr. Rel. **1989**, *8*, 267–274.

46. Bettini, R.; Colombo, P.; Peppas, N.A. Solubility Effect on Drug Transport Through pH-Controlled Release Systems: Transport of Theophylline and Metoclopramide Monohydrochloride. J. Contr. Rel. **1995**, *37*, 105–111.
47. am Ende, M.T.; Peppas, N.A. Transport of Ionizable Drugs and Proteins in Crosslinked Poly(Acrylic Acid) and Poly(Acrylic Acid-*co*-2-Hydroxyethyl Methacrylate) Hydrogels. II. Diffusion and Release Studies. J. Contr. Rel. **1997**, *48*, 47–56.
48. Khare, A.R.; Peppas, N.A. Characterization of Water Structure in Relation to Release Behavior of Drugs from pH-Sensitive Hydrogels. Int. Symp. Contr. Rel. Bioact. Mater. **1991**, *19*, 200–201.
49. Ranijha, N.M.; Doelker, E. Solute Release Behavior from pH-Sensitive Acrylic Hydrogels for Colonic Drug Delivery. Symp. Contr. Rel. Bioact. Mater. **1998**, *25*, 886–887.
50. Negishi, M.; Hiroki, A.; Horikoshi, Y.; Miyajima, M.; Asano, M.; Karakai, R.; Yoshida, M. Swelling and Ketoprofen Release Characteristics of Thermo- and pH-Responsive Copolymer Gels. Drug Dev. Ind. Pharm. **1999**, *25*, 437–444.
51. Yilmazturk, B.; Ulubayram, K.; Hasirci, N. Controlled Release of Proteins from pH-Responsive Hydrogels. Symp. Contr. Rel. Bioact. Mater. **1999**, *26*, 1038–1039.
52. Yao, K.D.; Sun, S. pH-Stimulus Response of Complex-Formation Poly[(Ethylene Glycol-*co*-Propylene Glycol)-*g*-Acrylamide]:*cr*-Poly(Acrylic Acid). Polym. Int. **1993**, *32*, 19–22.
53. Yuk, S.H.; Cho, S.H.; Lee, H.B. pH-Sensitive Drug Delivery Systems Using O/W Emulsion. J. Contr. Rel. **1995**, *37*, 69–74.
54. Kono, K.; Kawakama, K.; Morimoto, K.; Takagishi, T. Effect of Hydrophobic Units on the pH-Responsive Release Properties of Polyelectrolyte Complex Capsules. J. Appl. Polym. Sci. **1999**, *72*, 1763–1773.
55. Bektorova, E.; Bimendina, L. Interpolymer Complexes. Adv. Polym. Sci. **1981**, *41*, 99–147.
56. Lowman, A.M.; Peppas, N.A. Analyses of Complexation and Decomplexation of Phenomenon in Polyelectrolyte Networks. Macromolecules **1997**, *30*, 4959–4965.
57. Lowman, A.M.; Peppas, N.A. Oscillatory Drug and Protein Release by a Complexation/Decomplexation Mechanism. Symp. Contr. Rel. Bioact. Mater. **1996**, *23*, 745–746.
58. Lowman, A.M.; Morishita, M.; Kajita, M.; Nagai, T.; Peppas, N.A. Oral Delivery of Insulin Using pH-Sensitive Complexation Gels. J. Pharm. Sci. **1999**, *88*, 933–936.
59. Torres-Lugo, M.; Peppas, N.A. Molecular Design and In Vitro Studies of Novel pH-Sensitive Hydrogels for the Oral Delivery of Calcitonin. Macromolecules **1999**, *32*, 6646–6651.
60. Eichenbaum, G.H.; Kiser, P.F.; Shah, D.; Simon, S.A.; Needham, D. Investigation of the Swelling Response and Drug Loading of Ionic Microgels: The Dependence on Functional Group Composition. Macromolecules **1999**, *32*, 8996–9006.
61. Kiser, P.F.; Wilson, G.; Needham, D. Lipid-Coated Microgels for the Triggered Release of Doxirubicin. J. Contr. Rel. **2000**, *68*, 9–22.
62. Siegel, R.A.; Firestone, B.A. pH-Dependent Equilibrium Swelling Properties of Hydrophobic Polyelectrolyte Copolymer Gels. Macromolecules **1988**, *21*, 3254–3259.
63. Siegel, R.A.; Falamarazin, M.; Firestone, B.A.; Moxley, B.C. pH-Controlled Release from Hydrophobic/Polyelectrolyte Copolymer Hydrogels. J. Contr. Rel. **1988**, *8*, 179–182.
64. Siegel, R.A.; Johannes, I.; Hunt, I.C.A.; Firestone, B.A. Buffer Effects on Swelling Kinetics in Polybasic Gels. Pharm. Res. **1992**, *9*, 76–81.
65. Firestone, B.A.; Siegel, R.A. Kinetics and Mechanism of Water in Hydrophilic. Ionic Copolymer Gels. J. Appl. Polym. Sci. **1991**, *43*, 901–914.
66. Falamarzian, M.; Varshosaz, J. Effect of Structural Changes on Swelling Kinetics of Polybasic/Hydrophobic pH-Sensitive Hydrogels. Drug Dev. Ind. Pharm. **1998**, *24*, 667–669.
67. Albin, G.; Horbett, T.A.; Ratner, B.D. Glucose Sensitive Membranes for Controlled Delivery of Insulin: Insulin Transport. J. Contr. Rel. **1985**, *2*, 153–164.
68. Albin, G.; Horbett, T.A.; Miller, S.R.; Ricker, N.L. Theoretical and Experimental Study of Glucose Sensitive. J. Contr. Rel. **1987**, *6*, 267–291.
69. Klumb, L.A.; Horbett, T.A. J. Contr. Rel. **1992**, *18*, 59–80.
70. Hariharan, D.; Peppas, N.A. Swelling Controlled Drug Release Cationic Polymers. Symp. Contr. Rel. Bioact. Mater. **1991**, *23*, 367–368.
71. Podual, K.; Doyle III, F.J.; Peppas, N.A. Preparation and Dynamic Response of Cationic Copolymer Hydrogels Containing Glucose Oxidase. Polymer **2000**, *41*, 3975–3983.
72. Podual, K.; Doyle III, F.J.; Peppas, N.A. Dynamic Behavior of Glucose Oxidase-Containing Microparticles of Poly(Ethylene)-Grafted Cationic Hydrogels in an Environment of Changing pH. Biomaterials **2000**, *21*, 1439–1450.
73. Hassan, C.M.; Peppas, N.A. Novel Ethylene Glycol-Containing pH-Sensitive Hydrogels for Drug Delivery Applications. In "*Molecular Gates*" *for Insulin*; ACS; Symp. Ser. **1999**, *728*, 54–69.

74. Gupta, K.C.; Ravi Kumar, M.N.V. Preparation, Characterization and Release Profiles of pH Sensitive Chitosan Beads. Polym. Int. **2000**, *49*, 141–146.
75. Qu, X.; Wirsen, A.; Albertsson, A. Structural Change and Swelling Mechanism of pH Sensitive Hydrogels Based on Chitosan and D,L-Lactic Acid. J. Appl. Polym. Sci. **1999**, *74*, 3186–3192.
76. Pillya, V.; Fassihi, R. In Vitro Release Modulation from Crosslinked Pellets for Site-Specific Drug Delivery to the Gastrointestinal Tract I. Comparison of pH-Responsive Drug Release and Associated Kinetics. J. Contr. Rel. **1999**, *59*, 229–242.
77. Soppimath, K.S.; Kulkarni, P.V.; Aminabhavi, T.M. pH-Sensitive Corboxylated Guar Gum-*g*-Acrylamide Microgels as Stimulus Responsive Drug Delivery Systems. Symp. Contr. Rel. Bioact. Mater. **2001**, *28*, 6006.
78. Soppimath, K.S.; Kulkarni, A.R.; Aminabhavi, T.M. Chemically Modified Polyacrylamide-*g*-Guar Gum Based Cross-Linked Anionic Microgels as pH-Sensitive Drug Delivery System: Preparation and Characterization. J. Contr. Rel. **2001**, *75*, 331–345.
79. Dorski, C.M.; Doyle, F.J.; Peppas, N.A. Preparation and Characterization of Glucose-Sensitive p(MAA-*g*-EG) Hydrogels. Polym. Mater. Sci. Proc. **1997**, *76*, 281–282.