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Chapter 4
Hydrogels

Hossein Omidian and Kinam Park

Abstract Hydrogels are crosslinked polymers with the ability to swell in an aqueous medium. Crosslinking in hydrogels occurs by chemical or physical means depending on the polymer properties and experimental conditions. Owing to a large variety in chemical structure and crosslinking methods, various hydrogels have been prepared for various applications in pharmaceutical and biomedical fields. This chapter begins with hydrogel classification, properties, and their methods of preparation. The chapter continues with intelligent hydrogels, which are able to respond to environmental changes such as temperature, pH, and solvent composition, by changing their dimensions. Hydrogel based on polysaccharides, hydrocolloids, and synthetic polymers are discussed accordingly. Finally, the chapter concludes with known hydrogel applications in the pharmaceutical area. These include superdisintegrants, ion exchanging resins, superporous hydrogels, hydrogel implants, hydrogel inserts, osmotic products (devices, implants, and tablets), as well as tissue expanding hydrogels and contact lenses.

4.1 Introduction

Section Title

4.1.1 Hydrosol and Hydrogel

In a simple binary system of a polymer and a liquid, a sol is formed when the polymer–liquid interaction are more favored than both polymer–polymer and liquid–liquid interactions. If the polymer is hydrophilic and the liquid is water, the

H. Omidian (✉)
Health Professions Division, College of Pharmacy, Nova Southeastern University, 3200 S. University Drive, Fort Lauderdale, FL, USA
e-mail: omidian@nova.edu

K. Park
Departments of Biomedical Engineering and Pharmaceutics
Purdue University, West Lafayette, IN, USA

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product of the polymer–liquid interaction is called a hydrosol. The extent of this reaction is generally dependent on the polymer structure, functional groups, type, and amounts of ions in the polymer structure as well as in the solution, pH, and temperature. The dissolution of a hydrophilic polymer in water can be prevented by adding crosslinks via either a physical or a chemical process. A crosslinked hydrosol is called a hydrogel and can only swell in the surrounding liquid to a certain swelling ratio, depending on the number of crosslinks, i.e., the crosslinking density.

4.1.2 Physical and Chemical Gels

In physical gels, the nature of the crosslinking process is physical. This is normally achieved via utilizing physical processes such as association, aggregation, crystallization, complexation, and hydrogen bonding. On the contrary, a chemical process, i.e., chemical covalent crosslinking is utilized to prepare a chemical hydrogel. Figures 4.1 and 4.2 show different approaches to make physical and chemical hydrogels, respectively. While physical hydrogels are reversible due to the conformational changes, chemical hydrogels are permanent and irreversible as a result of configurational changes. More details about the hydrogels are found in Table 4.1.

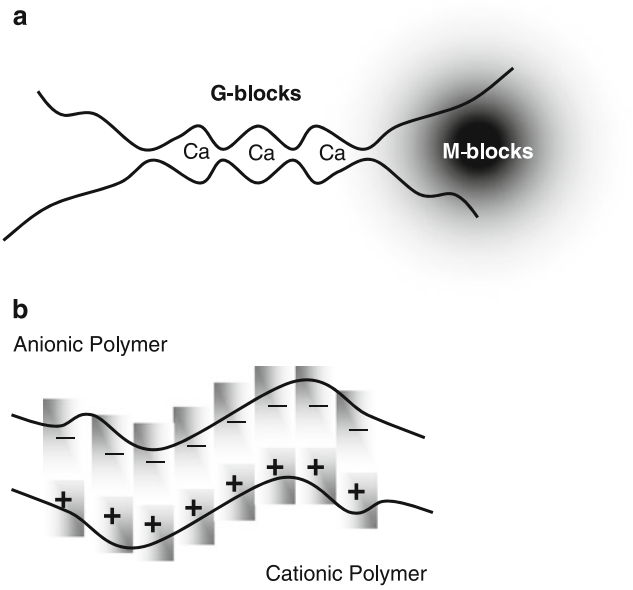

Fig. 4.1 Examples of physical hydrogels crosslinked by ion–polymer complexation (**a**), polymer–polymer complexation (**b**), hydrophobic association (**c**), chain aggregation (**d**), and hydrogen bonding (**e**)

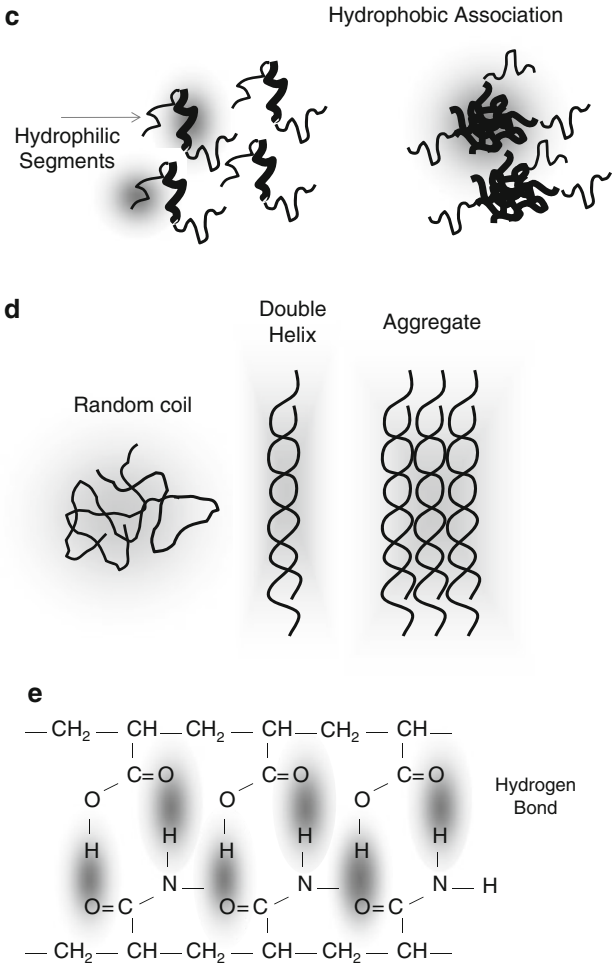

Fig. 4.1 (continued)

4.1.3 Responsive Hydrogels

Hydrogels are also classified as shown in Table 4.2 in terms of their interaction with the surrounding environment, i.e., responses to the changes in pH, temperature, and the composition of the surrounding liquid. Depending on its structure, hydrogel can respond to environmental changes by changing its size or shape. Most important factors that trigger a hydrogel response are pH, temperature, and swelling medium. While nonionic hydrogels are almost insensitive to pH changes, ionic hydrogels display a dramatic change in size with the pH change. As far as the temperature is

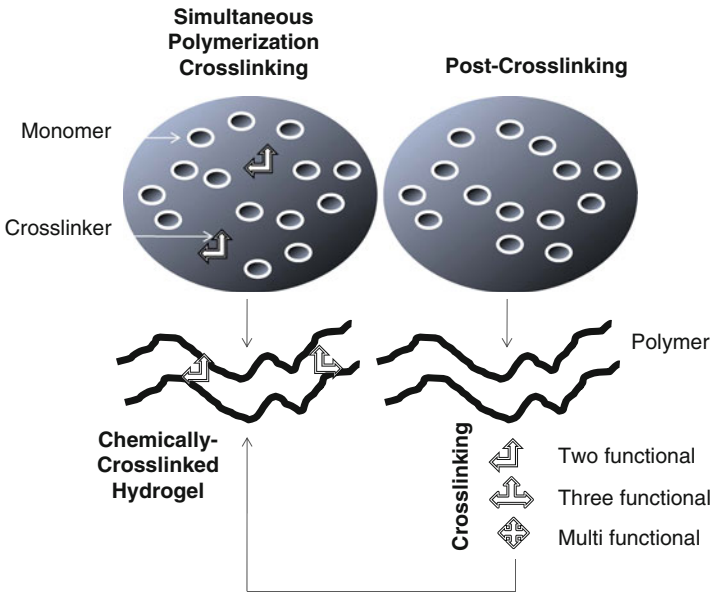

Fig. 4.2 Methods to prepare chemical hydrogels

Table 4.1 Sol–gel (hydrosol–hydrogel) transition in physical and chemical hydrogels

Physical hydrogels	Chemical hydrogels
Hydrophobic association: isopropyl groups in poly(*N*-isopropyl acrylamide); methyl groups in methyl cellulose; propylene oxide blocks in (ethylene oxide)–(propylene oxide)–(ethylene oxide) terpolymers	Covalent crosslinking using olefinic crosslinkers containing unsaturated bonds or reactive functional groups
Ion–polymer complexation: acrylic-based hydrogels treated with calcium, aluminum, iron; sodium alginate treated with calcium and aluminum; poly(vinyl alcohol) treated with borax	*Simultaneous polymerization and crosslinking*: Acrylic acid or acrylamide, crosslinked with methylene bisacrylamide, ethylene glycol diacrylate, ethylene glycol dimethacrylate, poly(ethylene glycol dimethacrylate)
Polymer–polymer complexation: alginate and chitosan; gum Arabic and gelatin	*Post-polymerization chemical crosslinking*: Acrylic-based hydrogel, crosslinked with glycerin; gelatin cross-linked with glutaraldehyde; poly(vinyl alcohol) crosslinked with an aldehyde
Chain aggregation: heat treatment of hydrocolloids in water	
Hydrogen bonding: poly(vinyl alcohol)/poly (vinyl alcohol) chains; poly(acrylic acid)/ polyacrylamide chains	

Table 4.2 Examples of hydrogels responsive to changes in environmental factors

Hydrogels responsive to:		
pH	Temperature	Liquid composition
(If the hydrogel is ionic)	(If the hydrogel can form hydrophobic association and chain aggregation)	(If the surrounding environment of the hydrogel contain nonsolvents and salts)
With increase in pH	*With increase in temperature*	*With changes in swelling medium*
Swelling increases in anionic hydrogels containing carboxyl group such as poly (sodium acrylate) and sodium alginate	*Solubility decreases in* cellulose derivatives such as cellulose-based polymers containing methyl or hydroxypropyl groups and poly(*N*-isopropyl acrylamide)	*Swelling decreases sharply in* ionic hydrogels such as poly(potassium acrylate) and sodium alginate with increase in concentration of nonsolvent, salts, as well as salt valence
Swelling decreases in cationic hydrogels containing amino groups such as poly (dimethyl aminoethyl) acrylate and chitosan	*Solubility increases in* hydrocolloids such as gelatin and agar agar	*Swelling decreases moderately in* nonionic hydrogels such as polyacrylamide and poly(vinyl alcohol) with increase in concentration of nonsolvent, salts as well as salt valence

concerned, hydrogels containing hydrophobic groups or those susceptible to chain aggregation respond to the temperature change to a great extent. Given the fact that solubility and swellability are driven by same forces, the response of the hydrogel to temperature change can be either direct or inverse. With the former, the solubility and swellability of the hydrogel can increase with increase in temperature, while an opposite trend is observed with inverse thermoresponsive hydrogels. Hydrogels can also change their size with the change in the composition of the swelling medium. Apparently the hydrogel response would be dramatic if the swelling medium contains salt and a nonsolvent. These facts are shown in Fig. 4.3.

4.1.4 Hydrogel Properties

Hydrogels are generally characterized by their ultimate capacity to absorb liquids (swelling thermodynamics), the rate at which the liquid is absorbed into their structure (swelling kinetics), as well as their mechanical property in wet or hydrated state (wet strength). Table 4.3 shows factors affecting the hydrogel properties among which, the crosslink density and the structural integrity (porosity, pore size and its distribution) have the most significant effect. Hydrogels

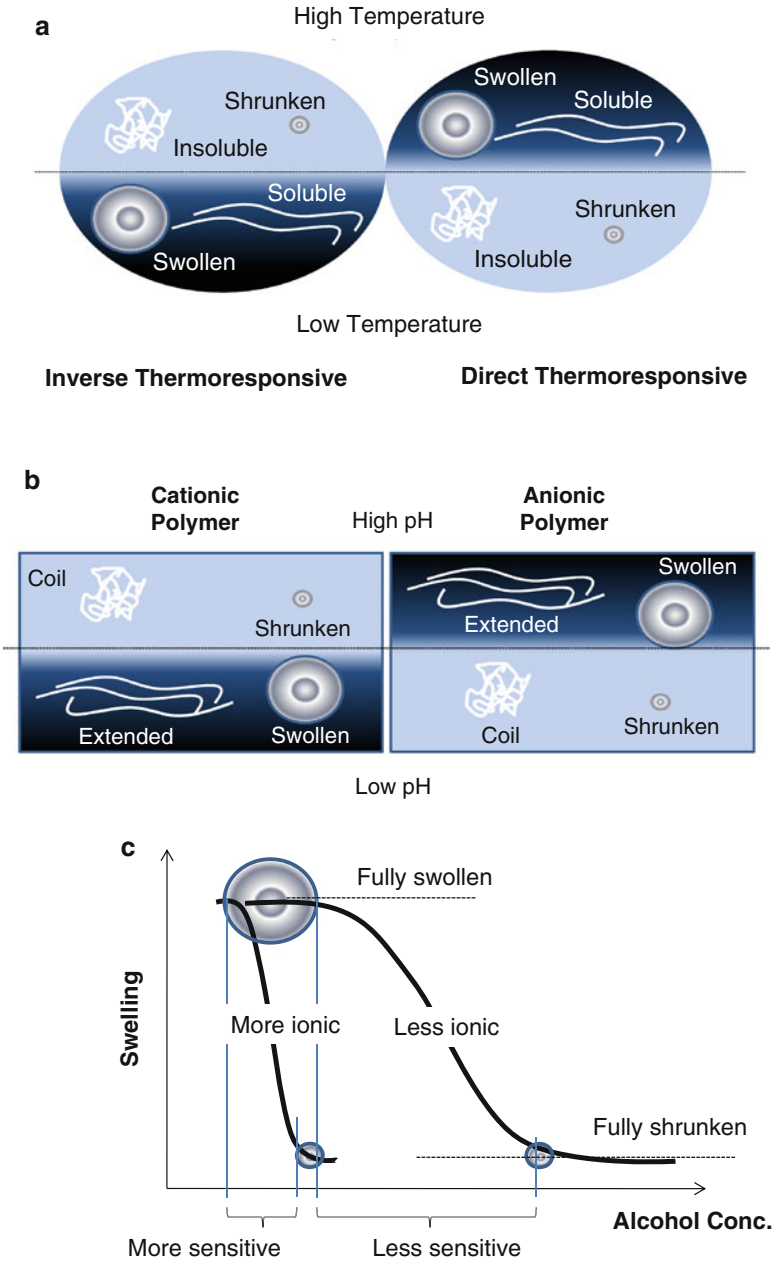

Fig. 4.3 Hydrogel swelling and hydrosol solubility dependence on (**a**) temperature, (**b**) pH, and (**c**) nonsolvent concentration

Table 4.3 Changes in hydrogel properties due to the hydrogel structure and liquid composition

Swelling capacity ↑	Swelling rate ↑	Wet strength ↑
Hydrogel structure: very hydrophilic polymers, ionic polymers containing monovalent ions, lower crosslink density, hydrophilic crosslinkers	*Hydrogel structure*: more hydrophilic, higher crosslink density, more porosity, open pores, interconnected pores	*Hydrogel structure*: high crosslink density (there is an optimum crosslink density at which, the mode of hydrogel failure changes from ductile to brittle), low porosity, more hydrophobicity
Liquid composition: more solvent, less salts, low ionic strength, less numbers of di and trivalent cations	*Liquid composition*: Presence of permeation enhancers for more hydrophobic hydrogels, more solvent	*Liquid composition*: more nonsolvent, more salts

have been attractive to the pharmaceutical industry for several reasons including the controlled release of an active pharmaceutical ingredient, disintegration of dosage forms, protecting an active and to increase the product life cycle management.

The general concepts and applications of hydrogels within the pharmaceutical area are outlined below with focuses on the most recent research activities in the field.

4.2 Hydrogels in Pharmaceutical Applications

4.2.1 Inverse Thermoresponsive Hydrogels

The solubility and swellability of the hydrogels containing hydrophobic groups and segments is dependent on the temperature of the swelling medium. Polyacrylamide derivatives containing hydrophobic pendant groups display reverse temperature sensitivity. These are soluble in water at low temperature and become insoluble when temperature rises. This behavior is a result of a delicate balance between the hydrogen bonding and hydrophobic interactions, which depends on temperature. The transition temperature at which a water soluble polymer becomes insoluble is called the lower critical solution temperature (LCST), below which, the hydrogen bonding and above which, hydrophobic association prevails. Below and above the LCST, the hydrogel displays a sharp transition in size from a sol to a gel (a so-called sol–gel transition point). Hydrogels based on poly(*N*-isopropyl acrylamide) (polyNIPAM), cellulose derivatives, and ethylene oxide–propylene oxide–ethylene oxide terpolymers display this behavior. In subcutaneous or parenteral drug delivery, a solution dosage form containing a drug and a thermosensitive

polymer are injected into the patient's body at room temperature. The polymer part of the dosage form then starts to gel at a higher body temperature, depending on its sol-gel transition temperature. Macromed, a US-based drug delivery company, has a delivery technology, ReGel®, based on ABA triblock copolymers in which the A and B blocks are poly(lactide-*co*-glycolide) and poly(ethylene glycol), respectively. ReGel® is a temperature sensitive and bioerodible hydrogel, which is intended for parenteral delivery [1].

4.2.1.1 Hydrogels Based on Acrylamide Derivatives

PolyNIPAM and its copolymer nanoparticles with acrylic acid have been prepared. The thermosensitive property of these hydrogels was shown to be manipulated by changing the molar ratio of the two monomers. The anticancer drug 5-fluorouracil (5-FU) was first loaded into both hydrogel nanoparticles with a loading efficiency as high as 4%. The release of the drug was found to be clearly dependent on temperature and pH [2]. A magnetic thermosensitive hydrogel has been prepared by incorporating superparamagnetic Fe_3O_4 particles into polyNIPAM hydrogels. A pulsatile drug release was remotely triggered and controlled by a high frequency alternating magnetic field [3]. Nanoparticles of poly(NIPAM-*co*-allylamine) and poly(NIPAM-*co*-acrylic acid) have been synthesized and crosslinked with glutaric dialdehyde and adipic acid dihydrazide, respectively. Dextrans of different molecular weights were used as a macromolecular drug for the release study. While dextran was not released from a highly crosslinked polyNIPAM gel, its release from NIPAM–allylamine copolymer gel was found to be temperature dependent. Low molecular weight dextrans were released from the NIPAM–acrylic acid copolymer gel almost independent of temperature [4]. An optically responsive hydrogel for drug delivery has been developed based on gold nanoparticles (60 nm) coated with a thermally responsive biocompatible hydrogel (20–90 nm). The hydrogel is based on NIPAM and acrylic acid and its properties can be tailored to exhibit a LCST slightly above the body temperature. Drug loaded hydrogel could be photothermally activated by an exposure to light, which can be absorbed by the plasmon resonance of the gold nanoparticle cores [5]. Thermosensitive copolymer hydrogels of NIPAM and butyl methacrylate have been prepared and examined for indomethacin delivery. A zero order kinetic at 20°C indicates that swelling and chain relaxation are rate determining steps (Case II diffusion). The release kinetic was found to be sigmoidal at 10°C, where a faster drug release is attributed to a faster swelling and disappearing the glassy core of the hydrogel [6]. Hydroxyethyl, hydroxybutyl and hydroxyhexyl derivatives of methacrylate polymer, and their copolymers with NIPAM and acrylic acid have been prepared. The surface, mechanical, and swelling properties of these hydrogels were measured using a dynamic contact angle analysis, tensile analysis, and thermogravimetry, respectively. The thermal transition points including the T_g and LCST were determined using modulated DSC and oscillatory rheometry, respectively. The drug chlorhexidine

diacetate was loaded into the hydrogels by immersing the hydrogel into the drug solution at a temperature below the LCST of the polymer [7].

4.2.1.2 PEG-Based Hydrogels

An aqueous solution of PEG–PLGA–PEG triblock copolymers at low molecular weight and specific composition has been shown to become gel at the body temperature. Drug release from these thermosensitive hydrogels has been examined in vitro by injecting the drug loaded polymer solution into a 37°C aqueous environment. Ketoprofen as a hydrophilic drug model was released over a 2 week period with a first order kinetic, while spironolactone, a hydrophobic model drug, was released over a two month period following a sigmoidal kinetic [8]. Gel paving hydrogels are locally applied or polymerized on vascular endoluminal surfaces and function as a physical barrier limiting deposition of cells and proteins, and hence reducing thrombogenicity. A thermoreversible and photopolymerizable gel paving system based on PEG-lactide hydrogels has been outlined [9]. A thermoreversible gel with gelling temperature close to the body temperature has been designed based on hyaluronic acid and poloxamer polymers. With an optimum hydrogel formulation, acyclovir could be released over a 6 h period [10].

A pH-sensitive and thermoresponsive hydrogel with higher swelling at higher pH and temperatures has been prepared based on hydroxyethyl chitin and polyacrylic acid. The hydrogel was claimed as an enteric delivery system for potassium diclofenac [11].

4.2.2 pH-Responsive Hydrogels

Polymers containing carboxyl groups or amino groups respond to the pH changes by changing their size in the swollen state. At low pH values, the carboxyl-containing anionic polymers display minimum ionization and hence reduced hydration. Once the pH of the swelling medium rises above the pK_a of the polymer, the carboxyl groups start to ionize and hydrate, which results in polymer expansion and hence higher swelling. On the contrary, cationic polymers containing amino groups (quaternary ammonium salts) display a stronger ionization and hence higher swelling at low pH. Current commercial products and ongoing research activities are overwhelmingly focused on acrylic or methacrylic acid functional groups to make a pH-sensitive carrier. Commercial polymers such as Eudragit® L100-55, L30D-55, L100, or S100 are anionic polymers with methacrylic acid as functional group. These are dissolved at pH above 5.5, which provide drug protection at low pH and drug release at high pH environment, which makes them suitable for drug delivery in duodenum, jejunum, ileum, and colon area. Eudragit® E100 is, on the contrary, a cationic polymer based on butyl and methyl methacrylate containing

dimethylaminoethyl methacrylate to provide a pH-sensitive functionality. The polymer is soluble in gastric juice and used for the taste or odor masking applications.

4.2.2.1 Acrylic Based Hydrogels

Silicone discs containing a pH-sensitive hydrogel have been used to release drugs with different water solubility and partitioning. The hydrogel granules were made of poly(acrylic acid), poly(ethylene oxide) interpenetrating networks; and salicylamide, nicotinamide, clonidine HCl, and prednisolone were used as the model drug. Owing to the anionic nature of the hydrogel blend, a bimodal release behavior was observed, a burst release at low pH and a high release later on at a higher pH medium. At high drug loading and at high pH medium, the release rate of clonidine HCl was reduced due to an ionic interaction with the carboxyl group of the IPN structure [12]. Hydrogels of glycidyl methacrylate dextran and poly(acrylic acid) have been prepared by UV irradiation for colon-specific drug delivery. The hydrogels displayed a pH-dependent swelling with the swelling capacity of 20 at the body temperature. The hydrogel displayed an enhanced swelling up to 45 fold in the presence of dextranase at pH 7.4, and is claimed as a dual sensitive drug carrier for sequential release in the gastrointestinal tract [13]. A pH-sensitive hydrogel has been prepared based on polyethylene glycol (PEG) and acrylic acid (AAc) in an aqueous solution utilizing gamma radiation. Swelling capacity of the hydrogel and the diffusion coefficient was found critically dependent on the pH and the ionic strength, respectively. Ketoprofen was used as a model drug to evaluate the hydrogel carrier for colon delivery at different pH [14]. An amphiphilic hydrogel has been prepared based on hydrophilic polyacrylic acid/hydrophobic polybutyl acrylate and tested for delivery of melatonin. The drug release was found pH dependent, and the burst effect associated with the hydrophilic networks was diminished due to the hydrophobic contribution of butyl acrylate [15]. Starch poly(acrylic acid-*co*-acrylamide) hydrogels have been prepared by physical mixing of the starch and polyacrylonitrile, followed by hydrolysis in the presence of sodium hydroxide. The hydrogel showed a swelling/shrinking cycle at pH 2 and 8, respectively. Poorly water soluble ibuprofen was released from the hydrogel much faster at the intestinal pH than at the gastric pH [16].

4.2.2.2 Methacrylic Based Hydrogels

An IPN network of poly(methacrylic acid) and poly(vinyl alcohol) crosslinked with glutaraldehyde has been prepared utilizing a water-in-oil emulsion system. The hydrogel displayed a pulsatile swelling behavior with the change in pH, and ibuprofen release was found dependent on the pH, crosslink density, and drug loading [17]. Two monomers of methacrylic acid and methacrylamide have been used to prepare hydrogels utilizing a free radical solution polymerization. The hydrogel was intended

for oral delivery of an antimalarial drug under physiological conditions. With high loading efficiency of about 98%, the amount of release in simulated gastric (pH 1.2) and colonic environment (pH 7.4) was extensively varied from 29 to 75% respectively [18]. A pH-sensitive hydrogel of hydroxyethyl methacrylate, methacrylic acid and ethylene glycol dimethacrylate was prepared, and its release behavior was examined utilizing a water-soluble drug (ephedrine HCl) and a water insoluble drug (indomethacin) [19].

4.2.2.3 Chitosan-Based Hydrogels

Enteric coated multiparticulate chitosan hydrogel beads with pH-sensitive property have been reported as potential orally administrable drug carriers for site specific colon delivery [20]. Satranidazole has been examined with this delivery system [21]. A water-soluble derivative of chitosan (2-carboxybenzyl chitosan) has been synthesized and characterized using FTIR, HNMR, and UV. The degree of carboxybenzyl substitution was determined using a colloid titration method. The hydrogel swelling was decreased with an increase in glutaraldehyde concentration, and was higher in basic medium than in acidic environment. The release of fluorouracil (5-FU), a poorly water soluble drug was found to be much faster at pH 7.4 than pH 1.0, which justifies the use of this hydrogel as a potential pH-sensitive carrier for the colon specific drug delivery [22]. A glutaraldehyde-crosslinked carboxymethyl chitosan hydrogel was prepared and its release behavior was tested using salicylic acid as the model drug. The hydrogel showed a significantly higher swelling capacity in alkaline than in acidic media [23]. A pH-sensitive semi-IPN hydrogel of *N*-carboxyethyl chitosan and 2-hydroxyethyl methacrylate was prepared via photopolymerization. The hydrogel showed a good mechanical strength in its hydrated wet state, claimed to be nontoxic and offered a prolonged release with 5-flurouracil as a model drug [24]. A hydrogel system composed of carboxymethyl chitosan (a water soluble derivative of chitosan) and alginate blended with genipin (naturally occurring crosslinker) has been developed for controlled delivery of bovine serum albumin. The protein was released up to 20 and 80% respectively at simulated gastric and intestine conditions, which suggests its application as a potential drug carrier for site-specific intestinal delivery [25].

4.2.2.4 Miscellaneous Hydrogels

Methacrylic anhydride and succinic anhydride derivatives of inulin have been synthesized via UV irradiation to produce a pH-sensitive hydrogel. Diflunisal at different concentrations was used as a model drug [26]. A pH-sensitive hydrogel of methyl methacrylate and dimethylaminoethyl methacrylate crosslinked with divinyl benzene was prepared and its release behavior was tested using a water soluble drug, aminopyrine [27]. Acrylamide has been grafted onto xanthan gum to prepare a pH-sensitive hydrogel network. Drug release from the hydrogels was

studied using ketoprofen. FTIR, DSC/X-ray, and SEM were respectively used to confirm grafting/hydrolysis, to determine the crystal nature of the loaded drug, and to monitor the porosity of the hydrogel structure. Different release behavior was observed at low and high pH conditions [28].

4.2.3 Natural Polymer Based Hydrogels

Drug release from a controlled release platform is practically controlled by a delicate balance of solubility and swellability (gelling properties) of the drug carrier. Depending on their source and structure, hydrocolloids offer a vast range of solubility and gelling properties in aqueous media. Moreover, rheological properties of the drug solutions, dispersions, or emulsions can also be modified using hydrocolloids or hydrocolloid hybrids. They are also well established as food ingredients in nutraceutical industries.

4.2.3.1 Cellulose Derivatives

As an important class of excipients, polysaccharides such as methyl cellulose (MC), carboxymethyl cellulose (CMC), and different grades of hydroxypropyl methylcellulose (HPMC) have found numerous applications as binder, disintegrant, and most importantly as a controlled release platform. HPMC polymers offer different solubility and gelling properties, which are critically dependent on the degree of substitution, hydroxypropyl content, molecular weight, and temperature. Currently, there are about 130 drugs in the US market, which contain HPMC (hypromellose) as a matrix of controlled delivery. These include simvastatin niacin extended release (Simcor®), carbamazepine extended release (Carbatrol®), fluvastatin sodium (Lescol®), alprazolam (Zanax XR®), niacin, and lovastatin (Advicor®) [29]. Different grades of HPMC with different viscosities were used to study the release of buflomedil pyridoxal phosphate. Study of HPMC hydrogels coated with an impermeable membrane shows that the drug release is not affected by the polymer viscosity, but it is very dependent on the contact area with the dissolution medium [30].

4.2.3.2 Hydrocolloids

Owing to their attractive solution properties, molecular weight, structure, and availability, various hydrocolloids such as alginate, xanthan, guar gum, and a few others have been added to the list of pharmaceutical excipients. They are used in designing new dosage forms and formulations, novel drug delivery systems, in

microparticle and microcapsule preparation, and to control the rheology of liquid (solution, suspension, and emulsion), semisolid (wax based), and solid dosage forms (powders).

Konjac, a plant extract gum, can be used as a thickener and gelling agent and is intended for colon specific drug delivery if blended with xanthan gum at a particular concentration [31]. Gellan, a microbial gum has been suggested as a swelling agent (in disintegration of ibuprofen tablets) [32], tablet binder [33], and a rheology modifier [34]. Gellan gum can be found in Timoptic-XE® 0.25% and 0.5% (timolol maleate) ophthalmic gel forming solution [29]. Carrageenan, a seaweed extract, has been claimed for capillary electrophoresis as a chiral selector [35] as well as for topical delivery systems (examined as a viscosity modifier in sodium fluorescein delivery) [36]. Carrageenan can be found in Vantin® (cefpodoxime proxetil) oral suspension [29]. Chitosan, an animal extract gum, has been tested as a taste masker [37], dietary fiber [38], drug delivery matrix [39, 40], protein and peptide delivery platform [41], disintegrant [42], absorption enhancer of macromolecular drugs [43], and used in emulsion-like solutions and creams [44], mucoadhesive delivery [45], microparticle formation [46], local or systemic delivery of drugs and vaccines [47], and for biomedical and cosmetic applications [48, 49]. Other polysaccharides have also been mentioned as a drug delivery carrier for different applications. These include alginate (for microencapsulation) [50, 51], scleroglucan (for theophylline release) [52], guar gum (as a tablet binder for paracetamol [53] and for colon specific delivery [54]), heparin (as an anticoagulant) [55], schizophyllan (in cancer therapy as immunostimulant) [56, 57] and xanthan (as rheology modifier [58], tablet binder [59], and swelling agent [60]). Xanthan gum can be found in many dosage forms in the US market including Tricor® (fenofibrate) 145 mg tablets, Pepcid for oral suspension, Pepcid® PRD orally disintegrating tablets (famotidine), and Renova® (tretinoin) cream 0.02% [29]. Sodium alginate is used in a variety of commercially available dosage forms such as Prolixin® (fluphenazine), Tolinase® (tolazamide) tablets, and Axid® (nizatidine) oral solution [29].

Hydrogels Based on Alginic Acid

Composite hydrogel of collagen and alginate has been used for ocular protein delivery. The hydrogel provides 11 days sustained release for bovine serum albumin in neutral buffer and supports corneal epithelial cell growth with good mechanical strength and transparency [61]. Sodium alginate/carboxymethyl guar gum hydrogels have been prepared via an ion complexation with barium ions. This anionic hydrogel has displayed swelling capacity of about 15 and 310% in simulated gastric (pH 1.2) and intestinal fluids (pH 7.4), respectively. The hydrogel was able to release 20 and 70% of its loaded vitamin B12 in gastric and intestinal medium respectively. Hydrogels crosslinked with 5 or 6 w/v% barium chloride solution displayed 50% loading efficiency [62].

Hydrogels Based on Guar Gum

Poly(vinyl alcohol) guar gum IPN hydrogels have been prepared utilizing glutaraldehyde as a crosslinker. It was shown that an increased crosslink density changes the release of nifedipine from Fickian to non-Fickian. The drug release was found to be dependent on the crosslink density, drug loading, and loading method [63]. A graft copolymer hydrogel of acrylamide and guar gum has been prepared utilizing glutaraldehyde as a crosslinker. It was loaded with two water soluble (verapamil hydrochloride) and water insoluble (nifedipine) antihypertensive drugs. The drugs were added into the hydrogel after crosslinking or incorporated during the hydrogel preparation [64].

Hydrogels Based on Chitosan

A transparent, water soluble and water miscible gel has been developed as an ointment base by dissolving 93% deacetylated chitosan F in a solution of lactic acid. Using rheological tests, the gel was proved to be stable when loaded with drugs such as clotrimazole, piroxicam, estradiol, progesterone, lidocaine HCl, or a sodium salt of heparin but loses its stability with metronidazole or suspending hydrocortisone [65]. The swelling behavior and in vitro release of nifedipine from alginate–chitosan hydrogel beads has been investigated. The hydrogels were prepared via ionotropic gelation and characterized by FTIR (structure) and SEM (morphology) [66]. Microcrystalline chitosan hydrogel alone and in combination with methylcellulose or Carbopol has been studied for the release of diclofenac-free acid and its salt. Drug release and rheological properties of the drug carrier were studied in the presence of hydrophilizing agents such as 1,2-propylene glycol and glycerol [67]. $NaBO_3$-treated chitosan with different molecular weights has been used to coat theophylline tablets to evaluate their sustained release properties. The release rate of theophylline was decreased with increasing the amount of coated chitosan and increased with decreasing the chitosan molecular weight [68]. Carboxymethyl–hexanoyl chitosan has been synthesized with desirable swelling properties and used as a drug carrier for amphiphatic agents. The hydrogel has both hydrophilic (carboxymethyl) and hydrophobic (hexanoyl) moieties, but the hydrophobic part retards the deswelling process, causing better water-retention properties. It was shown that partially hydrophobic drugs such as ibuprofen has better encapsulation efficiency in this hydrogel than in chitosan or carboxymethyl chitosan, which are more hydrophilic [69]. Chitosan-coated polyphosphazene-Ca^{2+} hydrogel have been prepared by dropping polyphosphazene into calcium chloride/chitosan gelling solution. With myoglobin as a model drug, an encapsulation efficiency of 93% has been obtained [70]. Chitosan grafted with acrylic acid and acrylamide have been prepared utilizing gamma irradiation. The hydrogels showed ampholytic and reversible pH responsive properties and claimed for controlled release of antibiotics (amoxicillin trihydrate) into the gastric medium.

The release is driven by the ratio of hydrogel swelling to erosion capacity [71]. Chitosan/tripolyphosphate and chitosan/tripolyphosphate/chondroitin sulfate core–shell biocompatible hydrogels have been prepared and used for the delivery of ofloxacin. It was shown that chondroitin sulfate as a second polyanion contributed to an increased mechanical strength of the hydrogel [72]. Release behavior of cimetidine from glutaraldehyde-crosslinked chitosan has also been studied [73]. An aqueous solution of photo-crosslinkable chitosan containing azide groups and lactose moieties containing paclitaxel has been reported to form an insoluble hydrogel following an ultraviolet irradiation for 30 s. The hydrogels effectively inhibited tumor growth and angiogenesis in mice. The study shows that chitosan hydrogel may be a promising site specific carrier for drugs such as FGF-2 and paclitaxel to control vascularization [74].

Hydrogels Based on Carrageenan

Betamethasone acetate, a water soluble model drug, has been loaded into a hydrogel blend of carrageenan and sodium alginate. Maximum loading was found to be dependent on temperature and pH as it appeared to be 71% at pH 4.8 and 55°C. The hydrogel was compared with two other similar systems of Ca-alginate and K-Carrageenan at different pH [75]. To enhance its therapeutic effectiveness, the hydrophobic anticancer drug, camptothecin, was solubilized in a cationic surfactant (dodecyltrimethylammonium bromide) and loaded into an anionic kappa-carrageenan hydrogel [76]. A repetitive pulsatile drug release was displayed when dibucaine hydrochloride as a model drug loaded into an erodible hydrogel system based on kappa-carrageenan. This behavior was attributed to the carrageenan oscillatory loss during the drug release process [77].

Scleroglucan-Based Hydrogels

In the presence of borax, scleroglucan can form a gel. The hydrogel has been used as a matrix for tablets loaded with three different model molecules, theophylline, vitamin B12, and myoglobin. The release pattern of the drug theophylline was also studied in gastric and intestinal conditions. Results showed that the scleroglucan hydrogel has the potential to be used in sustained release formulations, in which the drug release is dependent on the size of the drug molecule [78–80]. Borax treated scleroglucan polymer for delivery of theophylline has also been tested and proposed for delivery of vitamin B12 and myoglobin [81]. The efficacy of bFGF (basic fibroblast growth factor)–gelatin hydrogel complex for bone regeneration around implants has been studied for the development of a new drug delivery system [82].

Hydrogels Based on Hyaluronic Acid

Hyaluronan (HA) has the ability to control cell migration, differentiation, proliferation, and contribute to the invasiveness of human cancers. A study shows that a crosslinked hyaluronan can be used to investigate the sensitivity of cancer cells to antimitotic agents [83]. New hyaluronic acid (HA) based hydrogels has been developed by converting the HA to adipic dihydrazide derivative, followed by crosslinking with poly(ethylene glycol)-propiondialdehyde. Dried film of this hydrogel could swell sevenfold in volume in buffer in less than 2 min. Morphology and enzymatic degradation of hydrogel by hyaluronidase were examined using SEM and a spectrophotometric assay. This novel biomaterial has been claimed for controlled release of therapeutic agents at wound sites [84].

Pectin Based Hydrogels

Drug release from high methoxy pectin has been studied in terms of tablet compression force, amount, and type of pectin. The drug release was found to be unaffected by compression force [85]. Acrylamide grafted pectin was characterized by FTIR, DSC and X-ray diffraction. The polymer was crosslinked with glutaraldehyde and tested for salicylic acid release using a Franz diffusion cell. A grafted hydrogel displayed better film-forming properties than pectin [86]. Hydrogel membrane based on pectin and polyvinylpyrrolidone have been prepared by physical blending and conventional solution casting methods. The release of salicylic acid was monitored at different aqueous media using a UV–Vis spectrophotometer at 294 nm wavelength. The presence of secondary amide, decrease in crystallinity at higher PVP ratio, increased T_g of pectin-PVP blend and hydrogel cytocompatibility was shown by FTIR, XRD, DSC and B16 melanoma cells respectively [87]. Amidated pectin complexes with calcium were used in preparation of a multiparticulate system with the potential for site-specific colon delivery. Indomethacin and sulphamethoxazole release was found to be dependent on the pH and drug loading. Although drug release in both low and high pH media was higher for a more water-soluble drug, it was significantly reduced when particles were coated with chitosan [88].

Miscellaneous Hydrocolloid-Based Hydrogels

IPN hydrogels of acrylamide and gelatin were prepared and their swelling in water and citric acid phosphate buffer at various pH studied. More specifically, the hydrogel swelling behavior at physiological pH was studied in the temperature range of 25–60°C [89]. Agarose hydrogel nanoparticles prepared in an emulsifier-free dispersion system have been claimed for protein and peptide delivery. A study with ovalbumin protein has shown a temperature dependent, diffusion controlled release [90]. Dextran based hydrogels for controlled drug release and tissue

engineering have also been reviewed [91]. Inulin hydrogel has been prepared by derivitizing a vinyl containing inulin (methacrylated inulin) followed by free radical polymerization with redox initiating systems. It was characterized using linear oscillatory shear measurement (for gelation), dynamic mechanical analysis, and solution viscosity [92, 93].

4.2.4 Nonionic Synthetic Hydrogels

Hydrogels of this class do not carry functional groups, and hence they are not sensitive to the pH of the swelling medium. As a result, their swelling will be solely governed by the polymer–liquid interaction forces, which determine the polymer solubility in the liquid medium. These hydrogels are generally based on hydroxyethyl methacrylate, acrylamide, ethylene oxide, ethylene glycol, and vinyl pyrrolidone. Owing to the lack of electrostatic forces that operate in the pH sensitive hydrogels, these hydrogels swell to a limited extent.

4.2.4.1 Hydrogels Based on Hydroxyethyl Methacrylate

Poly (2-hydroxyethyl methacrylate) (polyHEMA) is known as a biocompatible polymer, which resists biodegradation and microbial attack. Copolymers of this polymer have been used as a subcutaneous reservoir hydrogel implant, capable of long term delivery of predetermined doses of various active compounds [94]. Hydrogel sponges were prepared based on HEMA and ethylene glycol dimethacrylate (EGDMA), and characterized for iontophoretic drug delivery. The effect of different sterilization techniques, gamma irradiation, ethylene oxide, and autoclave on hydrogel properties has been examined [95]. A biomedical membrane based on HEMA and *p*-vinylbenzyl-poly (ethylene oxide) (V-PEO) macromonomer has been synthesized utilizing photoinitiation polymerization. Infrared, thermal, and SEM analysis was used for the hydrogel characterization. The study showed that the V-PEO content could affect the thermal stability and hydrophobicity of the HEMA hydrogel. The hydrogel containing the highest PEO content was used to study the release of an antibiotic as a potential transdermal antibiotic carrier [96]. A hydrogel based on HEMA and *N*,*N*′-dimethyl-*N*-methacryloyloxyethyl-*N*-(3-sulfopropyl) ammonium betaine has been studied with sodium salicylate as a model drug [97]. Thin films of a novel polyacrylate-based hydrogel were claimed to be a good drug carrier in orthopedic field. HEMA, poly(ethylene glycol) diacrylate, and acrylic acid were used to prepare hydrogels utilizing an electrochemical polymerization. X-ray photoelectron spectroscopy and water content measurement were used to characterize the structure and swelling behavior of the hydrogels [98]. Feasibility of using solid hydrogels of EGDMA-crosslinked HEMA and crosslinked dextran has been studied for injecting drugs in to the eye upon application of low current iontophoresis. The hydrogels were examined for their mechanical suitability,

absorption of drug solution, and in vitro release properties into a solid-agar surface [99]. The HEMA hydrogels have been tested for the release of dexamethasone phosphate [100] and gentamicin sulfate [101] into healthy rabbit eyes. The drug loss and side effects associated with eye drops could potentially be alleviated by using disposable soft contact lenses based on HEMA. The contact lens is loaded with the drug in a microemulsion system stabilized with silica, and releases the drug for 8 days at the therapeutic level. The delivery rates could be tailored by controlling the particle size and the drug loading [102].

4.2.4.2 Poly (Ethylene Glycol) Hydrogels

Bovine serum albumin and poly(ethylene glycol) were polymerized and used as a controlled release system for soluble, hydrophobic, even protein drugs. The study shows that the hydrogel has a very high water content (>96%) and releases the drug by a diffusion-controlled mechanism. Drugs such as theophylline, lysozyme, and hydrocortisone have been tested [103]. In order to modulate the release properties, the hydrogel thickness and its composition was also changed [104]. A poly(ethylene glycol) based copolymer hydrogel containing multiple thiol (−SH) groups has been claimed as a suitable carrier for protein delivery, offering sustained release feature of 2–4 weeks and prolonged biological activity [105]. An acrylated poly (ethylene glycol)-poly(propylene glycol) amphiphilic hydrogel polymer has been developed utilizing inverse emulsion photopolymerization. The matrix contains hydrophobic propylene glycol domains, which can incorporate hydrophobic drugs. Doxorubicin has been incorporated to a 9.8w/w% level [106]. Poly(ethylene oxide) gels crosslinked by urethane bonds have been studied for the release of acetaminophen and caffeine. The study showed an inverse correlation between the release and the hydrogel crystallinity, which is perturbed even at low drug concentrations. With acetaminophen, this behavior has been attributed to drug hydrogel complexation. Hydrogel crystallinity and structural transition were studied using small and wide angle X-ray scattering [107, 108]. PLGA-PEG-PLGA polymers with molecular weight of 3 K–7 K have been synthesized from L-lactide and glycolide as well as PEG with molecular weight of 1 K–4.6 K. A dynamic viscoanalyzer and fluorescence spectroscopy were used to investigate the sol–gel transition of the hydrogel system and to understand the gelling mechanism of the hydrogel respectively. Ceftazidime was used for the controlled release study [109].

4.2.4.3 Hydrogels Based on Poly (Vinyl Alcohol)

Glutaraldehyde-crosslinked poly(vinyl alcohol) hydrogel films have been optimized for controlled delivery of theophylline in terms of crosslinker concentration, drug loading, and release mechanism [110]. Composite hydrogels of poly (vinyl alcohol) and PLGA have been prepared and suggested for long term protein delivery. Bovine serum albumin was encapsulated into PVA nanoparticles, and the

nanoparticles were then loaded into the PLGA microspheres. The composite hydrogel provided a two month delivery of BSA [111]. IPN hydrogels of polyacrylamide and poly(vinyl alcohol) have been prepared and tested for controlled delivery of crystal violet and bromothymol blue as model drugs [112]. In order to alleviate the associated problems with low encapsulation efficiency and high burst effect in biodegradable microcapsules, pentamidine/poly(vinyl alcohol) hydrogels were prepared via freeze-thawing, then microencapsulated in PLGA using a solvent evaporation technique [113].

4.2.4.4 Acrylamide Based Hydrogels

Drug binding ability of albumin has been utilized in preparing hydrogels of acrylamide crosslinked with bovine serum albumin and claimed to be the cause of sustained release of salicylic acid from the BSA-crosslinked hydrogel [114]. Copolymer hydrogel of acrylamide and itaconic acid was prepared and studied for the controlled release of paracetamol in aqueous media of varying pH [115]. Polymer blends made by electrochemical polymerization of polypyrrole onto polyacrylamide were intended as a controlled release device for the delivery of safranin. Drug release from this device was expected to be controlled by an electrochemical potential. Voltametry and Raman spectroscopy were used for hydrogel characterization [116]. Copolymer hydrogels of *N*-isopropylacrylamide, trimethyl acrylamidopropyl ammonium iodide, and 3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate have been developed. The release of caffeine was found to increase with hydrogel swelling. The anionic solute phenol red was found to strongly interact with the cationic hydrogel, and its release was hence found to be very slow [117].

4.2.4.5 Polyvinylpyrrolidone-Based Hydrogels

Polyvinylpyrrolidone iodine liposomal hydrogel has been suggested as a drug delivery platform for wound treatment in which antiseptic and moist treatment are desirable in the healing process. Compared to the normal PVP-iodine complex, the liposomal formulation was proven to enhance epithelization [118]. Ferrogels, gels containing ferromagnetic nanoparticles have been prepared based on polyvinylpyrrolidone via irradiation. Bleomycin A5 Hydrochloride, a wide spectrum anticancer drug was immobilized in the ferrogel and its release was studied in vitro [119]. A new micro particulate hydrogel has been obtained by gamma irradiation of poly [*N*-(2-hydroxyethyl)-DL-aspartamide]. With various concentrations of gastric enzymes, pepsin and alpha-chymotrypsin, the hydrogel degradation was not observed over a 24-h exposure period. The hydrogel was evaluated for oral delivery of an anti-inflammatory drug, diflunisal [120]. Polyvinylacetal diethylaminoacetate hydrogel has also been suggested for nasal delivery [121].

4.2.5 Superdisintegrants

Superdisintegrants are crosslinked hydrophilic polymers with the ability to swell in an aqueous medium. Although they are not as potent as super water absorbent polymers (with swelling capacity of 100–1,000 g/g), they have enough potency (swelling capacity of 10–40 g/g) to fulfill their task in the pharmaceutical dosage forms. The swelling power of a superdisintegrant is controlled by its backbone structure, the crosslink density, and the amount of substitution.

4.2.5.1 Hydrogels Based on Cellulose

Crosslinked carboxymethyl cellulose (sodium salt) is prepared by internal crosslinking (in the absence of a chemical crosslinker) and carboxymethylation of cellulose. In fact, crosslinking is induced by partially changing sodium carboxymethyl groups to their free acids followed by heating. It has an anionic backbone with sodium as counterion, which causes the polymer swelling to be very sensitive to the pH, salts (mono, di, and trivalence) and the ionic strength of the swelling medium. Swelling power of this polymer is significantly reduced at low pH and in concentrated solution of salts especially in the presence of di- and trivalent cations. It is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.

4.2.5.2 Hydrogels Based on Polyvinylpyrrolidone

Crosslinked polyvinylpyrrolidone is prepared via a popcorn polymerization of vinyl pyrrolidone monomer. This polymerization method utilizes the excessive heat of polymerization to establish random crosslinking into the polymer structure. The polymer is essentially nonionic, and hence its swelling power is independent of the pH. The disintegrant is expected to reach its maximum swelling power independent of the type of salts in the swelling medium.

4.2.5.3 Starch-Based Hydrogels

Similar to the crosslinked CMC, the crosslinked starch glycolate (sodium slat) is an anionic polymer and produced by crosslinking and carboxymethylation of potato starch. Although other sources of starch including maize, wheat, and rice can also be used, the sodium starch glycolate from potato is preferred. More details on this class of crosslinked hydrogels are found in Table 4.4 [29, 122].

Table 4.4 Examples of commercial superdisintegrants

Crosslinked carboxymethyl cellulose is used in more than 150 drugs in the US market	
Sodium croscarmellose Ac-Di-Sol® (FMC Biopolymer); Primellose® (DMV-Fonterra)	Diltiazem hydrochloride; clarithromycin (Biaxin Filmtab®); niacin (Niacor®); fenofibrate (Triglide®); sildenafil citrate (Viagra®); atorvastatin calcium (Lipitor®); celecoxib (Celebrex®); fexofenadine HCl (Allegra®); ibuprofen (Motrin®); oxazepam (Serax®)
Crosslinked polyvinylpyrrolidone is used in more than 100 drugs in the US market	
Crospovidone Kollidone CL®, CL-M® (BASF); Polyplasdone XL®, XL10® (ISP)	Amoxicillin (Amoxil®); rosuvastatin Calcium (Crestor®); diphenhydramine (Benadryl®); fenofibrate (Tricor®); metformin HCl (Glumetza®); alprazolam (Niravam®); omeprazole (Prilosec®)
Crosslinked starch glycolate is used in more than 155 drugs in the US market	
Primojel® (DMV-Fonterra)	Acyclovir (Zovirax®); theophylline (Theo-Dur®); diltiazem (Cardizem® LA); cimetidine (Tagamet®); fenofibrate (Lipofen®); metoprolol tartrate (Lopressor®)

4.2.6 Ion Exchanging Hydrogels

Ion exchange resins are crosslinked polymers (some with hydrophilic and some with hydrophobic backbone) with anionic or cationic structures. While the crosslinked nature of the polymer allows absorption of the aqueous fluids into their structure, the ionic nature of these polymers allows exchanging their mobile ions with another cation or anion respectively. These hydrogels have found extensive applications in pharmaceutical industries as an active pharmaceutical ingredient to treat certain electrolyte imbalance (hyperkalimia), to reduce cholesterol (via sequestering bile acids), to taste-mask a drug, to control the drug release, to enhance drug stability, and to help dosage forms with their disintegration process. More details about this class of hydrogels can be found in Table 4.5 [29, 122].

4.2.7 Macroporous Hydrogels

One way to change the release properties of a typical hydrogel is to introduce porosity into its structure. The pores inside the hydrogel structure can be either isolated or interconnected. While both can offer a faster absorption and release compared to the conventional nonporous hydrogels, the latter offers a much faster absorption and release. Besides, the equilibrium swelling capacity of these hydrogels can be reached in seconds or minutes regardless of their size in the dry state. These hydrogels can be prepared using hydrophilic, ionic, nonionic, or even hydrophobic monomers through simultaneous polymerization and crosslinking processes. Acrylamide, acrylic or methacrylic acid and their salts, vinyl pyrrolidone, NIPAM, hydroxyethyl methacrylate, and more have already been

Table 4.5 Examples of commercial ion-exchange resins

Amberlite: This ion-exchange polymer is used for example in risperidone orally disintegrating tablets (Risperdal® M-Tab), propoxyphenenapsylate, and acetaminophen (Darvocet®-N100)
Amberlite® IRP64: poly(methacrylic acid) crosslinked with divinyl benzene (DVB), not neutralized, with hydrogen as counterion, a weak acid
Amberlite® IRP88 is a similar polymer with potassium as counterion, a weak acid
Amberlite® IRP69 is sulfonated polystyrene crosslinked with DVB, a strong acid with sodium as counterion
Cholestyramine: This ion-exchange resin is used for example in Questran® for oral suspension
A chloride salt of a strong basic anion exchange resin, polystyrene crosslinked with DVB, a cholesterol lowering agent
Sodium polystyrene sulfonate: Kionex®, and Kayexalate®
A cation exchange resin prepared with an in vitro exchange capacity of approximately 3.1 mEq of potassium per gram, the sodium content is approximately 100 mg (4.1 mEq) per gram of the drug, administered orally or in an enema
Colestipol hydrochloride: Colestid®
A lipid lowering agent for oral use, colestipol is an insoluble, high molecular weight basic anion exchange copolymer of diethylenetriamine and 1-chloro-2, 3-epoxypropane

used in preparation of superporous hydrogels [123–125]. Owing to their unique swelling properties, this class of hydrogels has been found to be attractive enough for more specific pharmaceutical and biomedical applications where another important property, mechanical strength is very much desirable. Hydrogels in general and porous hydrogels in particular suffer from weak mechanical strength in their wet or hydrated state. Approaches have been taken to enhance hydrogel mechanical properties, among which IPN structures comprising a synthetic monomer and a hydrocolloid have found to be the most effective [126–128]. With this approach, an aqueous monomer solution containing an iono-gelling hydrocolloid is polymerized in the presence of a chemical crosslinker and treated with salts afterward. Salts can change the semi-IPN structure of the hydrogel to a full IPN hydrogel with enhanced wet strength. Alternatively, various concentrations of different salts can be used to manipulate the hydrogel mechanical properties [129–131]. These hydrogels have so far been investigated as a controlled release platform for proteins [132–134], as a gastroretentive platform to enhance bioavailability of the drugs with narrow absorption window [127] as well as a tablet superdisintegrant [135].

4.2.8 Other Hydrogel Products

4.2.8.1 Hydrogel Implants

Histrelin acetate (Supprelin LA®, Vantas) subcutaneous implant is a long term delivery platform for the nonapeptide histrelin acetate. The drug is used to treat the symptoms of advanced prostate cancer and is released from this synthetic nonbiodegradable platform over a 12-month period. The hydrogel platform

(3.5 cm × 3 mm cylinder) is composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, and other nonpolymeric additives [29].

4.2.8.2 Hydrogel Inserts

The vaginal insert Cervidil® is composed of a crosslinked polyethylene oxide/urethane polymer (rectangle shape, 29 mm × 9.5 mm × 0.8 mm) and has been designed to release dinoprostone at about 0.3 mg/h in vivo. Once placed in a moist environment, the platform swells and releases the drug [29].

4.2.8.3 Osmotic Devices

Ionsys™ provides 40 μg dose of fentanyl per activation, which takes about 10 min. The system has two hydrogel reservoirs. The anode hydrogel contains fentanyl HCl and the cathode hydrogel contains inactive excipients including polacrilin and poly(vinyl alcohol) [29].

4.2.8.4 Osmotic Implants

Viadur® (leuprolide acetate implant) is a sterile nonbiodegradable implant (45 mm × 4 mm, 1.1 g) that has been designed to deliver leuprolide acetate over a 12-month period. The implant utilizes Alza's Duros technology and is inserted subcutaneously. The platform is composed of a polyurethane rate controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator [29]. The osmotic force, which drives long-term delivery of the active, is originated from the osmotic tablets composed of sodium chloride, sodium carboxymethyl cellulose, and povidone.

4.2.8.5 Osmotic Tablets

Paliperidone is an atypical antipsychotic medication for the acute and maintenance treatment of schizophrenia. Invega® is an osmotically driven delivery system (in tablet form), which uses osmotic pressure to deliver paliperidone at a controlled rate. The delivery system is composed of a trilayer core (osmotically active), subcoat, and a semipermeable membrane and has two laser-drilled orifices on the drug layer. In an aqueous environment, water enters the tablet through the semipermeable membrane at a controllable rate. The hydrophilic polymers of the core generally poly(ethylene oxide) hydrate and swell and create a gel mass containing paliperidone, which is pushed out of the tablet orifices [29]. Concerta®, Ditropan®XL, and Glucophage®XR utilize a similar concept to deliver methylphenidate HCl (a central nervous system

stimulant), oxybutynin chloride (an antispasmodic, anticholinergic agent), and metformin HCl (an antidiabetic), respectively.

4.2.8.6 Tissue Expanders

The idea of growing extra skin for reconstructing purposes is a neat one. Conventionally, a silicone rubber is inserted subcutaneously, and then is filled with saline to stretch the skin and to induce its growth. Silicone expanders are used for breast reconstruction and deformities, damaged skins, burns, scars, skin cancer, and more. In order to stretch the tissue to the desired size, the balloon needs to be filled with saline over and over, which may cause infection and rejection by patients. Osmed, a Germany based company has utilized a similar concept except the balloon is self inflated and it is not filled with fluids. The Osmed expander is a crosslinked copolymer of methyl methacrylate and *N*-vinyl pyrrolidone similar to the materials used in soft contact lenses. It absorbs the fluid from surrounding tissues and swells to 3–12 times its own volume. The slow swelling expanders are supplied as rectangle, round and cylinder with swelling time ranging from 10 to 180 days, while the faster ones are supplied as semi sphere, sphere and pin with swelling time of a few days [136–138]. Alternatively, the liquid contents of a conventional silicone expander can be converted to a semisolid mass to minimize the fluid leakage from the device. Hydrogels based on crosslinkable macromonomers with polymerizable end-groups are under development for breast reconstruction applications [139].

4.2.8.7 Contact Lenses

A contact lens material should have a combination of properties such as ease of manufacturing, FDA acceptability, wetability, and permeability. There are generally three types of contact lenses, i.e., hard, soft, and gas permeable (GP or RGP). Hard lenses are originally based on poly(methyl methacrylate) and their service temperature is below the polymer glass transition temperature. To make the lens material, methyl methacrylate monomer is polymerized in bulk in the presence of crosslinker and initiator via a radiation technique (ultraviolet or infrared). Hard lenses prepared in this way are then cut with a precision lathe. Hard lenses are now obsolete and have been replaced by soft and gas permeable lenses. Soft contact lenses are typically formed via a simultaneous polymerization and cast molding or spin casting. These are generally based on 2-hydroxyethyl methacrylate with either *N*-vinyl pyrrolidone or methacrylic acid monomer, crosslinked with ethylene glycol dimethacrylate. Alternatively, soft lenses are manufactured based on polydimethylsiloxane, so called siloxane lenses. Focus Night and Day® (Ciba Vision), Acuvue Oasys® (Vistakon) and PureVision® (Bausch and Lomb) are silicon based hydrogel lenses. Some recently approved soft contact lenses by the FDA are Omafilcon A® (a copolymer of 2-hydroxyethyl methacrylate and 2-methacryloyloxyethyl phosphorylcholine

crosslinked with ethylene glycol dimethacrylate), Methafilcon A® (a hydrophilic copolymer of 2-hydroxyethyl methacrylate and methacrylic acid, crosslinked with ethylene glycol dimethacrylate), and Hioxifilcon A® (ultrahigh-molecular-weight random copolymer of 2-hydroxyethyl methacrylate and 2,3-dihydroxpropyl methacrylate (glycerol methacrylate) crosslinked with ethylene glycol dimethacrylate [140]). Some recently approved gas permeable contact lenses are Pahrifocon A® (a crosslinked copolymer of acrylate, silicone acrylate, and fluorosilicone acrylate monomers, dimers and oligomers), Hexafocon A®, Enflufocon B®, and Enflufocon A® (aliphatic fluoroitaconate siloxanyl methacrylate copolymer available with or without UV blocker) [140].

4.3 Conclusion

Swelling and mechanical features of hydrogel polymers have enabled them to find extensive applications in traditional, modern, and novel pharmaceutical area. Desirable hydrogel properties for a given application can be achieved by selecting a proper hydrogel material, crosslinking method, as well as processing techniques. These biocompatible materials are currently used in pharmaceutical dosage forms as superdisintegrant, ion exchangeable material, and controlled release platform. On the contrary, nondisposable hydrogels with longer term of service have found applications as biomedical inserts and implants. Superporous hydrogels are an exclusive class of hydrogels that can potentially be used for both short- and long term applications including superdisintegrant, controlled release platform, and a gastroretentive drug delivery system.

References

1. Celia H, Special Delivery. http://pubs.acs.org/cen/coverstory/7838/7838scit1.html
2. Chen H et al (2007) Characterization of pH- and temperature-sensitive hydrogel nanoparticles for controlled drug release. PDA J Pharm Sci Technol 61(4):303–313
3. Satarkar NS, Hilt JZ (2008) Magnetic hydrogel nanocomposites for remote controlled pulsatile drug release. J Control Release 130(3):246–251
4. Huang G et al (2004) Controlled drug release from hydrogel nanoparticle networks. J Control Release 94(2–3):303–311
5. Kim JH, Lee TR (2006) Discrete thermally responsive hydrogel-coated gold nanoparticles for use as drug-delivery vehicles. Drug Dev Res 67(1):61–69
6. Okuyama Y et al (1993) Swelling controlled zero-order and sigmoidal drug-release from thermoresponsive poly(n-isopropylacrylamide-co-butyl methacrylate) hydrogel. J Biomater Sci Polym Ed 4(5):545–556
7. Jones DS et al (2008) Characterization of the physicochemical, antimicrobial, and drug release properties of thermoresponsive hydrogel copolymers designed for medical device applications. J Biomed Mater Res B Appl Biomater 85B(2):417–426

8. Jeong B, Bae YH, Kim SW (2000) Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers. J Control Release 63 (1–2):155–163
9. Slepian MJ (1996) Polymeric endoluminal gel paving: therapeutic hydrogel barriers and sustained drug delivery depots for local arterial wall biomanipulation. Semin Interv Cardiol 1 (1):103–116
10. Mayo L et al (2008) A novel poloxamers/hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and in vitro release properties. Eur J Pharm Biopharm 70 (1):199–206
11. Zhao Y et al (2006) Study on preparation of the pH sensitive hydroxyethyl chitin/poly (acrylic acid) hydrogel and its drug release property. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 23(2):338–341
12. Bilia A et al (1996) In vitro evaluation of a pH-sensitive hydrogel for control of GI drug delivery from silicone-based matrices. Int J Pharm 130(1):83–92
13. Kim IS, Oh IJ (2005) Drug release from the enzyme-degradable and pH-sensitive hydrogel composed of glycidyl methacrylate dextran and poly(acrylic acid). Arch Pharm Res 28 (8):983–987
14. Ali Ael-H, Hegazy el-SA (2007) Radiation synthesis of poly(ethylene glycol)/acrylic acid hydrogel as carrier for site specific drug delivery. J Biomed Mater Res B Appl Biomater 81(1):168–174
15. Liu YY et al (2006) pH-responsive amphiphilic hydrogel networks with IPN structure: a strategy for controlled drug. Int J Pharm 308(1–2):205–209
16. Sadeghi M, Hosseinzadeh H (2008) Synthesis of starch-poly(sodium acrylate-co-acrylamide) superabsorbent hydrogel with salt and pH-responsiveness properties as a drug delivery system. J Bioact Comp Polym 23(4):381–404
17. Mundargi RC et al (2008) Sequential interpenetrating polymer network hydrogel microspheres of poly(methacrylic acid) and poly(vinyl alcohol) for oral controlled drug delivery to intestine. J Microencapsul 25(4):228–240
18. Bajpai SK, Saggu SPS (2007) Controlled release of an anti-malarial drug from a pH-sensitive poly(methacrylamide-co-methacrylic acid) hydrogel system. Desig Monom Polymer 10 (6):543–554
19. Varshosaz J, Hajian M (2004) Characterization of drug release and diffusion mechanism through hydroxyethylmethacrylate/methacrylic acid pH-sensitive hydrogel. Drug Deliv 11 (1):53–58
20. Jain SK et al (2007) Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS PharmSciTech 8(3):E56
21. Jain SK et al (2007) Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS PharmSciTech 8:E34–E41
22. Lin YW, Chen Q, Luo HB (2007) Preparation and characterization of *N*-(2-carboxybenzyl) chitosan as a potential pH-sensitive hydrogel for drug delivery. Carbohydr Res 342(1):87–95
23. Sun LP et al (2004) The synthesis of carboxymethylchitosan hydrogel and the application in drug controlled release systems. Acta Polymerica Sinica 2:191–195
24. Zhou YS et al (2008) A pH-sensitive water-soluble *N*-carboxyethyl chitosan/poly (hydroxyethyl methacrylate) hydrogel as a potential drug sustained release matrix prepared by photopolymerization technique. Polymer Adv Technol 19(8):1133–1141
25. Chen SC et al (2004) A novel pH-sensitive hydrogel composed of N, O-carboxymethyl chitosan and alginate crosslinked by genipin for protein drug delivery. J Control Release 96(2):285–300
26. Castelli F et al (2008) Differential scanning calorimetry study on drug release from an inulin-based hydrogel and its interaction with a biomembrane model: pH and loading effect. Eur J Pharm Sci 35(1–2):76–85
27. Varshosaz J, Falamarzian M (2001) Drug diffusion mechanism through pH-sensitive hydrophobic/polyelectrolyte hydrogel membranes. Eur J Pharm Biopharm 51(3):235–240

28. Kulkarni RV, Sa B (2008) Evaluation of pH-sensitivity and drug release characteristics of (Polyacrylamide-Grafted-Xanthan)-carboxymethyl cellulose-based pH-sensitive interpenetrating network hydrogel beads. Drug Develop Ind Pharm 34(12):1406–1414
29. http://www.rxlist.com
30. Bettini R et al (1994) Swelling and drug-release in hydrogel matrices – polymer viscosity and matrix porosity effects. Eur J Pharm Sci 2(3):213–219
31. Alvarez-Mancenido F et al (2006) Characterization of diffusion of macromolecules in konjac glucomannan solutions and gels by fluorescence recovery after photobleaching technique. Int J Pharm 316(1–2):37–46
32. Antony PJ, Sanghavi NM (1997) A new disintegrant for pharmaceutical dosage forms. Drug Dev Ind Pharm 23(4):413–415
33. Antony PJ, Sanghavi NM (1997) A new binder for pharmaceutical dosage forms. Drug Dev Ind Pharm 23(4):417–418
34. Deasy PB, Quigley KJ (1991) Rheological evaluation of deacetylated Gellan gum (Gelrite) for pharmaceutical use. Int J Pharm 73(2):117–123
35. Beck GM, Neau SH (2000) Optimization of lambda-carrageenan as a chiral selector in capillary electrophoresis separations. Chirality 12(8):614–620
36. Valenta C, Schultz K (2004) Influence of carrageenan on the rheology and skin permeation of microemulsion formulations. J Control Release 95(2):257–265
37. Binello A et al (2004) Synthesis of chitosan-cyclodextrin adducts and evaluation of their bitter-masking properties. Flav Fragr J 19(5):394–400
38. Chae SY, Jang MK, Nah JW (2005) Influence of molecular weight on oral absorption of water soluble chitosans. J Control Release 102(2):383–394
39. El Fattah EA et al (1998) Physical characteristics and release behavior of salbutamol sulfate beads prepared with different ionic polysaccharides. Drug Dev Ind Pharm 24(6):541–547
40. Felt O, Buri P, Gurny R (1998) Chitosan: a unique polysaccharide for drug delivery. Drug Dev Ind Pharm 24(11):979–993
41. George M, Abraham TE (2006) Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan – a review. J Control Release 114(1):1–14
42. Singla AK, Chawla M (2001) Chitosan: some pharmaceutical and biological aspects – an update. J Pharm Pharmacol 53(8):1047–1067
43. Thanou M, Verhoef JC, Junginger HE (2001) Oral drug absorption enhancement by chitosan and its derivatives. Adv Drug Deliv Rev 52(2):117–126
44. Grant J, Cho J, Allen C (2006) Self-assembly and physicochemical and rheological properties of a polysaccharide-surfactant system formed from the cationic biopolymer chitosan and nonionic sorbitan esters. Langmuir 22(9):4327–4335
45. Harding SE (2006) Trends in mucoadhesive analysis. Trends Food Sci Technol 17 (5):255–262
46. Kas HS (1997) Chitosan: properties, preparations and application to microparticulate systems. J Microencapsul 14(6):689–711
47. Senel S, McClure SJ (2004) Potential applications of chitosan in veterinary medicine. Adv Drug Deliv Rev 56(10):1467–1480
48. Wu J et al (2007) Water soluble complexes of chitosan-g-MPEG and hyaluronic acid. J Biomed Mater Res A 80(4):800–812
49. Yu SY et al (2006) Stable and pH-sensitive nanogels prepared by self-assembly of chitosan and ovalbumin. Langmuir 22(6):2754–2759
50. Chan LW, Lee HY, Heng PWS (2002) Production of alginate microspheres by internal gelation using an emulsification method. Int J Pharm 242(1–2):259–262
51. Dusseault J et al (2006) Evaluation of alginate purification methods: effect on polyphenol, endotoxin, and protein contamination. J Biomed Mater Res A 76(2):243–251
52. Daraio ME, Francois N, Bernik DL (2003) Correlation between gel structural properties and drug release pattern in scleroglucan matrices. Drug Deliv 10(2):79–85

53. Deodhar UP, Paradkar AR, Purohit AP (1998) Preliminary evaluation of *Leucaena leucocephala* seed gum as a tablet binder. Drug Dev Ind Pharm 24(6):577–582
54. Rubinstein A, Glikokabir I (1995) Synthesis and swelling-dependent enzymatic degradation of Borax-modified guar gum for colonic delivery purposes. Stp Pharma Sciences 5 (1):41–46
55. Desai UR, Linhardt RJ (1995) Molecular-weight of heparin using C-13 nuclear-magnetic-resonance spectroscopy. J Pharm Sci 84(2):212–215
56. Fuchs T, Richtering W, Burchard W (1995) Thermoreversible gelation of a polysaccharide with immunological activity – rheology and dynamic light-scattering. Macromol Symp 99:227–238
57. Munzberg J, Rau U, Wagner F (1995) Investigations on the regioselective hydrolysis of a branched beta-1,3-glucan. Carbohydr Polymers 27(4):271–276
58. Song KW, Kim YS, Chang GS (2006) Rheology of concentrated xanthan gum solutions: steady shear flow behavior. Fibers & Polymers 7(2):129–138
59. Tobyn MJ et al (1996) Prediction of physical properties of a novel polysaccharide controlled release system 1. Int J Pharm 128(1–2):113–122
60. Uekama K et al (1995) Modification of rectal absorption of morphine from hollow-type suppositories with a combination of alpha-cyclodextrin and viscosity-enhancing polysaccharide. J Pharm Sci 84(1):15–20
61. Liu WG, Griffith M, Li FF (2008) Alginate microsphere-collagen composite hydrogel for ocular drug delivery and implantation. J Mater Sci Mater Med 19(11):3365–3371
62. Bajpai SK, Sharma S (2006) Investigation of pH-sensitive swelling and drug release behavior of barium alginate/carboxymethyl guar gum hydrogel beads. J Macromol Sci Part A-Pure Appl Chem 43(10):1513–1521
63. Soppimath KS, Kulkarni AR, Aminabhavi TM (2000) Controlled release of antihypertensive drug from the interpenetrating network poly(vinyl alcohol)-guar gum hydrogel microspheres. J Biomater Sci Polym Ed 11(1):27–43
64. Soppirnath KS, Aminabhavi TM (2002) Water transport and drug release study from crosslinked polyacrylamide grafted guar gum hydrogel microspheres for the controlled release application. Eur J Pharm Biopharm 53(1):87–98
65. Knapczyk J (1993) Chitosan hydrogel as a base for semisolid drug forms. Int J Pharm 93 (1–3):233–237
66. Dai YN et al (2008) Swelling characteristics and drug delivery properties of nifedipine-loaded pH sensitive alginate-chitosan hydrogel beads. J Biomed Mater Res B Appl Biomater 86B(2):493–500
67. Bodek KH (2000) Evaluation of properties microcrystalline chitosan as a drug carrier. Part 1. In vitro release of diclofenac from mictocrystalline chitosan hydrogel. Acta Pol Pharm 57 (6):431–440
68. Kubota N (1993) Molecular-weight dependence of the properties of chitosan and chitosan hydrogel for use in sustained-release drug. Bull Chem Soc Jpn 66(6):1807–1812
69. Liu TY et al (2006) Synthesis and characterization of amphiphatic carboxymethyl-hexanoyl chitosan hydrogel: water-retention ability and drug encapsulation. Langmuir 22(23):9740–9745
70. Qiu LY (2004) Preparation and evaluation of chitosan-coated polyphosphazene hydrogel beads for drug controlled release. J Appl Polym Sci 92(3):1993–1999
71. Taleb MFA (2008) Radiation synthesis of polyampholytic and reversible pH-responsive hydrogel and its application as drug delivery system. Polym Bull 61(3):341–351
72. Vodna L, Bubenikova S, Bakos D (2007) Chitosan based hydrogel microspheres as drug carriers. Macromol Biosci 7(5):629–634
73. Yao KD et al (1994) pH-dependent hydrolysis and drug-release of chitosan polyether interpenetrating polymer network hydrogel. Polym Int 34(2):213–219
74. Ishihara M et al (2006) Chitosan hydrogel as a drug delivery carrier to control angiogenesis. J Artif Organs 9(1):8–16

75. Mohamadnia Z et al (2007) pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery. J Bioact Compat Polym 22(3):342–356
76. Liu JH, Li L, Cai YY (2006) Immobilization of camptothecin with surfactant into hydrogel for controlled drug release. Eur Polym J 42(8):1767–1774
77. Makino K et al (2001) Design of a rate- and time-programming drug release device using a hydrogel: pulsatile drug release from kappa-carrageenan hydrogel device by surface erosion of the hydrogel. Colloids Surf B Biointerfaces 20(4):355–359
78. Coviello T et al (2003) Structural and rheological characterization of Scleroglucan/borax hydrogel for drug delivery. Int J Biol Macromol 32(3–5):83–92
79. Coviello T et al (2003) Scleroglucan/borax: characterization of a novel hydrogel system suitable for drug delivery. Biomaterials 24(16):2789–2798
80. Coviello T et al (2005) A new scleroglucan/borax hydrogel: swelling and drug release studies. Int J Pharm 289(1–2):97–107
81. Palleschi A et al (2006) Investigation on a new scleroglucan/borax hydrogel: structure and drug release. Int J Pharm 322(1–2):13–21
82. Hayashi K et al (2007) Development of new drug delivery system for implant bone augmentation using a basic fibroblast growth factor-gelatin hydrogel complex. Dent Mater J 26 (2):170–177
83. David L et al (2008) Hyaluronan hydrogel: an appropriate three-dimensional model for evaluation of anticancer drug sensitivity. Acta Biomater 4(2):256–263
84. Luo Y, Kirker KR, Prestwich GD (2000) Crosslinked hyaluronic acid hydrogel films: new biomaterials for drug delivery. J Control Release 69(1):169–184
85. Sungthongjeen S et al (1999) Studies on pectins as potential hydrogel matrices for controlled-release drug delivery. Drug Dev Ind Pharm 25(12):1271–1276
86. Sutar PB et al (2008) Development of pH sensitive polyacrylamide grafted pectin hydrogel for controlled drug delivery system. J Mater Sci Mater Med 19(6):2247–2253
87. Mishra RK, Datt M, Banthia AK (2008) Synthesis and characterization of pectin/PVP hydrogel membranes for drug delivery system. AAPS PharmSciTech 9(2):395–403
88. Munjeri O, Collett JH, Fell JT (1997) Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug release. J Control Release 46 (3):273–278
89. Ramaraj B, Radhakrishnan G (1994) Interpenetrating hydrogel networks based on gelatin and polyacrylamide – synthesis, swelling, and drug-release analysis. J Appl Polym Sci 52 (7):837–846
90. Wang N, Wu XS (1997) Preparation and characterization of agarose hydrogel nanoparticles for protein and peptide drug delivery. Pharm Dev Technol 2(2):135–142
91. Chen F, Wu Z, Jin Y (2005) Application research on dextran-based hydrogel and its drug controlled release. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 19(11):919–922
92. Vervoort L et al (1997) Inulin hydrogels as carriers for colonic drug targeting: I. Synthesis and characterization of methacrylated inulin and hydrogen formation. Pharm Res 14 (12):1730–1737
93. Vervoort L et al (1999) Inulin hydrogels as carriers for colonic drug targeting. Rheological characterization of the hydrogel formation and the hydrogel network. J Pharm Sci 88 (2):209–214
94. Kuzma P et al (1996) Subcutaneous hydrogel reservoir system for controlled drug delivery. Macromol Symp 109:15–26
95. Eljarrat-Binstock E et al (2007) Preparation, characterization, and sterilization of hydrogel sponges for iontophoretic drug-delivery use. Polymer Adv Technol 18:720–730
96. Arica MY et al (2005) Novel hydrogel membrane based on copoly(hydroxyethyl methacrylate/p-vinylbenzylpoly(ethylene oxide)) for biomedical applications: properties and drug release characteristics. Macromol Biosci 5(10):983–992
97. Blanco MD, Rego JM, Huglin MB (1994) Drug-release with simultaneous dimensional changes from a new copolymeric hydrogel. Polymer 35(16):3487–3491

98. De Giglio E et al (2009) Electrosynthesis of hydrogel films on metal substrates for the development of coatings with tunable drug delivery performances. J Biomed Mater Res A 88(4):1048–1057
99. Eljarrat-Binstock E et al (2004) Hydrogel probe for iontophoresis drug delivery to the eye. J Biomater Sci Polym Ed 15(4):397–413
100. Eljarrat-Binstock E et al (2005) Transcorneal and transscleral iontophoresis of dexamethasone phosphate using drug loaded hydrogel. J Control Release 106(3):386–390
101. Eljarrat-Binstock E et al (2004) Delivery of gentamicin to the rabbit eye by drug-loaded hydrogel iontophoresis. Invest Ophthalmol Vis Sci 45(8):2543–2548
102. Gulsen D, Chauhan A (2005) Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle. Int J Pharm 292(1–2):95–117
103. Gayet JC, Fortier G (1995) Drug-release from new bioartificial hydrogel. Artif Cells Blood Substit Immobil Biotechnol 23(5):605–611
104. Gayet JC, Fortier G (1996) High water content BSA-PEG hydrogel for controlled release device: evaluation of the drug release properties. J Control Release 38(2–3):177–184
105. Qiu B et al (2003) A hydrogel prepared by in situ crosslinking of a thiol-containing poly (ethylene glycol)-based copolymer: a new biomaterial for protein drug delivery. Biomaterials 24(1):11–18
106. Missirlis D, Tirelli N, Hubbell JA (2005) Amphiphilic hydrogel nanoparticles. Preparation, characterization, and preliminary assessment as new colloidal drug carriers. Langmuir 21 (6):2605–2613
107. Shekunov BY et al (2007) Structure and drug release in a crosslinked poly(ethylene oxide) hydrogel. J Pharm Sci 96(5):1320–1330
108. Shekunov BY, Taylor P, Grossmann JG (1999) Structural phenomena in hydrogel-drug systems. J Crystal Growth 198:1335–1339
109. Lin H et al (2006) Synthesis, characterization and drug release of temperature-sensitive PLGA-PEG-PLGA hydrogel. Chem J Chinese Universities-Chinese 27(7):1385–1388
110. Varshosaz J, Koopaie N (2002) Crosslinked poly (vinyl alcohol) hydrogel: study of swelling and drug release behaviour. Iranian Polym J 11(2):123–131
111. Wang N, Wu XS, Li JK (1999) A heterogeneously structured composite based on poly(lactic-co-glycolic acid) microspheres and poly(vinyl alcohol) hydrogel nanoparticles for long-term protein drug delivery. Pharm Res 16(9):1430–1435
112. Ramaraj B, Radhakrishnan G (1994) Hydrogel capsules for sustained drug-release. J Appl Polym Sci 51(6):979–988
113. Mandal TK et al (2002) Poly(d, l-lactide-co-glycolide) encapsulated poly(vinyl alcohol) hydrogel as a drug delivery system. Pharm Res 19(11):1713–1719
114. Tada D et al (2005) Drug release from hydrogel containing albumin as crosslinker. J Biosci Bioeng 100(5):551–555
115. Stanojevic M et al (2006) An investigation into the influence of hydrogel composition on swelling behavior and drug release from poly(acrylamide-co-itaconic acid) hydrogels in various media. Drug Deliv 13(1):1–7
116. Barthus RC, Lira LM, de Torresi SIC (2008) Conducting polymer-hydrogel blends for electrochemically controlled drug release devices. J Braz Chem Soc 19(4):630–636
117. Lee WF, Chiu RJ (2002) Thermoreversible hydrogel. XVII. Investigation of the drug release behavior for [N-isopropylacrylamide-co-trimethyl acrylamidopropyl ammonium iodide-co-3-dimethyl (methacryloyloxyethyl) ammonium propane sulfortate] copolymeric hydrogels. J Appl Polym Sci 86(7):1592–1598
118. Reimer K et al (2000) An innovative topical drug formulation for wound healing and infection treatment: in vitro and in vivo investigations of a povidone-iodine liposome hydrogel. Dermatology 201(3):235–241
119. Chen J et al (2005) Preparation and characterization of magnetic targeted drug controlled-release hydrogel microspheres. Macromol Symp 225:71–80

120. Giammona G et al (1997) A hydrogel based on a polyaspartamide: characterization and evaluation of in-vivo biocompatibility and drug release in the rat. J Pharm Pharmacol 49 (11):1051–1056
121. Aikawa K et al (1998) Drug release from pH-response polyvinylacetal diethylaminoacetate hydrogel, and application to nasal delivery. Int J Pharm 168(2):181–188
122. http://www.drugs.com
123. Chen J, Park H, Park K (1999) Synthesis of superporous hydrogels: hydrogels with fast swelling and superabsorbent properties. J Biomed Mater Res 44(1):53–62
124. Chen J, Park K (1999) Superporous hydrogels: fast responsive hydrogel systems. J Macromol Sci-Pure Appl Chem A36(7–8):917–930
125. Chen J, Park K (2000) Synthesis and characterization of superporous hydrogel composites. J Control Release 65(1–2):73–82
126. Omidian H, et al (2005) Hydrogels having enhanced elasticity and mechanical strength properties in US patent 6,960,617
127. Omidian H, Rocca JG (2006) Formation of strong superporous hydrogels in US patent 7,056,957
128. Omidian H, Rocca JG, Park K (2006) Elastic, superporous hydrogel hybrids of polyacrylamide and sodium alginate. Macromol Biosci 6(9):703–710
129. Omidian H, Park K (2008) Swelling agents and devices in oral drug delivery. J Drug Deliv Sci Technol 18(2):83–93
130. Omidian H, Park K, Rocca JG (2007) Recent developments in superporous hydrogels. J Pharm Pharmacol 59(3):317–327
131. Omidian H, Rocca JG, Park K (2005) Advances in superporous hydrogels. J Control Release 102(1):3–12
132. Dorkoosh FA et al (2001) Development and characterization of a novel peroral peptide drug delivery system. J Control Release 71(3):307–318
133. Dorkoosh FA et al (2002) Intestinal absorption of human insulin in pigs using delivery systems based on superporous hydrogel polymers. Int J Pharm 247(1–2):47–55
134. Dorkoosh FA et al (2002) Evaluation of superporous hydrogel (SPH) and SPH composite in porcine intestine ex-vivo: assessment of drug transport, morphology effect, and mechanical fixation to intestinal wall. Eur J Pharm Biopharm 53(2):161–166
135. Yang SC et al (2004) Application of poly(acrylic acid) superporous hydrogel microparticles as a super-disintegrant in fast-disintegrating tablets. J Pharm Pharmacol 56(4):429–436
136. Wiese KG (1996) Tissue expander inflating due to osmotic driving forces of a shaped body of hydrogel and an aqueous solution. US Patent #5,496,368
137. Wiese KG et al (2001) Biomaterial properties and biocompatibility in cell culture of a novel self-inflating hydrogel tissue expander. J Biomed Mater Res 54(2):179–188
138. Osmed (GMBH), Hydrogel competence: self-inflating tissue expander. http://www.osmed.biz
139. Akina, Tissue expanding hydrogel (Resitex). http://www.akinainc.com
140. List of contact lenses allowed to be sold in the United States. Food and Drug Administration Website, http://www.fda.gov/cdrh/contactlenses/lenslist.html