Chapter 6
Polymeric Hydrogel: A Flexible Carrier System for Drug Delivery

Surbhi Dubey, Rajeev Sharma, Nishi Mody and S. P. Vyas

1 Introduction

Progress in modern drug delivery and in the area of polymer science has shifted the interest on polymer-based drug delivery systems to obtain spatiotemporal release of the therapeutics. The advent of effective and precise biological therapeutics has accelerated the polymer-based smart delivery systems for both pulsatile dose delivery and implantable reservoir systems. A great number of polymers of both natural and synthetic origin constitutes a vital area of biopharmaceutics in which linear or branched polymer chains have been exploited as polymeric drug carriers.

A through study of underlying mechanisms of transitional behavoiur of polymers under applied stimulus can help design the polymers with well-ordered molecular and structural to give a well-defined reaction to the external conditions. Such stimuli responsive polymers are used for formulating sensitive carriers which deliver drug(s) in response to the varying biological conditions/stimulus present in body. Polymers carrying therapeutics can themselves be bioactive which in addition to drug provide their own therapeutic benefit as well. These polymers are biodegradable and prevent carrier accumulation in the biological system. Pharmaceutical agents can also be conjugated to the polymer through biologically labile bonds to dissociate in particular bioenvironment in response to change like pH, temperature, enzyme or ionic strength etc. The polymer-drug conjugation provides advantages including prolonged circulation half-life and sustained the drug release. Active targeting can be achieved by conjugating the polymeric backbone with the ligand specific to the overexpressed cell surface receptor of the affected tissue. The targeted nanocarriers which are taken up by the receptor mediated endocytosis are taken by the endosome follow an endolysomal pathway

S. Dubey (✉) · R. Sharma · N. Mody · S. P. Vyas
Drug Delivery Research Laboratory, Department of Pharmaceutical Sciences,
Dr. H.S. Gour University Sagar, Sagar 470003, M.P., India
e-mail: surbhi.dubey3@gmail.com

V. K. Thakur and M. K. Thakur (eds.), *Polymer Gels*, Gels Horizons: From Science to Smart Materials, https://doi.org/10.1007/978-981-10-6083-0_6

where majority of drug molecules are degraded, curtailing the intracellular therapeutic concentration. Hence, new polymeric materials are being explored and undergo endosomal escape preventing entry into the lysosomes and promoting cytoplasmic drug delivery. Therefore, drug delivery research based on polymeric material has produced precognitive systems which allow cytoplasmic delivery of novel therapeutics. The polymeric novel drug delivery carrier systems comprise of microspheres, nanoparticles, nanospheres, nanocapsules, polymeric micelle, polymer-drug conjugates, dendrimers, transdermal patches, and polymeric gels (hydrogel). Hydrogels offer a wide platform for the delivery of various types of therapeutics (small molecules, chemotherapeutics, proteins, antigens, conjugated) owing to their amenability be designed as bioadhesive as well as environment-sensitive systems using various stimuli-sensitive polymers as illustrated in Table 1.

Pharmaceutical gels are mainly represented by hydrogel. The hydrogel is a three-dimensional crosslinked network of hydrophilic polymers. These polymers are insoluble in water but are capable of absorbing large volume of water. Hydrogels can be structured as slabs, microparticles (microgel), nanoparticles (nanogel), coatings, and films from polymers of both natural and synthetic origins. Various kinds of material (polymers) used for the fabrication of hydrogels are classified in Table 2, and the properties of ideal material required for the formulation of hydrogel are given in Table 3.

1.1 Advantages of Hydrogels

- Hydrogels are highly flexible and elastic structures which can be tuned and tailored as per need by modifying crosslinking densities.
- Therapeutic molecules can be easily incorporated by anchoring them covalently to the polymer or entrapping into polymer matrix.
- Hydrogels offer three-dimensional milieus for molecular-level biological interactions.
- They possess lower tendency to adsorb biological proteins and adhere to cells because of their inert and hydrophilic surfaces. A hydrogel is a soft and rubbery substance that avoids irritation to the adjoining tissue.
- Hydrogel undergoes sol–gel transition; the property in particular renders these systems safe for in vivo use. Hydrogels can be manipulated to respond to externally applied factors (stimuli-sensitive), such as temperature, ionic strength, solvent polarity, electric/magnetic field, light, or small biomolecules.
- Hydrogels offer pharmacokinetic benefits for drug delivery as a depot formulation is created upon administration from which the drug is released slowly in the neighbouring tissue, thereby generating high local concentration of drug over prolonged period of time.

Table 1 Hydrogel used in drug delivery

S.No	Polymer	Drug/ bioactive	Delivery site	Stimuli	Advantages/Application	Ref
1.	Poly(N-isopropylacrylamide) (PNIPAAm)	4-Cetamidophen	-	Temperature	Hydrogel microparticles into a crosslinked gelatin matrix	Klouda and Mikos (2008)
2.	IPNs of poly (acrylic acid) and polyacrylamide (PAAm) or P(AAm–co-BMA)	Ketoproprofen	-	Temperature	Positive temperature dependence of swelling	Owens et al. (2007)
3.	Poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO) Pluronics® (or Poloxamers®) and Tetronics®.	Ketoprofen, Spironolacto-ne	-	Temperature	The release of a hydrophilic model drug (ketoprofen) and a hydrophobic model drug (spironolactone) were first-order and S-shaped, respectively.	Qiu and park 2012
4.	Copolymers of methyl methacrylate and N,N′-dimethylaminoethylmethacrylate (DMAEM)	Caffeine	-	pH	It was not released at neutral pH, but released at zero-order at pH 3–5	Siegelet al. 1988
5.	Semi-IPN of crosslinked chitosan and PEO	Antibiotics, such as amoxicillin and metronidazole	-	pH	More swelling under acidic conditions	Patel and Amiji (1996)
6.	Hydrogels made of polyanions (e.g. PAA) crosslinked with azoaromatic crosslinkers	Model drug	-	pH	Swelling of such hydrogels in the stomach is minimal and thus, the drug release is also minimal	Peppas and Peppas 1990; Khare and Peppas 1990
7.	NIPAAm, acrylic acid and 2-hydroxyethyl methacrylate	Streptokinase and heparin	-	Terpolymer hydrogels, pulsatile delivery	Function of stepwise pH and temperature changes	Vakkalanka et al. 1996; Brazel and Peppas 1996

(continued)

Table 1 (continued)

S.No	Polymer	Drug/ bioactive	Delivery site	Stimuli	Advantages/Application	Ref
8.	Nonionic poly (N-isopropylacrylamide) hydrogel	-	-	Specific ion-sensitive hydrogels	A sharp volume phase transition at a critical concentration of sodium chloride in aqueous solution	Starodoubtsev et al. (1995)
9.	N-isopropylacrylamide (NIPAAm) monomer and a dextran macromer containing multiple hydrolytically degradable oligolactate-(2-hydroxyetheyl methacrylate) units (Dex-lactateHEMA)	insulin	-	thermoresponsive	Insulin release from the hydrogel occurs for duration of one week and the release kinetics can be modified by changing the polymer ratio of NIPAAm and Dex-lactateHEMA and altering the physical size of the hydrogels.	Misra et al. (2009)
10.	Poly(ethylene glycol) hydrogels	Doxycycline	Eye and skin	-	superior wound healing efficacy for mustard injuries in the eye and skin	Anumolu et al. (2010)
11.	polyacrylic acid polymers	metronidazole (MTZ)	skin		Bioadhesive	Calixto et al. (2015)
12.	PLGA–PEG–PLGA hydrogel	dexamethasone acetate	ocular	thermosensitive	thermosensitive in situ gel-forming material for ocular drug delivery, may improve the bioavailability, efficacy of some eye drugs.	Gaoa et al. (2010)
13.	dextrin grafted with poly (2-hydroxyethyl methacrylate) [Dxt-g-p(HEMA)]	ornidazole	colon	pH	Controlled delivery of ornidazole in the colonic region in a controlled way. first order kinetics by non-Fickian diffusion mechanism ornidazole release from hydrogel follows	Das et al. (2013)
14.	Schiff's base cross-linked hydrogels (PFA/PPLL hydrogels)	metformin and 5-fluorouracil	colon carcinoma model	pH	pH dependant and controlled release of anticancer drug in colon	Wua et al. 2013

(continued)

Table 1 (continued)

S.No	Polymer	Drug/ bioactive	Delivery site	Stimuli	Advantages/Application	Ref
15.	poly-*N*-vinyl-2-pyrrolidone (PVP)	Acyclovir	nasal delivery		mucoadhesive polymeric hydrogels less damages to the nasal mucosal compared to formulation containing glycerol.	Alsarra et al. (2009)
16.	Pluronic F127 and carbopol 934P (C934P)	naproxen	oral		improve oral residence time and absorption of naproxen	Shin B-K et al. (2013)
17.	Supramolecular Hydrogel (methoxy poly(ethylene glycol) block polymer and α-cyclodextrin (α-CD)	diclofenac	ocular		Extended the retention time on the corneal surface in rabbits, compared with a plain micellar formulation	Zhang et al. (2016)
18.	polysaccharide cross-linked hydrogel	Avastin	Ocular		Avastin was sustained release from hydrogel with well structure stability	Xu et al. (2013)
19.	dextrin grafted with poly (2-hydroxyethyl methacrylate) [Dxt-g-p(HEMA)]	Ornidazole	colon	pH sensitive	delivers ornidazole successfully in the colonic region in a controlled way ornidazole release from hydrogel follows first order kinetics and a non-Fickian diffusion mechanism	
20.	crosslinked carboxymethyl sago pulp/pectin hydrogel beads	diclofenac sodium	colon	pH sensitive	Less than 9% of s released at pH 1.2 and the hydrogel beads sustain the drug release at pH 7.4 over 30 h.	Tan et al. (2016)
21.	P(CE-MAA-MEG)	5 - Aminosalicylic acid	colon	pH sensitive	Drug release in colon	Bai et al. (2016)
22.	chitosan-based hydrogel	Latanoprost		thermoresponsive	elevated intraocular pressure was significantly decreased within 7 days and remained at a normal level for the following 21 days in rabbit eyes	Cheng et al. (2016a)

(continued)

Table 1 (continued)

S.No	Polymer	Drug/ bioactive	Delivery site	Stimuli	Advantages/Application	Ref
23.	gellan or sodium alginate alone and combined with sodium carboxymethyl -cellulose (NaCMC)	Gatifloxacin	ocular	Ion-activated mucoadhesive gel	mucoadhesive hydrogel longer corneal residence duration	Kesavan et al. (2015)
24.	micellar supramolecular hydrogel (α-cyclodextrin (α-CD) and onomethoxy poly(ethylene glycol)-b-poly(ε-caplactone) (MPEG5000-PCL5000) micelles)	PTX	cancer	-	injectable drug delivery system. enhance the biological activity of encapsulated PTX compared to free PTX	Fu et al. 2016
25.	Supramolecular Hydrogel	10-Hydroxy Camptothecin	cancer		sustained long term and release of HCPT with high accumulated rate.	Ruixin et al. (2015)
26.	supramolecular hydrogels based on poly(ether-urethane) nanoparticles and α-CD	Hydrophobic (indomethacin) and hydrophilic drugs (rhodamine)	-	pH and oxidation dual-responsive	hydrogels demonstrate dual drug release behavior and the release rates could be appreciably accelerated by adding up of an oxidizing agent (H_2O_2) or increasing the environmental pH.	Cheng et al. (2016b)
27.	bis-imidazolium based supramolecular hdydrogel	anionic drugs like indomethacin and ibuprofen	topical		hydrogels are soft, stable in comparison to previous reported gels. Enhanced skin retention of drug Capable for the delivery of poor water soluble drugs used in the treatment of acute inflammation or other skin diseases.	Limón et al. (2015)
28.	Supramolecular hydrogel based on α-cyclodextrin (α-CD) and a PEGylated doxorubicin prodrug	Doxorubicin	cancer	pH	hydrogels could be degraded in the acidic environment of tumor cells and achieved the controlled delivery of DOX	Fei et al. (2015)

Table 2 Classification of polymers used for hydrogel fabrication

Natural polymer	• Cellulose Derivatives: methyl cellulose (MC), carboxymethyl cellulose (CMC), and various grades of hydroxypropyl methylcellulose (HPMC) • Hydrocolloids/Polyssacharides: alginate, xanthan, guar gum, konjac, gellan, chitosan, carrageenan, scleroglucan, hyaluronic acid, pectin, gelati, agaraose, inulin
Synthetic polymer	• Poly (2-hydroxyethyl methacrylate) (polyHEMA) • Poly (Ethylene Glycol) • Poly (Vinyl Alcohol) • Polyacrylamide • Polyvinylpyrrolidone • Polyurethane
Superdisintegrants	• Crosslinked carboxymethyl cellulose [(Ac-Di-Sol® (FMC Biopolymer); Primellose® (DMV-Fonterra)] • Crosslinked polyvinylpyrrolidone [Crospovidone Kollidone CL®, CL-M® (BASF); Polyplasdone XL®, XL10® (ISP)] • Crosslinked starch glycolate [Primojel® (DMV-Fonterra)]
Stimuli sensitive	• Temperature: poly(*N*-isopropylacrylamide) (PNIPAAm), poly(*N*,*N*'-diethylacrylamide) (PDEAAm) poly (ethylene oxide)-*b*-poly(provpylene oxide)-*b*-poly (ethylene oxide) (Pluronics , Tetronics , poloxamer), xyloglucan, Poloxamers • pH: Polyelectrolytes, poly(2-hydroxyethyl methacryate) (PHEMA), polymethyl methacrylate (PMMA), polyacrylamide (PAAm), polyacrylic acid (PAA), poly dimethylaminoethylmethacrylate (PDEAEMA) and polyethylene glycol, Cellulose acetate phthalate (CAP) • Ion-sensitive hydrogels: Gelrite (anionic extra cellular polysaccharide), alginate • Glucose: Concanavalin A (Con A), ph sensitive polymers • Antigen: Semi-IPN with grafted antibodies or antigens.

- Hydrogels can be prepared with properties in between two different materials, e.g. mix a swellable polymer with a temperature- or pH-responsive polymer to obtain the networks with a defined amount of swellability in response to changes in temperature or pH.
- Hydrogel can also be assembled to form various novel drug nanocarriers in tissue specific dimensions like microspheres, nanoparticles, nanogels, microgels, nanosponges.
- Hydrogels are highly biocompatible due to presence of high water content and the physiochemical similarity to the native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically.
- Hydrogel are highly flexible and deformable which enable them to acquire the shape of the surface to which they adhere thus rendering them suitable for drug delivery as mucoadhesive or bioadhesive dosage forms.

Table 3 Desired properties of ideal hydrogel material

– Possess high absorption ability with maximum possible equilibrium swelling capability in saline
– Preferred particle size and porosity for desired rate of absorption as per the application requirement.
– High absorbency under load (AUL)
– The lowest residual monomer and soluble content
– Should be cheap
– Should be stable and durable during swelling in the application area and during storage.
– Biocompatible and biodegradable
– Degrade without the formation of toxic molecules or residue
– Maintain ph-neutrality after swelling in water
– Colorless, odorless and non-toxic
– Should be photo stable
– Re-wetting capability

1.2 Demerits of Hydrogel

- Hydrogels possess low tensile strength which may lead to their drainage from site of application and limits their use in drug-bearing applications.
- Lack of homogeneity and low drug loading capacity for hydrophobic drugs.
- Rapid release of drug because of high water content and large pore size of hydrogel.
- Lack of ease of application, as many of the hydrogels do not possess sufficient deformability in order to be injectable and hence require surgical procedure for their application.

2 Classification of Hydrogel

2.1 Classification Based on Polymeric Composition

2.1.1 Homopolymeric Hydrogels

Polymer network of these hydrogels comprises of single monomer species that constitutes the basic structural units (Iizawa et al. 2007). Depending upon the properties of monomer and polymerization technique used, homoploymers may form a crosslinked skeletal.

2.1.2 Copolymeric Hydrogel

These hydrogels are made of two types of monomeric units one of which is esssentially hydrophilic in nature. The monomeric units may be organized in a block, random, or alternating configuration alongside the chain of the polymer network (Kubinova et al. 2010).

2.1.3 Multipolymer Interpenetrating Polymeric Hydrogel (IPN)

The polymeric network of these hydrogels is constituted of two independent crosslinked polymers (natural or synthetic). IPN is prepared by intimate blending of two polymers, in which one of the polymers is produced or crosslinked in the immediate presence of the other from which hydrogel matrix is prepared. The resulting hydrogel matrix is generally highly dense, stiff and strong mechanically. Further, they have manageable physical properties, and more proficient drug loading capacity as compared to conventional hydrogels (Mohamadnia et al. 2007).

2.1.4 Semi-inter Penetrating Network (Semi-IPN)

Semi-IPN consists of a combination of a crosslinked polymer and a linear polymer. Semi-IPN is formed when the linear polymer penetrates the crosslinked network of another polymer without formation of any chemical bond.

2.2 Classification Based on Polymeric Composition

Based upon the physical configuration and chemical composition, hydrogels can be classified as.

2.2.1 Amorphous Hydrogels

Hydrogel (non-crystalline) in which chains are randomly arranged.

2.2.2 Semicrystalline Hydrogels

These consist of a complex fusion of amorphous and crystalline phases along with the dense regions of ordered macromolecular arrangement.

2.2.3 Crystalline Hydrogels

The crystalline hydrogels have, chains which are arranged in proper sequence.

2.3 Classification Based on Type of Crosslinking

Based upon the nature of crosslinking connections in the polymeric network, hydrogels are classified into two following categories.

2.3.1 Physically Crosslinked Hydrogels/Reversible Hydrogels

Polymeric network is formed involving temporary interchain junctions arising from polymeric chains entanglements or physical interaction between polymer chains such as ionic interactions, hydrogen bonds, or hydrophobic interactions. Approaches employed for preparing physically crosslinked hydrogels include environmental triggers (pH, temperature, ionic strength) and a variety of physicochemical interactions (hydrophobic interactions, charge condensation, hydrogen bonding, stereocomplexation, or supramolecular chemistry) (Hoare and Kohane 2008).

2.3.2 Chemically Crosslinked Hydrogels/Permanent Hydrogel

These hydrogels are designed through formation of permanent junctions in the polymer network. Chemical crosslinking can be achieved by following methods: using crosslinkers (aldehydes, addition reactions, condensation reaction), grafting, or using radiation.

2.4 Classification According to Network Electrical Charge

Depending on the nature of charge present on the crosslinking chains, hydrogels are classified into four types (Mocanu et al. 2012, Deo et al. 2010 and Percec et al. 2002):

2.4.1 Anionic hydrogels (e.g. carboxymethylpullulan hydrogels, alginate);
2.4.2 Cationic hydrogels (e.g. *N*-isopropylacrylamide (NIPAM) and (3-acrylamidopropyl) trimethylammonium chloride (AAPTAC));
2.4.3 Neutral hydrogels (miscible composites from water-insoluble polymers like poly(2,4,4-trimethylhexamethylene terephthalamide);
2.4.4 Ampholytic hydrogels (e.g. acrylamide-based ampholytic hydrogels).

2.5 Classification on the Basis of Stimuli

These hydrogels are responsive to physical or chemical stimuli and releases drug as a result of the abrupt change in the physical nature of the network in response to the physical or chemical stimuli. Based on this property, hydrogels are classified as follows.

2.5.1 Physically Responsive Hydrogels

The polymeric network of these hydrogels consists if such polymers which undergo structural change alteration in molecular interactions by physical stimuli like temperature, electric or magnetic field.

2.5.2 Chemically Responsive Hydrogel

Drug release from these hydrogels occurs in response to the chemical stimulus like pH, change in ionic strength or presence of certain ions and chemical reagents as a result of molecular changes due to change in interaction between polymer chains and solvent.

3 Methods for Preparation of Hydrogel

3.1 Mechanism of Network Formation

The formation of hydrogel involves the creation of elastic network of polymeric chains through crosslinking. Therefore, any method which can be incorporated to generate a crosslinked polymeric network can be used to create a hydrogel (Ahmed 2015). This process of formation of crosslinked network is known as gelation and can be defined as the linking of macromolecular chains together which initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material.

Such hydrogels exhibit sol–gel transition which is most commonly employed for the formation of injectable depot preparations and ophthalmic gels. Sol is defined as the blend of polydispersed branched and soluble polymers. As the linking process proceeds, the size of the branching polymers goes on increasing with decreasing solubility resulting in the formation of gel. The linking can occur through physical (physical gelation) or chemical (chemical gelation) means. This transition of polymer from definite branched polymeric to vast network structure is referred to as as sol–gel transition or gelation. The critical point at which gel appears is known as gel point.

3.2 *Physically Crosslinked Hydrogel*

Physically crosslinked hydrogel can be formed through following methods.

3.2.1 Heating/Cooling a Polymer Solution

In this approach, the physically crosslinked gel is shaped upon cooling the hot solution of polymers. Upon cooling, the gel is formed as a result of helix formation, formation of junction, and association of helices (Funami et al. 2007). Example of polymer includes: carrageenan and gelatin. Above the melting transition temperature, the carrageenan is present in randomly coiled arrangement, and upon cooling, it transforms into rigid helical rods. In addition, stable aggregates are formed in the presence of positive ions (K^+, Na^+, etc.) due to screening of repulsive forces between sulphonic groups and increased attractive forces between negative (SO^{3-}) and positive moieties of salt (Na^+, K^+, etc.). Another simple approach which is used to obtain hydrogel is known as block copolymerization. It involves warming of polymeric solutions, for example hydrogel formed of polyethylene oxide–polypropylene oxide, polyethylene glycol–polylactic acid hydrogel.

3.2.2 Ionic Interaction-/Charge Interaction-Based Hydrogel

In this approach, charge interaction between a polymer and a counter ion or between two polymers of opposite charge leads to in situ formation of polymeric network to form hydrogel (Fig. 1). For example, under physiological conditions, elastin-like polypeptides are crosslinked through electrostatic interaction between the cationic lysine groups and anionic organophosphorus groups (Lim et al. 2007).

Polysaccharide, alginate is one of the most popular examples where crosslinks are fromed through ionic linkage. Gel formation occurs incorporation of calcium ions which crosslink the mannuronic and glucuronic acid residues (Gacesa 1988). The crosslinking can be carried out at room temperature and at physiological pH, that is why alginate is widely used to encapsulate living cells and proteins in its matrix (Goosen et al. 1985).

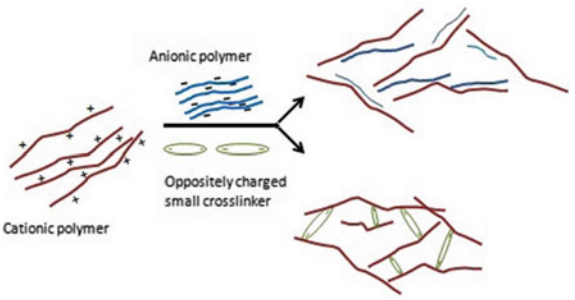


Fig. 1 Hydrogel formation through charge interaction

Another approach for the formation of ionic hydrogel does not necessitate the existence of ions on the polymer chain for the creation of ionic crosslinks. It is based on the ability of the metal ion to accumulate in the polymeric cage because of its small ionic radius, for example the formation of dextran, hydrogel in the presence of potassium ions. Dextran is deficient in ionic binding sites for cations; however, the ionic radius of the potassium ion easily and perfectly occupies the cage formed by six oxygen atoms of glucose entities of three polymer chains, in this manner making a microstructure (Watanabe et al. 1993). However, this dextran/potassium gel is less suitable for drug delivery purposes because it is unstable in water.

In addition, hydrogels can likewise be produced as a result of the formation of complex of polyanions with polycations, for example complex formation between chitosan and polyanions, such as dextran sulphate or polyphosphoric acid that generates ionically crosslinked chitosan hydrogels-based nanoparticles. (Janes et al. 2001). These chitosan hydrogel nanoparticles were loaded with doxorubicin, and reportedly shown a minimum burst release and exhibited good in vitro cytotoxicity due to the released drug.

pH-based ionic interactions can also lead to the formation of hydrogel. pH change promotes the ionization of the functional groups present on the polymer chain to form gel following interaction with the counter ion. Biodegradation of these hydrogels occurs easily by the ionic functionalities present in the extracellular fluid which bind competitively to the gel resulting in the breakdown of the polymeric network. For example, (i) peptides consisting of alternating positively and negatively charged groups can self-assemble through ionic interaction to form hydrogel in situ (Chen 2005) (ii) doxorubicin hydrochloride containing ionically crosslinked hydrogel formed from blend of quaternized chitosan and glycerophosphate which is optically clear and release drug as a function of pH (Wu et al. 2006).

Moreover, charge interactions can be used to crosslink gels to create three-dimensional particulate carriers like microparticle or nanoparticle with promising drug delivery properties. For example, dextran microspheres coated with anionic and cationic polymers reveal impulsive gelation upon mingling owing to ionic complex formation between the oppositely charged microparticles network (Van Tomme et al. 2005).

3.2.3 Crosslinking by Crystallization

Crystallization in Homopolymer Systems

Crystallization process involves subjecting the aqueous solution of water-soluble polymer to a series of freeze-thaw cycle resulting in crystallization of the polymer and formation of gel. For example, polyvinyl alcohol, a water-soluble polymer, forms a gel gradually when its aqueous solution is stored at room temperature but with weaker elasticity and strength. Surprisingly, when the solution of PVA was subjected to freeze-thaw process, a gel was formed having greater strength,

elasticity, and remained stable for 6 months at 37 °C (Yokoyama et al. 1986; Hassan and Peppas 2000). Mechanism for the formation of stronger gel is attributed to the formation of polymer crystals in the hydrogel network leading to more ordered arrangements of the polymeric chains and stronger anchorages. The properties of hydrogel are dependent on the molecular weight and concentration of PVA, temperature, time duration of freezing, and number of freeze-thaw cycle. This gel is ideal for encapsulation of proteins like BSA as the conformation of protein is retained during the release where the latter follows Fickian diffusion pattern.

The polymer crystals are also formed through hydrogen bonds formation does take place in the concentrated polymeric solution, and the gel gets converted into particulate form on stirring. For example, concentrated solution of dextran spontaneously formed hydrogel when stored at room temperature, and upon stirring, the solution of microspheres was obtained.

Crosslinking by Stereocomplex Formation

Polymers consisting of chiral, optically active, monomeric units can form crystallites. Similarly, on mixing the polymer/s with regions of opposite chirality, these regions can associate to form racemic crystalline domains, which are known as stereocomplexes. Thus, stereocomplex hydrogels can be produced by combining enantiomerically enriched polymers of opposite chirality. Instead, they can be formed simply from one polymeric species having regions of opposed chirality. One of the most relevant stereocomplexes is formed by semicrystalline PLLA and PDLA, the homopolymers of L-lactic acid and D-lactic acid, respectively. The strong interaction between polylactide blocks with L- and D-stereochemistry can be utilized for in situ forming hydrogels with high storage moduli (up to 14 kPa) as illustrated schematically in Fig. 2. Star diblock copolymers or multi-arm PEG-PLA dendrimers interact through stereospecific crosslinking to form hydrogel with transition temperatures extending from 10 to 70 °C. The transition temperature is governed by the polymer concentration and length of the PLA block (Hiemstra et al. 2006). These hydrogels have enormous potential to be used in drug delivery. Stereocomplex formation also occurs in mixtures of triblock copolymers, for example PLLA–PEG–PLLA and PDLA–PEG–PDLA, which can be easily transformed into particulate carriers to carry number of drug- and protein-based therapeutics. For example, Lim et al. studied and compared the release of BSA from microspheres formed by these triblock copolymers with the microspheres formulated with single enantiomeric triblock copolymer and with PLLA microspheres (Lim and Park 2000). Natural polymers can also be crosslinked through stereocomplex formation by grafting of enantiomers on their backbone, for example grafting of D- and L-lactic acid oligomers on the dextran backbone (Hennink et al. 2004; Bos et al. 2004). Hydrogel is formed by spontaneous gelation in water without the need of any harsh condition or organic solvent or chemical crosslinkers or the hydrophobic domains thus they are suitable for the delivery of proteins. They have excellent biocompatibility and biodegradability.

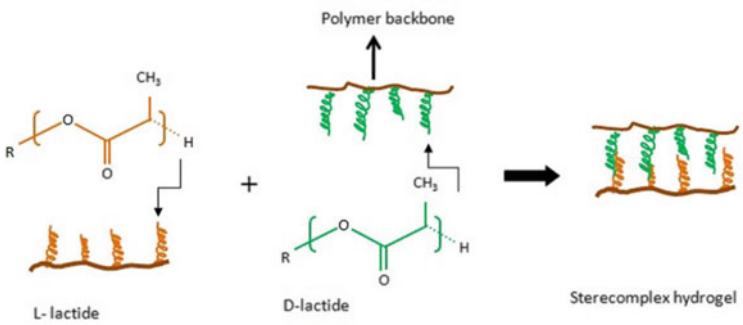


Fig. 2 Hydrogel formation through stereocomplex formation

Hydrogels based on stereocomplex crosslinking, however suffer from demerit of limited range of polymers available which are capable of forming strong hydrogel. A small change in the composition or stoichiometry during synthesis can disrupt or weaken the stereochemical interaction. The stereocomplex hydrogels are degraded in biological conditions due to the existence of hydrolysable oligomeric lactide side chains and are used for drug delivery applications. They are also degraded in body by means of the degradable structure anchored on the polymer base or by tailoring polymeric backone with degrading groups. For example, hydrogel can be made degradable by involving grafts and linking biosusceptible groups between the polymer chains.

However, many of the seterocomplex hydogels do not contribute as a good candidate for controlled release formulation because the rate of hydrolysis is faster than that required to provide adequate gel strength and to assure drug retention over several weeks or months. Physiologically stable stereocomplex hydrogels capable of releasing drug for several weeks or months are still to be designed, devised and developed.

3.2.4 H-Bonding-Based Hydrogels

Hydrogen bonding-based physically crosslinked gel structure is formed by interaction between polymeric chains consisting of active oxygen and a chain consisting of hydrogen bonding atoms like H, N, or F. These hydrogels are formulated as injectable hydrogels based on sol–gel viscoelastic transition. Such individual polymers remain in solution form which upon blending undergo viscoelastic changes (rheological synergism) due to hydrogen bonding and form the gel. Upon subjecting to shear during injection, hydrogen bonds are cleaved, thereby allowing ease of administration; for example, polyacrylic acid (PAA) and polymethacrylic acid (PMA) make complexes with polyethylene glycol (PEG) as a result of hydrogen bonding interaction between oxygen of PEG and hydrogen from carboxylic group of PAA and PMA (Eagland et al. 1994). The polymeric gel from

these polymers can also be prepared by dissolving in ethanol. This gel upon injecting into body diffuses ethanol and converts into gel which degrades gradually as the complex dissociates. Other examples of physically interconnected gel-like structures which are injectable too include combinations of natural polymers such as gelatin-agar (Liu et al. 2005), starch-carboxymethyl cellulose (Bajpai and Shrivastava 2005), and hyaluronic acid-methylcellulose (Gupta et al. 2006).

These hydrogels are formed only upon the protonation of carboxylic acid groups and exhibit pH-dependent swelling behaviour. However, on in vivo administration these hydrogen-bonded networks get diluted and disperse owing to inflow of water, hence constraining their usage to comparatively short-acting drug release systems unless additional crosslinking agent is also used.

Carboxylic group containing polymers can form hydrogel on lowering of pH. For example, sodium CMC forms a hydrogen-bonded hydrogel when dispersed in 0.1 M HCl solution (Takigami et al. 2007). The Na^+ ion in CMC is replaced by the hydrogen ion present in the acid solution which results in the hydrogen bond formation followed by a decrease in the solubility of CMC and formation of hydrogel. Based on the similar mechanism, polyacrylic acid and polyethylene oxide (PEO-PAAc) also form a hydrogen-bonded hydrogel as the pH of the aqueous solution decreases (Hoffman 2002). Polymeric blend of xanthan and alginate forms an insoluble hydrogel network due to formation of strong intermolecular bonds.

3.2.5 Supramolecular Complex-Based Hydrogel

Supramolecular hydrogels represent a solid three-dimensional structure shaped involving non-covalent bonds like hydrogen bond, hydrophobic interaction, and cation–π and π–π interactions. While chemical crosslinkers are responsible for stabilizing the hydrogel network of the chemical gels, the non-covalent interactions in supramolecular three-dimensional structure provide strength and stability through the formation of macromolecular polymer and three dimensional gel network.

Supramolecular hydrogels are produced from hydrophilic molecules. Stimuli-responsive supramolecular hydrogel can be made by incorporating some reversible bonds. Furthermore, such reversible supramolecular hydrogels also show self-healing properties and have enormous potential to contribute in drug delivery application.

The most widely used supramolecular complexes include the inclusion complexes formed by the interaction of cyclodextrin and poly(alkylene oxide) polymers like PEO and PPO (Hoare and Kohane 2008). These are capable of forming reversible hydrogels which are easily injectable and therefore utilized to prepare controlled release injectable formulations. Combination of complexation with hydrophobic interaction has resulted in a stronger, denser, and/or more stable hydrogel network. For example, a self assembled supramolecular structure comprising of cyclodextrin and a biodegradable poly(ethylene oxide)–poly[(R)-3-hydroxybutyrate]–poly(ethylene oxide) (PEO–PHB–PEO) triblock copolymer

was reported by many researchers. The collaborative outcome of complexation of PEO segments with a-cyclodextrin and the hydrophobic interaction between PHB blocks give rise to the development of the supramolecular hydrogel with a robust macromolecular network (Saboktakin and Tabatabaei 2015). Table 4 summarizes various types of supramolecular hydrogel and their compositions.

3.3 Covalently/Chemically Crosslinked Hydrogels

Chemical crosslinking involves the use of a crosslinking agent to link two polymer chains or grafting of monomers on the backbone of the polymers. The functional groups present on the natural or synthetic polymers can react with the crosslinkers (such as glutaraldehyde, adipic acid dihydrazide) resulting in the crosslinking of chains and formation of hydrogel.

There are a number of approaches stated in the literature to form permanent chemical hydrogels. These methods are as illustrated in Fig. 3 and exemplified using chitosan. The major chemical methods employed are use of crosslinkers, grafting and radiation in solid and/or aqueous state. Other chemical crosslinking methods such as IPN (polymerize a monomer contained by additional solid polymer to form interpenetrating network structure) and hydrophobic interactions (including a polar hydrophilic group by hydrolysis or oxidation followed by covalent crosslinking) are also employed to achieve chemically crosslinked permanent hydrogels.

3.3.1 Crosslinking by Radical Polymerization

Low molecular weight monomers (vinyl and acrylic acid) can be crosslinked in the presence of crosslinking agents. It proceeds through three processes, viz. initiation, propagation, and termination. Initiation of the reaction generates a free radical active site, which attaches monomers in a chain-like manner. Wichterle and Lim (1960) first described hydrogel based on poly(2-hydroxyethyl methacrylate) (pHEMA) polymer, and it is one of the commonly studied hydrogel system. This hydrogel is synthesized by polymerization of hydroxyethyl methacrylate (HEMA) in the presence of crosslinking agent like ethylene glycol dimethacrylate. This approach is used to synthesize pH- or a temperature-sensitive hydrogel by integrating methacrylic acid or *N*-isopropylacrylamide, respectively, in the vicinity of suitable crosslinking agents. For example, PVA has been crosslinked chemically with monomer (methacrylic acid) in aqueous medium using ethylene glycol dimethacrylate (EGDMA) as crosslinking agent and benzoyl peroxide as a reaction initiator to produce pH-sensitive hydrogel which is a promising delivery system for colonic delivery of 5-fluorouracil in colorectal cancer (Minhas et al. 2013). Various water soluble polymers of synthetic, semi-synthetic, and natural origin have been used for the design of hydrogels using this route. These water-soluble polymers

Table 4 Types and properties of supramolecular hydrogels for drug delivery

S.No	Hydrogel Type	Polymer/ Mechanism of formation	Properties	Ref
1.	Supramolecular hydrogels as intrarenal drug delivery systems (UPy-modified prepolymers and UPy-functionalized peptides)	introduction of UPy-moieties on poly (ethylene glycol) (PEG) prepolymers enzyme-triggered drug release mechanism via the degradation of encapsulated hydrogels.	The drug release of occurs at physiological temperature. the drug release rate can be controlled by by changing the enzyme concentration and/or temperature.	Dolman et al. (2010)
2.	Injectable systems based on supramolecular hydrogels	in situgel-forming system composed of hyaluronic acid-tyramine (HA-Tyr) conjugates using a peroxidase-catalyzed oxidation (horseradish peroxidase) reaction.	Do not need surgical removal after treatment. No toxic molecules is formed on degradation in the body, Excellent biocompatibility and 2. biodegradability formation of hydrogels without any inflammation andredundant reactions, Prolonged and sustained drug release can be achieved bycontrolling the hydrogel degradation, can be programmed throughthe design of the cross-link density	Vemula et al. (2006)
3.	Supramolecular hydrogels based on nonsteroidalanti-inflammatory drugs and small peptides.	The covalent linkage of Phe–Phe and NSAIDs results in conjugates that self-assemble in water to form molecular nanofibers as the matrices of hydrogels	better selectivity toward their targets. peptides consisting of d-amino acids facilitate to protect the activities of NSAIDs. Offers a new molecular hydrogels for topical use.	
4.	Novel supramolecular hydrogels based on Cyclodextrin and copolymers	Hydrogel self-assembled between a-cyclodextrin and a biodegradablepoly (ethylene oxide)–poly[(R)-3-hydroxybutyrate]–poly(ethyleneoxide) (PEO–PHB–PEO) triblock copolymer The cooperation effect of complexation of PEO segments with a-cyclodextrin and the hydrophobic interaction between PHBblocks resulted in the formation of the supramolecular hydrogel with a strong macromolecular network	relatively long term sustained controlled release of drugs can be attained thixotropic and reversible	Takashima et al. (2012)

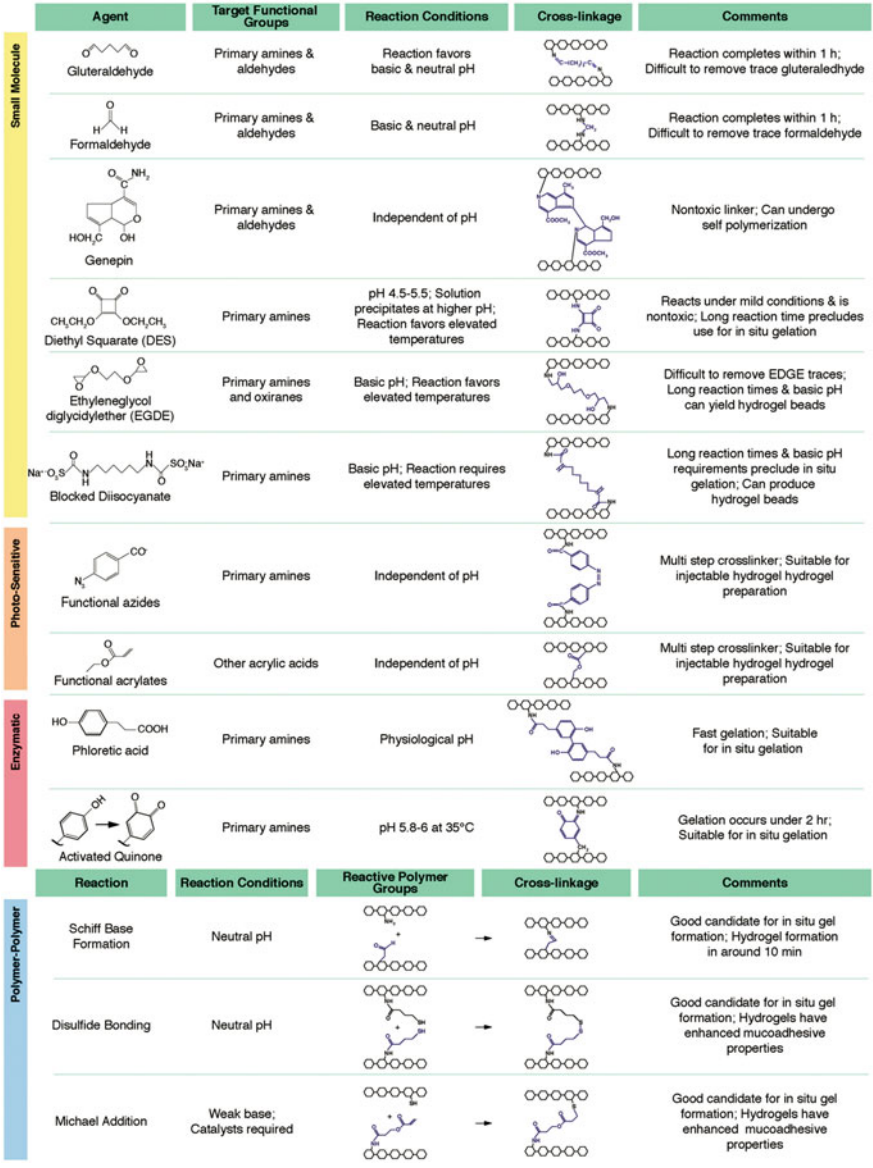


Fig. 3 Various crosslinking groups and structures in covalently crosslinked chitosan hydrogels

after being derivitized with polymerizable groups can be crosslinked into hydrogels by free radical polymerization, for example dextran, albumin, (hydroxyethyl) starch, poly-aspartamide, poly(vinyl alcohol), and hyaluronic acid. Among these polymers, dextran is most widely exploited for hydrogel preparation and explored for the delivery of drugs, proteins, and imaging agents (Mehvar 2000). In addition,

dextran-based hydrogels are under research as a colon delivery system due to the existence of dextranase in the colon. Polymerizable dextran is prepared by reacting aqueous solution of dextran with glyce dylacrylate to produce acryl dextran. Acryl dextran forms a hydrogel following free radical polymerization in the presence of *N*,*N*,*N*′*N*′-tetramethylene-diamine and ammonium peroxydisulphate as an initiator. Polyacryldextran hydrogel-based microspheres are capable of immobilizing enzyme efficiently with full retention of their activity.

3.3.2 Crosslinking by Complementary Groups Chemical Reaction

Hydrophilic groups, namely NH_2, COOH and OH present on the hydrophilic polymers may be used for the hydrogel development. Covalent linkages among polymer chains occurs through the reactions, for example an amine-carboxylic acid or an isocyanate-OH/NH_2 reaction or Schiff base formation, which may be used to recognize covalent linkages between polymer chains.

3.3.3 Crosslinking with Aldehydes

–OH groups carrying hydrophilic polymers, e.g. polyvinyl alcohol. may be crosslinked through glutaraldehyde (Zu et al. 2012). Conditions are applied (like low pH, methanol added as a quencher, high temperature) to establish crosslinking are well defined and required to be maintained carefully. However, polymer bearing amine functional group can be crosslinked even under mild conditions through the formation of intermediate Schiff base. This approach is used to form protein -based hydrogels like, gelatin and albumin and the amine containing polysaccharides.

3.3.4 By Addition Reactions

Water soluble polymer can be crosslinked to form hydrogels using bis or higher functional crosslinking agents such as divinylsulfone and 1,6-hexanedibromide through an addition reaction. The properties of hydrogel network can be simply customized to attain the desired characters by changing the concentration of crosslinking agent and the dissolved polymer. In this approach, the crosslinking reactions are performed in organic solvent since water may react with the crosslinking molecules if used. This increases the cost of synthesis and also the toxicity issues thereby, reducing the safety margin for in vivo use. In addition, the crosslinking agents are highly toxic which require the complete removal of unreacted reagent. The drug is loaded after the hydrogel preparation and reagent extraction which results in first-order drug release profile along with the narrow duration of the release and therefore renders such hydrogels unsuitable specifically for sustained and controlled release formulation.

3.3.5 By Condensation Reactions

Condensation reactions among hydroxyl (–OH) groups or amine (–NH2) with carboxyl group (–COOH) result in the formation of polyesters and polyamides, respectively. These reactions are used for the synthesis of hydrogel from water-soluble polymers. One of the most efficient and widely used crosslinking agents to crosslink water-soluble polymers with amide bonds is *N*,*N*-(3-imethylaminopropyl)-*N*-ethyl carbodiimide (EDC). This reaction involves the addition of *N*-hydroxysuccinimide (NHS) to suppress the side reactions and increase the density and yield of hydrogel (Kuijpers et al. 2000).

These hydrogels have potentials to deliver active pharmaceutical agent as well as protein-based therapeutics over a prolonged period of time. For example, hydrogel loaded with lysozyme could release the enzyme for 2 days both in vitro and in vivo. The loading capacity of the these hydrogels can be increased by incorporating negatively charged agent; for example, addition of negatively charged polysaccharide chondroitin sulphate augmented the loading capability of protein in hydrogel besides retarding the release of the protein from hydrogel due to electrostatic interactions between the cationic protein and anionic polysaccharide.

Another method known as Passerini and Ugi condensation reaction is also used to prepare polysaccharides-based hydrogels (de Nooy et al. 2000). Passerini condensation employs a reaction between carboxylic acid and an aldehyde or ketone with an isocyanide to yield an α-(acryloxy). These hydrogels are degradable at ambient temperature and at pH 9.5 because of the existence of ester bond in the crosslinks. Ugi condensation is extension of Passerini approach, in which amine is added to the above reaction mixture to finally yield α-(acylamino) amide. These are more stable than Passerinin hydrogel under similar conditions due to amide bond in crosslinks. The advantage of these methods is that the reaction can be supported out at room temperature and in water at slightly acidic pH.

3.4 Crosslinking by High Energy Irradiation

Unsaturated substances can be polymerized by employing high energy radiations like gamma and electron beams (Amin 2012). Hydrophilic polymers which are derivatized with vinyl group can be transformed into hydrogels by means of high energy radiation. Alternatively, radiation-induced polymerization can also be used to synthesize hydrogel from a fusion of a monofunctional acrylate (e.g. acryloyl-L-proline methyl ester) and an appropriate crosslinker (Caliceti et al. 2001).

High energy radiation can also induce formation of hydrogel from water-soluble polymer through free radical formation which do not require the presence of vinyl groups. Free radicals are formed from the polymeric chain (e.g. haemolytic fission of C–H bond) when the aqueous polymeric solution is irradiated. Additionally,

hydroxyl radicals are also generated by radiolysis of water molecules which can attack polymer chains resulting in the formation of macroradicals (Peppas and Mikos 1986). The macroradicals react with the polymeric chain functionality through covalent bond formation resulting in crosslinked structure. Radiation is usually accomplished in an inert (nitrogen, argon) atmosphere to avoid the generated macroradicals to react with oxygen. Well-acknowledged examples of polymers which can be crosslinked with high energy irradiation are poly(vinyl alcohol), poly (ethylene glycol), and poly(acrylic acid).

The characteristics of the gels, particularly swelling and permeability properties, are reliant on the amount of the polymer used and dose of radiation employed: In general, the crosslinking density rises with the increase in polymer concentration and amount of radiation dose. The major benefit of preparing hydrogel by means of radiation-induced crosslinking is that this synthesis can be used in presence of water under mild conditions (room temperature and physiological pH). In addition, the use of toxic crosslinking agents is not required. Nevertheless, the loading of biologically active compound is to be done after the formation of hydrogel to avoid radiation-induced damage to the pharmaceutically active substance and/or possible interaction between the radical and the therapeutic moiety. The gel formed from PEG and PVA are non-biodegradable due to presence of C–C bonds in the crosslinks.

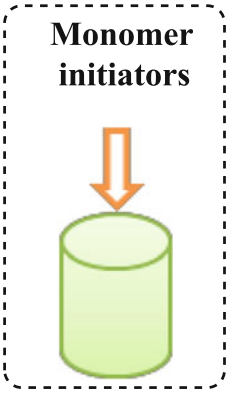
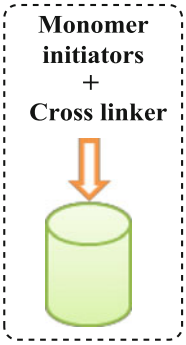
4 Polymerization Techniques in Hydrogel Synthesis

Hydrogels can be prepared from monomers or polymers of synthetic or natural polymers by using techniques which are capable of crosslinking these units through polymerization. The various synthesis polymerization techniques reported for the synthesis biomedical hydrogels are described in Table 5 (Ahmed 2015; Sahu et al. 2012).

5 Characterization of Hydrogel

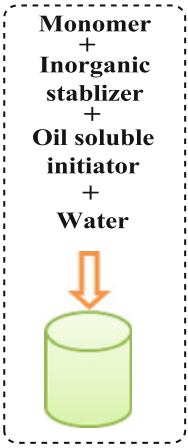
Mostly, hydrogels are characterized for their various parameters such as morphological characterization, crystalline/thermal behaviour, morphological integrity, rheological, swelling, mechanical and biochemical properties, and in vitro release behaviour. The important features of hydrogels are summarized in Table 6 (Sahu et al. 2012; Chauhan et al. 2012; Rowley et al. 1999; Khare and Peppas 1995).

Table 5 Various polymerization techniques employed in hydrogel formation

Name of technique	Description	Advantages	Disadvantages
Bulkpolymerization 	It is the simplest technique whichinvolves only monomer and monomer-soluble initiators. The choice of a suitable initiator depends upon the type of monomers and solvents being used. In this method hydrogels can be prepared by using one ormore types of monomers andowing to the high concentration of monomer,the high degree of polymerization and high rate polymerizationoccurs. However,The viscosity of the system is low initially to allow ready polymerizationreaction andviscosityincreases markedly with the conversions. In this polymerization process monomers make a homogeneous hydrogel system produces a very rigid, transparent, glassy polymer matrix. This glassy polymer matrix when put in contact with aqueous medium,swells to become soft and flexible gel.*Ex.* vinyl monomers based hydrogels (Suda 2007).	❖ Simple method ❖ Minimum chance to contamination	❖ Irregular polymerization ❖ An increase temp will increase the polymerization rate ❖ Near the end of polymerization, the viscosity is very high and difficult to control the rate
Cross-linking/Solution polymerization 	In cross-linking method, the ionicor neutral monomers are mixed with or without cross-linking agents. It requires the correct selection of the solvents. Both the initiator and monomer be soluble in each other and that the solvent are suitablefor boiling points, regarding the solvent-removal steps.The polymerization is initiated thermally byUV-irradiation or by a redox initiator system. The solvent is employed to lower the viscosity of	❖ Solvent reduces viscosity, making processing easier ❖ Thermal control is easier than in the bulk	❖ Reduce monomer concentration which results in decreasing the rate ofthe reaction and the degree of polymerization ❖ Difficult to remove solvent from final form, causing degradation of bulkproperties ❖ Not suitable for dry polymers

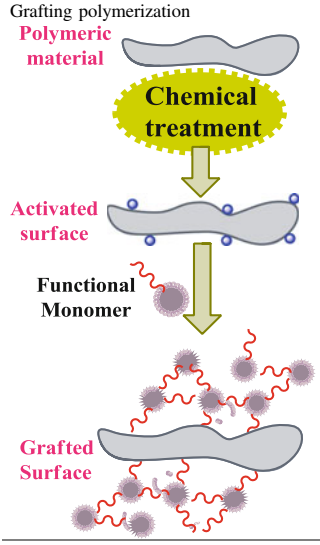
(continued)

Table 5 (continued)

Name of technique	Description	Advantages	Disadvantages
	the reaction thus help in the heat transfer and reduceauto accelerationis the major advantage ofthis method over bulkpolymerization.In this technique, the prepared need to be washed hydrogels formulation with distilled/deionized waterto remove the cross-linking agents,monomers, oligomers, initiators, and other impurities. Various cross-linking techniques such as ionic interactions, protein interaction, hydrogen bonds, crystallization, and crosslinking by hydrophobic interactions have been investigated for the synthesis of physically cross link gels (Ganji and Farahan 2009; Stringer and Peppas 1996).		
Suspension polymerization or inverse-suspension polymerization 	Suspension polymerization is an advantageous method sincethe products are obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water(O/W), the polymerization is referred to as "inverse suspension".In this polymerization consists of an aqueous system withmonomer as a dispersed phase and results in polymer as a dispersedsolid phaseIn this technique, the monomers and initiator are dispersedin the hydrocarbon phase as a homogenous mixture. The dispersion is	❖ Polymerization to high conversion ❖ Low viscosity due to the suspension ❖ Easy heat removal due to the high heat capacity of water ❖ Excellent heat transfer because of the presence of the solvent ❖ Solvent cost and recovery operation are cheap	❖ Contamination by the presence of suspension and other ❖ Must separate and purify polymer, or accept contaminatedproduct ❖ Reactor cost may higher than the solution cost

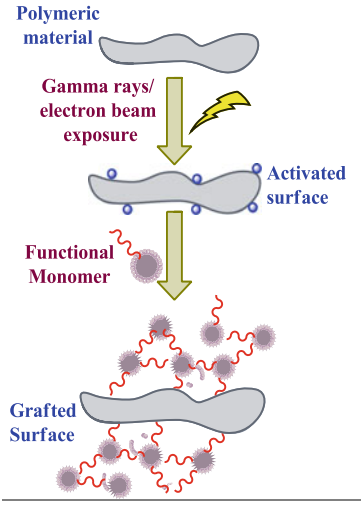
(continued)

Table 5 (continued)

Name of technique	Description	Advantages	Disadvantages
	thermodynamically unstable and requires bothcontinuous agitation and addition of a low hydrophilic–lipophilic-balance (HLB) suspending agent.Near the end of polymerization, the particles are hardened, are the bead or pearl shaped polymers recovered by filtration, and followed by washing step (Watanabe et al. 1993; Hunkeler 1992).		
Grafting polymerization 	This involves the polymerization of a monomer on the backbone of a preformedpolymer. In this process polymer chains are activated bythe action of chemical reagents, or highenergy radiation treatment. This technique involves the generation of free radicals onto a stronger support surface and then polymerizingmonomers directly onto it as a result a chain of monomers are covalently bonded to the support (Tong and Zhang 2005; Said et al. 2004).	❖ To improve the mechanical properties	
Polymerization by irradiation	In this techniqueionizing high energy radiations/ electron beams like gamma rays has been used to initiate the free radicalspolymerization of polymer on the backbone.Also, radiolysis of water molecules results in the generation of hydroxyl	❖ Initiator-free hydrogels and relatively pure	

(continued)

Table 5 (continued)

Name of technique	Description	Advantages	Disadvantages
	radicals, whichalso attack the polymer chains, resulting in the formation of macro-radicals. Recombination of the macro-radicals on different chainsresults in the formation of covalent bonds, so finally, across-linked structure is formed. Some examples of polymers cross-linked by the radiation method are poly(acrylic acid), poly(ethylene glycol), poly (vinyl alcohol)etc (Enas et al. 2008; Das et al. 2006)		

6 Smart Hydrogels

Stimuli-responsive hydrogels are of great potential with a number of applications. Some environmental variations like increased temperature and low pH are found in the body in diseased conditions, and due to this reason, either temperature-responsive and/or pH-responsive hydrogels can be used for site-specific controlled drug delivery. Hydrogels can also respond to specific molecules like antigen and glucose thus find applications in triggered drug delivery and as biosensors (Leda 2015). Apart from temperature and pH, hydrogels may also respond to light, pressure, and electrical variation, thereby giving rise to light-sensitive, pressure-responsive, and electro-sensitive hydrogels, respectively. The disadvantage associated with these stimuli-responsive hydrogels is that they respond very slowly, and to overcome this drawback, nowadays thinner and smaller hydrogels are formulated. Different stimuli-responsive hydrogels with their drug delivery applications are discussed as follows.

6.1 Temperature-Sensitive Hydrogel

Temperature-sensitive hydrogels are most likely and the most frequently studied group of stimuli-responsive hydrogel networks in drug delivery research (Qiu and Park 2012). A number of polymers show temperature-responsive phase transition

Table 6 Characterization parameters of hydrogel

S. No.	Parameter	Description
1.	Morphological characterization	In general, morphological evaluations of hydrogels performed by using equipment like stereomicroscope. However, Scanning electron microscope (FE-SEM) and atomic force microscopic (AFM) methodsareextensively used as a visualizing aid and to ensure thetexture,real microstructure, composition, surface topographyand other properties such as electrical conductivity of hydrogels. These are the powerful techniques widely used to capture the characteristic 'network' structure in hydrogels (Szepes et al. 2008).
2	Crystalline / Thermal behavior	This analysis is quite a popular study for the morphological characterizationof hydrogels. This analysis helps to understand whether the polymers in hydrogel retain their crystalline structure or they get deformed during the fabricationprocessing or pressurization process. The retention of crystalline structure or their deformation during pressurization has played a vital role.The estimation of amorphous or crystalline characteristics or determines the pattern of the arrangement of layers in hydrogelis studied by diffraction analysis techniques. X-ray diffraction (XRD), Differential scanning calorimetry (DSC) and Thermo Gravimetric Analysis (TGA) techniques are commonly used for the evaluation of thermal or crystalline behavior which is related with stabilityof the hydrogels(Yu and Xiao 2008)
3.	Impurities/ Morphological integrity	By using spectroscopic techniques,it is an easy way to identify the presence of functional groups in a molecule which is present in hydrogels. Fourier Transform Infrared Spectroscopy (FTIR) is a useful technique for identifying chemical structure or chemical characterization of a substance and to confirm the identity of a pure compound or to detect the presence of certain impurities.Any change in the morphological integrity of hydrogels structure changes their IR absorption spectra due to stretching and O-H vibration. The stretching or bending vibrations are basically responsible for the changes in IR absorption spectraThis technique is widely used to investigate the structural arrangement in hydrogel by comparison with the starting materials (Mansur et al. 2004).
4.	Rheology	The rheological properties of hydrogels are important parameter and basically dependent on the types of structure such as cross-links, entanglement and association present in the system. Hydrogel formulations are evaluated for viscosity under constant temperature (usually 4°C) by using cone plate type viscometer and also determined by the simple equation of determining the angle of repose through which height and length is determined [Shultz et al., 2008]
6.	Swelling behavior	Swelling or rate of swelling is the most important characteristic and favorable propertyof the hydrogel system.It is ability to swell or water holding capacity, when put in contact with a compatible medium.It is determined by several physicochemical factorsparticularly the sample/particle size, porosity extentand the type of the porous structure. The time

(continued)

Table 6 (continued)

S. No.	Parameter	Description
		and degree of swelling are significant because these effect on the release kinetic of loaded bioactive(s) from swelling controlled systems.The hydrophobic / hydrophilic balance of thehydrogels, the degree of cross-linking, and especially,the degree of ionization and its interaction withcounterions are the important parameters whichcontrol the equilibrium swelling, dimensional changeand the release patterns of drugs from these carriers[18].Hence, in the past decades various mathematical modelshavegained considerable attentionfor predictability of swelling behavior.In case of polymeric hydrogels,the polar hydrophilic groups are first to be hydrated upon contact withaqueous medium or medium of specific pH to know the swellability of this polymeric network.These polymers show increase in dimensions related to swelling. The hydrogels swell in water to form the polymeric network. The formation of this polymeric network is responsible for the morphological characterization of drug. Polymers are characterized by light scattering and size exclusion chromatography,viscosity methods, osmometryetc. (Ganji and Farahan 2009; Yin et al. 2002, 2008)
7.	Mechanical properties	Mechanical properties of the hydrogelsis importantbecause the hydrogels couldbe used in various biomedical applications such as wound dressing material, ligament and tendon repair, tissue engineering as in cartilagereplacement and matrix for drugdelivery, which need hydrogels with different properties. FDA provides strict guidelines for the samedepending upon the type of application. As for example, adrug delivery device should maintain its integrity duringthe lifetime of the application (Mi et al., 2001; Toshikazu et al. 1992)
8.	Biocompatible properties	Biocompatibility is also most important characteristic property required by the hydrogel. Biocompatibility means compatibility with the body immune system and its degradation products should be nontoxic. Ideally they should be metabolized into harmless products or can be excreted by the renal filtration process. Generally, hydrogels possess a good biocompatibility since their hydrophilic surface has a low interfacial free energy when in contact with body fluids, which results in a low tendency for proteins and cells to adhere to these surfaces. Moreover, the soft and rubbery nature of hydrogels minimizes irritation to surrounding tissue (De Groot et al. 2001; Anderson & Langone, 1999; Smetana 1993).
3.	*In-vitro* release profile	Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application. The *in- vitro*diffraction study is quite popular for studying the release profile of hydrogel. One that basis the bioequivalencestudy is carried out to estimate the release of dosage forms. The parameters are matched with the standard plot so that the equivalence between the drug solutions is carried out (Szepes et al. 2008; Yu and Xiao 2008).

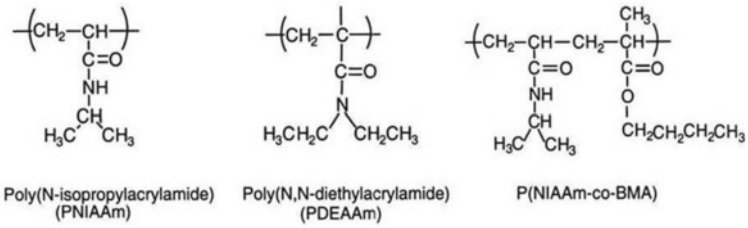


Fig. 4 Structures of some temperature-sensitive polymers

behaviour. The assemblies of some of those polymers are shown in Fig. 4. The presence of hydrophobic moieties like alkyl group is the most common characteristic of temperature-sensitive polymers. The **lower critical solution temperature** (**LCST**) represents that critical temperature below which the all the components of a mixture are miscible at every compositions. LCST is an important factor while selecting polymers for temperature-dependent hydrogels. Generally, polymers with LCST ranging from 28 to 32 °C are considered as good candidate to formulate temperature-sensitive drug delivery systems. Water-soluble polymers shows a proportional relation between solubility and temperature; i.e. as the temperature of the solvent is increased, the solubility of hydrophilic polymers also increases. Conversely, polymers possessing LCST follow inverse relation between temperature and aqueous solubility. Hydrogels comprising of such polymers undergo shrinkage as the temperature rises above LCST. The polymers chains of LCST polymers are linked by temperately hydrophobic groups or contain a mixture of hydrophilic and hydrophobic segments. If the chains are linked with severely hydrophobic groups, then the polymer will lose water solubility. As the temperature is lowered, the aqueous solubility of polymer increases because hydrogen bonding between hydrophilic segments and water molecules dominates the hydrophobic interaction. But, as the temperature increases the hydrophobic interactions among hydrophobic segments become stronger, the overall net effect leads to shrinkage of polymer to form hydrogel through strong hydrophobic interactions between segments of the chain. In general, increase in the hydrophobic constituents of the polymer chain leads to lowering of LCST (Schild 1992).

Different types of block copolymers made of poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO) also display an opposite temperature-sensitive property. The LCST of these polymers lies close to the physiological temperature, and hence, they are widely employed for the formulation of sol–gel-conversion-based controlled drug delivery systems.

Other temperature-sensitive polymers include poly (*N*-isopropylacrylamide) (PNIPAM) which is perhaps the most broadly used temperature-responsive polymer. Another example of such polymer which is widely employed as gel-sol system in vivo includes poly(*N*,*N*-diethylacrylamide (PDEAM) because of its lower critical solution temperature (LCST) in the range of 25–32 °C, which is close to the body

temperature. The LCST of the polymers can be modified by adding other monomers; for example, copolymers of NIPAAm can be prepared using additional monomers, e.g. butylmethacrylate (BMA), to adjust the LCST (Cai and Suo 2011).

6.1.1 Properties of Temperature-Sensitive Hydrogels

Temperature-sensitive hydrogels can experience sol–gel phase transitions, alternative to the typical swelling–shrinking transitions if the polymer chains in hydrogels are non-covalently crosslinked. These thermally reversible gels with inverse temperature dependence are sol at elevated temperatures. Polymers that express this kind of behaviour are block copolymers of PEO and PPO.

Alternatively, the temperature-responsive hydrogels can also be prepared by using such crosslinking agents that possess temperature sensitivity.

Water soluble artificial polymer and a distinct protein-folding motif, the coiled coil were used to form a hybrid hydrogel system (Wang et al. 1999). The hydrogel experienced temperature-induced folding owing to the cooperative conformational shift. Incorporating temperature sensitivity through temperature-sensitive crosslinking agents provides a innovative platform in assembling temperature-sensitive hydrogels-based drug delivery systems.

6.1.2 Negatively Thermosensitive Drug Release Systems

Negatively thermo-responsive hydrogels are those polymers whose volume will decrease tends to increase in the temperature. Negatively responsive hydrogels can liberate encapsulated substances while shrinking with an increase of the temperature.

The examples of such hydrogels include crosslinked P(NIPAAm–co-BMA) hydrogels (Okuyama et al. 1993) and interpenetrating polymer networks (IPNs) of P(NIPAAm) and poly(tetra methylene ether glycol) (PTMEG). The mechanical strength of the NIPAAm gel can be increased by integrating hydrophobic comonomer BMA (Zhang et al. 2009). These hydrogel matrices are used to generate on–off drug release profile with varying temperature conditions; for example, the topically used indomethacin loaded hydrogel showed drug release (on) at low temperature while off at higher temperature. A dense and relatively impermeable layer of gel (designated as skin type barrier) was formed due to sudden temperature change resulting from faster collapse of the surface as compared to the interior part of the gel. This external shrinking was regulated by the length of the methacrylate alkyl side-chain, i.e. the hydrophobicity of the comonomer (Yoshida et al. 1991). The results, moreover, proposed that the drug in the polymeric matrices diffused from the inside to the surface during the off state even when no drug release was observed.

Temperature-sensitive hydrogels can also be positioned within a firm capsule bearing holes or apertures. The on–off release is accomplished by the flexible bulk variation of temperature-sensitive hydrogels (Dinarvand and Emanuele 1995; Gutowska et al. 1997). Such a device is named as a squeezing hydrogel as the drug release is affected by the dimensions and bulk volume of the hydrogel.

Temperature sensitive hydrogels can be strengthened by inserting in them a classified rigid matrix or by grafting them to the surface of rigid membranes. A composite membrane was prepared by dispersing PNIPAAm hydrogel microparticles into a crosslinked gelatin matrix (Chun and Kim 1996). The release of a model drug, 4-acetamidophen, was studied and was found to be dependent on the temperature which determined the swelling status of the PNIPAAm hydrogel microparticles in the microchannels of the membrane. A similar approach was used to develop a reservoir-type microcapsule drug delivery system by encapsulating the drug core with ethylcellulose containing nano-sized PNIPAAm hydrogel particles (Ichikawa and Fukumori 2000). For making stable thermally controlled on–off devices, PNIPAAm hydrogel can be grafted onto the entire surface of a rigid porous polymer membrane.

6.1.3 Positive Thermosensitive Drug Release Systems

Hydrogels formed by IPNs display positive thermosensitive effect which means that they swell at high temperature and shrink on lowering the temperature, for example IPNs of poly (acrylic acid) and polyacrylamide (PAAm) or P(AAm–co-BMA). The swelling behaviour of these hydrogels was reversible depending on the temperature which also resulted in concurrent reversible release of the drug like ketoprofen from that formulated monolithic system.

6.1.4 Thermo-Reversible Gels

Pluronics® and Tetronics® are the most popular form of thermo-reversible gels. Thermo-reversible hydrogels are not ideal for parenteral application since they are non-biodegradable. However, they can be converted to biodegradable form by replacing the PPO segment of PEO–PPO–PEO block copolymers by a biodegradable poly (L-lactic acid) segment (Jeong et al. 1999; Jeong et al. 2000).

The molecular architecture does not remain restricted to the A–B–A-type block copolymer, but can be extended into three-dimensional, hyper-branched structures, such as a star-shaped assembly. Gels with varying LCST values can be achieved by using appropriate combinations of molecular weight and polymer architecture. The hydrogel is formed by introducing the polymer loaded with drug (hydrophilic or hydrophobic) in aqueous solution, and the resulting hydrogel exhibits generally a first-order and S-shaped drug release, respectively.

6.2 pH-Sensitive Hydrogels

pH-sensitive polymers usually comprised of polyelectrolytes that either release or accept protons in response to change in the surrounding pH. They contain a large number of ionizable groups that undergo pH-dependent ionization. Poly (*N*,*N*′-diethylaminoethyl methacrylate) (PDEAEM) gets ionized at low pH, while poly (acrylic acid) (PAA) gets ionized at high pH. While the cationic polyelectrolytes, such as PDEAEM, display rapid dissolution and higher swelling when crosslinked at low pH owing to ionization of the polyanions, such as PAA, and undergo dissolution at high pH.

6.2.1 Properties of pH-Sensitive Hydrogels

Hydrogels prepared from crosslinked poly-electrolytes demonstrate vast differences in swelling properties in response to the changing pH of the environment. The pendant acidic or basic groups arranged on the polyelectrolytes undergo ionization parallel to acidic or basic groups of monoacids or monobases. However, the electrostatic forces applied by the neighbouring ionized groups render the ionization of polyelectrolytes difficult.

Polyelectrolyte polymers can show a swelling behaviour far better than the nonelectrolytic polymers because of the existence of ionizable groups arranged along polymer length. The reason behind the swelling of the polyelectrolyte based hydrogels is the presence of electrostatic repulsion between the charges that lie on the polymer chain. The extent of swelling depends on the magnitude of electrostatic repulsion under any condition like pH, ionic strength, and type of counterions present. The pH responsiveness and swelling can be further modified by adding neutral comonomers of different types. These monomers provide varying hydrophobic character to the polymer chain which results in different pH-responsive behaviour. Examples of such monomers include maleic anhydride, 2-hydroxyethyl methacrylate, and methyl methacrylate.

6.2.2 Applications of pH-Sensitive Hydrogels

Controlled Drug Delivery

pH-sensitive hydrogels are often used for developing controlled release formulations for oral administration because of varying pH conditions present in the gastrointestinal tract. The varying GIT pH range starting from neutral pH of mouth to acidic pH of the stomach to the alkaline pH of the intestine is exploited to elicit pH-dependent behaviour of polyelectrolyte hydrogels. The polycationic-based

hydrogels show minimal swelling at neutral pH, and hence, it is used for the delivery of offensive drugs in the neutral pH of mouth. Semi-IPNs made from polycationic hydrogels are employed for the delivery of drug in the stomach.

For example, semi-IPN of crosslinked chitosan and PEO presented more swelling when exposed to the acidic conditions which is ideal for localized delivery of antibiotics, such as amoxicillin and metronidazole, in the stomach for the management of Helicobacter pylori infection.

Furthermore, hydrogels which are functional at neutral pH are formulated using PAA or PMA. These hydrogels are used for delivering drug at neutral pH (Khare and Peppas 1993). Hydrogels can also be used for preparing enzyme sensitive drug delivery systems by incorporating crosslinkers through such bonds which can be cleaved by biological enzymes. These hydrogels are capable of providing localized or targeted drug delivery owing to the cleavage of bond in the environment (or tissue) where the enzyme responsible for bond cleavage is present. For example, for colon-specific drug delivery, drug loaded hydrogel is prepared by crosslinking polyanion like PAA by using azoaromatic crosslinkers. The drug is released in colon after the cleavage of azoaromatic bond by the azoreductase present in the microbial flora of the intestine (Fig. 5). These hydrogels show slower rate of swelling, and hence, drug release is also slow and minimal.

Depending upon the need of the therapy and site of drug release, the polymer composition and the type of crosslinker can be changed; for example, terpolymer-based hydrogels comprising of NIPAAm, acrylic acid, and 2-hydroxyethyl methacrylate were synthesized for the pulsatile delivery of streptokinase and

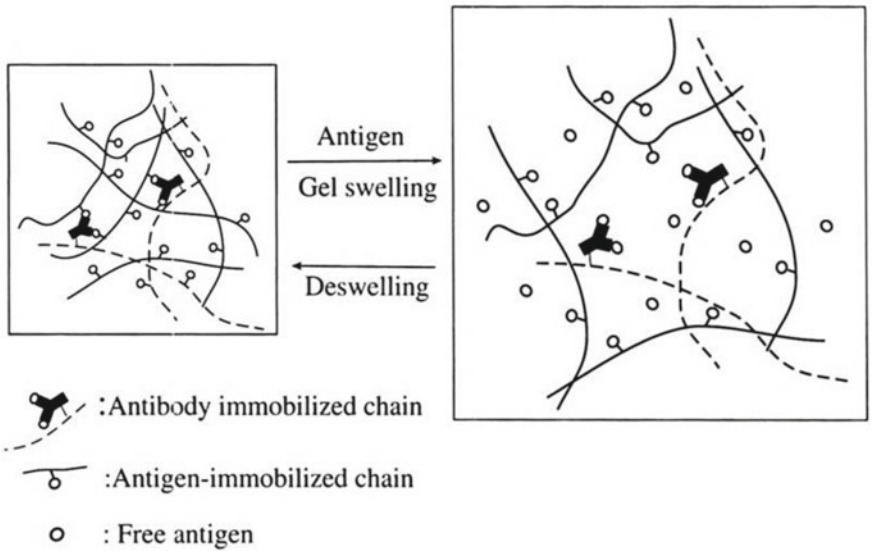


Fig. 5 Swelling of an antigen–antibody-based semi-IPN hydrogel with the amount of free antigen

heparin based on the progressive pH and temperature variations (Vakkalanka et al. 1996; Brazel and Peppas 1996).

6.3 Specific Ion-Sensitive Hydrogels

Salt concentration can affect the swelling behaviour of a few hydrogels. A nonionic poly (*N*-isopropylacrylamide) hydrogel showed a strident volume phase transition at a acute concentration of sodium chloride in aqueous solution. Below the LCST, the amount of water present in the hydrogel is dependent on the concentration of sodium chloride. The gel collapses suddenly at a critical concentration of sodium chloride which too is found to be dependent on the temperature. Rise in temperatures results into a equivalent drop in the critical concentration of sodium chloride.

A number of salts are tested, but none of them show such behaviour outside the salting-out region. However, sodium ions form the common part of all the salt taken under investigation, and hence, it is concluded that chloride ions perform a significant role in this phase transition. Although the mechanism of ion sensitivity is unknown, the LCST of the system was found to decrease on increasing the concentration of the chloride ions.

This exclusive phase transition behaviour could be applied for creating chloride ion-sensitive biosensors. The additional salts investigated for phase transition behaviour did not induce network collapse in the studied concentration range, and alternative theory known as ion pair and multiplet (ionomer effect) theory was suggested to clarify these interesting experimental outcomes.

6.4 Specific Antigen-Responsive Hydrogels

For certain biomedical applications, it is essentially required being beneficial to cultivate a material or device, which generates response to particular proteins present in the biological system. One such device based on sol–gel phase-reversible hydrogels was prepared using antigen–antibody interactions which rely on the similar concept as used for glucose-sensitive phase-reversible hydrogels. A semi-interpenetrating network hydrogel was prepared by fixing an antigen and a corresponding antibody to dissimilar polymer grids. The spontaneous crosslinking interaction between antigen and antibody gives rise to a three-dimensional hydrogel network.

Hydrogel swelling is activated in the presence of free antigens that strive with the polymer-bound antigen, resulting in a reduction in the crosslinking density (Fig. 6).

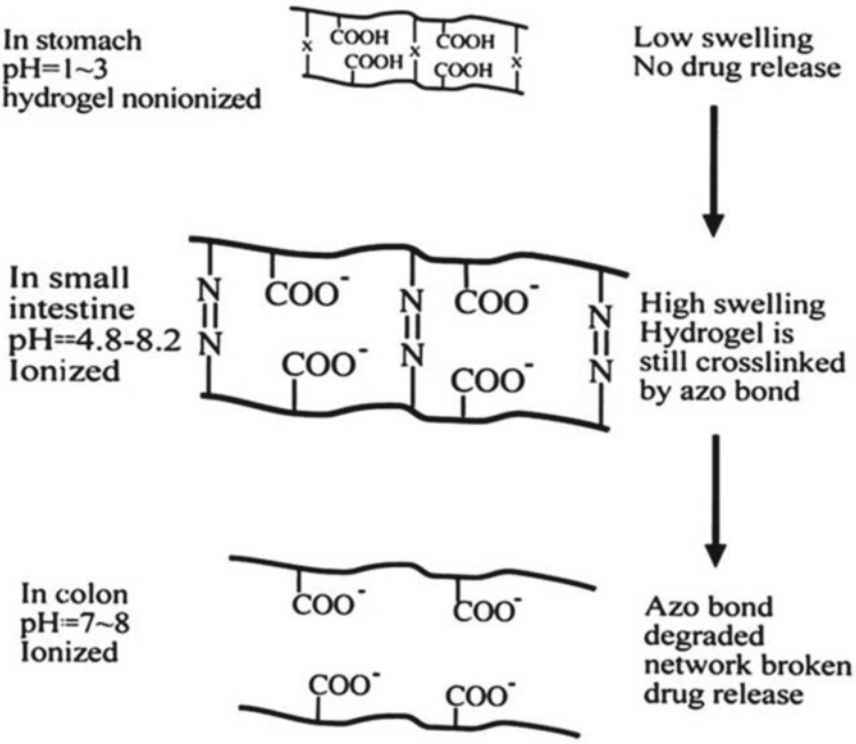


Fig. 6 Representation of oral colon-specific drug delivery based on biodegradable and pH-sensitive hydrogels. The azoaromatic groups in the crosslinks are indicated by –N=N–

7 Conclusion and Future Prospectives

Hydrogel-based drug delivery has emerged as a prospective drug delivery system owing to its distinctive characteristics, and a number of hydrogel-based patents are filed which are in different phase of clinical trials (Table 7). They are relatively biodegradable, elastic, flexible, soft, have minimum tendency to tissue adhesion, and possess high water content which makes them compatible to the living tissue, abolishing irritation to the tissue to which they are administered. However, the high water content of hydrogel results in poor mechanical strength which confers a major disadvantage for their use in drug delivery. Poor mechanical strength presents complexity in fabrication and administration and causes burst release with incomplete release of the active agent. To overcome the issue, hydrogel with improved mechanical strength is prepared through interpenetrating polymer network (IPN), but their synthesis requires the use of chemical crosslinkers which lead to toxicity following their degradation in body.

Table 7 Few patents available on hydrogel

S.No.	Patent no	Patent name	Comment	Inventor/s
1.	EP 0 524 718 A1	hydrogels suitable for transdermal iontophoretic delivery of drugs	polyurethane hydrogel matrices, can be employed as passive transdermal reservoirs.	Hahn Soonkap
2.	US Patent 8,409,606 B2	a system that provided the release of specific drugs through punctal plugs.	soft biodegradable covalently crosslinked hydrogels, high-swelling capability, remain in situ (in the punctum or lacrimal canal) with greater comfort for the patient.	Amarpreet S. Sawhney, Peter Jarrett, Michael Bassett, Charles Blizzard
4.	US Patent 5,514,380	Biodegradable hydrogel copolymer as drug delivery matrix	Synthesized from a hydrophilic soft block and a hydrophobic, biodegradable hard block.	Soo S. Song, Ho H. Kim, Yil W. Yi
5.	US Patent 8,383,153 B2	Poly(amidoamine) oligomer hydrogel for drug delivery and drug carrier using the same	temperature- and pH-sensitive hydrogel, avoid the initial burst drug release and was instead capable of providing a sustained release.	Doo Sung Lee, Bong Sup KIM, Minh Khanh Nguyen
6.	US Patent 7,066,904 B2.	Triggered release hydrogel drug delivery system	triggering release of a drug from a hydrogel polymer to tissue at a desired location of the body using a catheter, catheter allows the inclusion and the immobilisation of a significant quantity of drug into the hydrogel, which is released by a triggering agent or under different condition in the desired location.	Arthur Rosenthal, James J. Barry, Ronald Sahatjian
7.	US Patent application WO1998043615 A1	Method for oral delivery of proteinsA hydrogel matrix	made of poly (methacrylic acid-g-ethylene glycol) cross-linked with tetraethylene glycol dimethacrylate for oral delivery of different active ingredients, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) pH-sensitive swelling behavior	Nicholas A. Peppas, Anthony M. Lowman, Tsuneji Nagai, Mariko Moris

(continued)

Table 7 (continued)

S.No.	Patent no	Patent name	Comment	Inventor/s
8.	US 20070122362 A1	Hydrogel sheets and shapes for oral care	Can be modified to afford a denture fixative or can be ladened with a whitening agent or other loading materials for treatment of alveolitis or malodor, inter alia.	Martin Giniger, Matthew Spaid
9.	US 20150017105 A1	Anhydrous hydrogel composition and delivery system	mucoadhesive (oral compositions) or as topical agents, can be used deliver an active agent such as active pharmaceutical agents (API's), coagulants, fragrances, flavors, and other actives and excipients.	John Borja
10.	US 20020019369 A1	Injectable drug delivery systems with cyclodextrin-polymer based hydrogels	the composition may be injected subcutaneously, intramuscularly, intradermally, or intracranially.	Jun Li, Hanry Yu, Kam Leong
11.	US 20150366975 A1	Thermosensitive injectable hydrogel for drug delivery	Thermosensitive injectable hydrogel based on HA and a copolymer of polyethylene oxide (PEO) and polypropylene oxide (PPO), having a gel formation temperature from 30.degree. C. to 37.degree. C.	Hua-Jing Ho, Hsiu-O Sheu, Ming-Thau Shen, Shing Chuan Ho, Yuan Soon, Liu Jun-Jen
12.	WO 2001087276 A1	Hydrogel composition for transdermal drug delivery containing acrylate polymers like acrylic acid polymer, methacrylic acid polymer, alkyl acrylate polymer, alkyl methacrylate polymer or copolymers	enable both hydrophilic and lipophilic permeation enhancers to be applicable in the hydrogel composition in order to effectively control skin penetration of drugs.	Ho Chin Kim, Hye Jeong Yoon

(continued)

Table 7 (continued)

S.No.	Patent no	Patent name	Comment	Inventor/s
13.	US 8409606 B2	Drug delivery through hydrogel plugs	a punctal plug comprising a Dehydrated covalently crosslinked synthetic hydrophilic polymer dehydrated hydrogel having dimensions to pass through a puncta lacrimali which absorb physiological water to swell to at least 1 mm in cross-sectional width to conformably fit a canaliculus, therapeutic agent dispersed through the hydrogel for sustained release through the proximal face to the tear film of the eye in an effective amount over a period of at least about seven days	Amarpreet S. Sawhney, Peter Jarrett, Michael Bassett, Charles Blizzard

Therefore, there is a need to form hydrogels with such gelators capable of providing ease of administration and have precise gelation temperature to provide smooth injectability evading gelation in the syringe. Furthermore, strategies are needed to be developed to form covalently crosslinked hydrogel without toxic crosslinkers or with biodegradable crosslinkers which are still to be explored.

There is also a need to develop hydrogels which vary in drug release kinetics. Such hydrogels will expand the area of application based on the release profile desired or required for both drug delivery and tissue application. Hydrogels can also be modulated to follow diverse degradation profile so as to meet the kinetic issues. The stimuli-responsive hydrogel system offers an approach where the rate of drug release can be modulated on off overtime so that hydrogel can be used in conditions where varying doses of drug are required over the time (e.g. delivery of insulin). There is also a need for improvement in hydrogel for the delivery of hydrophobic drugs as well as susceptible molecules like proteins, antibodies, or nucleic acids. The method of synthesis applied for in situ crosslinking the hydrogels (thermal, physically gelling polymers, or the functional group chemistry) may affect the biological properties of entrapped drug molecules. Therefore, an effective method for pre-encasulation or complexation of these bioactive before the in situ gel formation is needed to be developed to solve this issue.

Although a number of interesting physical and chemical methods are presently known, there is certainly a need for other methods. It is expected that principles from the expanding research area of supramolecular chemistry will be applied to design novel type of hydrogels with tailored properties which can preferably be prepared in an aqueous environment. Also, protein engineering might contribute to the development of hydrogel systems with a very precise control over their microstructure and thus their properties. Finally, it can be foreseen that systems in which gel formation is induced by a specific trigger (temperature, pH, or a specific compound) will be developed precisely for application in pharmaceutical and biomedical purposes.

References

Ahmed EM (2015) Hydrogel: preparation, characterization, and applications: a review. J Adv Res 6:105–121

Alsarra IA, Hamed AY, Mahrous GM, El Maghraby GM, Al-Robayan AA, Alanazi FK (2009) Mucoadhesive polymeric hydrogels for nasal delivery of acyclovir. Drug Dev Ind Pharm 35 (3):352–362

Amin MCIM (2012) Synthesis and characterization of thermo and pH-responsive bacterial cellulose/acrylic acid hydrogels for drug delivery. Carbohydr Polym 88:465–473

Anderson JM, Langone JJ (1999) Issues and perspectives on the biocompatibility and immunotoxicity evaluation of implanted controlled release systems. J Control Rel 57:107–113

Anumolu SNS, DeSantis AS, Menjoge AR, Hahn RA, Beloni JA, Gordon MK, Sinko PJ (2010) Doxycycline loaded poly(ethylene glycol) hydrogels for healing vesicant-induced ocular wounds. Biomaterials 31(5):964–974

Bai XY, Yan Y, Wang L, Zhao LG, Wang K (2016) Novel pH-sensitive hydrogels for 5-aminosalicylic acid colon targeting delivery: in vivo study with ulcerative colitis targeting therapy in mice. Drug Deliv 23(6):1926–1932

Bajpai AK, Shrivastava J (2005) In vitro enzymatic degradation kinetics of polymeric blends of crosslinked starch and carboxymethyl cellulose. Polym Int 54(11):1524–1536

Bos GW, Jacobs JJL, Koten JW, Van Tomme S, Veldhuis T, van Nostrum CF (2004) In situ crosslinked biodegradable hydrogels loaded with IL-2 are effective tools for local IL-2 therapy. Eur J Pharm Sci 21(4):561–567

Brazel CS, Peppas NA (1996) Pulsatile local delivery of thrombolytic and antithrombotic agents using poly(N-isopropylacrylamide–co-methacrylic acid) hydrogels. J Control Rel 39:57–64

Bromberg LE, Ron ES (1998) Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery. Adv Drug Deliv Rev 31:197–221

Cai S, Suo Z (2011) Mechanics and chemical thermodynamics of phase transition in temperature-sensitive hydrogels. J Mech Phys Solid 59:2259–2278

Caliceti P, Salmaso S, Lante A, Yoshida M, Katakai R, Martellini F, Mei LHI, Carenza M (2001) Controlled release of biomolecules from temperature-sensitive hydrogels prepared by radiation polymerization. J Control Release 75:173–181

Calixto G, Yoshii AC, Rocha e Silva H, Stringhetti Ferreira Cury B, Chorilli M (2015) Polyacrylic acid polymers hydrogels intended to topical drug delivery: preparation and characterization. Pharm Dev Technol 20(4):490–496

Chan Y-P, Meyrueix R, Rivail C, Chatellier J (2011) Medusa: an innovative formulation. Approach to improve pharmacoinetic & safety profiles of biotherapeutics, www.ondrugdelivery, pp 4–6

Chauhan S, Harikumar SL, Kanupriya (2012) Hydrogels: a smart drug delivery system. IJRPC 2(3):603–614

Chen P (2005) Physicochemical and engineering aspects. Colloids Surf A 257–258:1–554

Cheng X, Jinc Y, Suna T, Qia R, Lic H (2016a) An injectable, dual pH and oxidation-responsive supramolecular hydrogel for controlled dual drug delivery. Colloid Surf B 141:44–52

Cheng Y-H, Tung-Hu Tsa, Jhan Y-Y, Chiu AW-H, Tsai K-L, Chien C-S, Chiou S-H, Liu CJL (2016b) Thermosensitive chitosan-based hydrogel as a topical ocular drug delivery system of latanoprost for glaucoma treatment. Carbohyd Polym 144:390–399

Chun SW, Kim JD (1996) A novel hydrogel-dispersed composite membrane of poly (N-isopropylacrylamide) in a gelatin matrix and its thermally actuated permeation of 4-acetamidophen. J Control Release 38:39–47

Das A, Wadhwa S, Srivastava AK (2006) Cross-linked guargum hydrogels discs for colon-specific delivery of ibuprofen, formulation and in-vitro evaluation. Drug Del 13:139–142

Das D, Das R, Ghosh P, Dhara S, Panda AB, Pal S (2013) Dextrin cross linked with poly(HEMA): a novel hydrogel for colon specific delivery of ornidazole. RSC Adv 3:25340–25350

De Groot CJ, Van Luyn MJA, Van Dijk-Woltheris WNE, Cadee JA, Plantinga JA, Otter WD, Hennink WE (2001) In vitro biocompatibility of biodegradable dextran-based hydrogels tested with human fibroblasts. Biomaterials 22:1197–1203

de Nooy AEJ, Capitani D, Masci G, Crescenzi V (2000) Ionic polysaccharide hydrogels via the Passerini and Ugi multicomponent condensations: synthesis, behavior and solid-state NMR characterization. Biomacromolecules 1:259–267

Deo N, Ruetsch S, Ramaprasad K, Kamath Y (2010) Stable environmentally sensitive cationic hydrogels for controlled delivery applications. J Cosmet Sci 61:421

Dinarvand RD, Emanuele A (1995) Use of thermoresponsive hydrogels for on–off release of molecules. J Control Release 36:221–227

Dolman MEM, Harmsen S, Storm G, Hennink WE, Kok RJ (2010) Drug targeting to the kidney: advances in the active targeting of therapeutics to proximal tubular cells. Adv Drug Deliv Rev 62:1344–1357

Eagland D, Crowther NJ, Butler CJ (1994) Complexation between polyoxyethylene and polymethacrylic acid—the importance of the molar mass of polyoxyethylene. Eur Polym J 30:767–773

Enas M, Awad AM, Ahmed MA (2008) Development of a multicomponent fertilizing hydrogel with relevant techno-economicindicators. Am-Euras J Agric Environ Sci 3(5):764–770

Fei L, Jinlin H, Mingzu Z, Kam CT, Peihong N (2015) Injectable supramolecular hydrogels fabricated from PEGylated doxorubicin prodrug and α-cyclodextrin for pH-triggered drug delivery. RSC Adv 5:54658–54666

Fu C, Lin X, Wang J, Zheng X, Li X, Lin Z, Lin G (2016) Injectable micellar supramolecular hydrogel for delivery of hydrophobic anticancer drugs. J Mater Sci Mater Med 27(4):735682–735689

Funami T, Hiroe M, Noda S, Asai I, Ikeda S, Nishimari K (2007) Influence of molecular structure imaged with atomic force microscopy on the rheological behavior of carrageenan aqueous systems in the presence or absence of cations. Food Hydrocolloids 21:617–629

Gacesa P (1988) Alginates. Carbohydr Polym 8:161–182

Ganji F, Farahan EV (2009) Hydrogels in controlled drug delivery systems Iranian. Polym J 18(1): 63–88

Gaoa Y, Sunb Y, Renc F, Shen Gao (2010) PLGA–PEG–PLGA hydrogel for ocular drug delivery of dexamethasone acetate. Drug Dev Ind Pharm 30(10):1131–1138

Goosen MFA, O'Shea GM, Gharapetian HM, Chou S, Sun AM (1985) Optimization of microencapsulation parameters: semipermeable microcapsules as a bioartificial pancreas. Biotechnol Bioeng 27:146–150

Gupta D, Tator CH, Shoichet MS (2006) Fast-gelling injectable blend of hyaluronan and methylcellulose for intrathecal, localized delivery to the injured spinal cord. Biomaterials 27(11):2370–2379

Gutowska A, Bark JS, Kwon IC, Bae YH, Kim SW (1997) Squeezing hydrogels for controlled oral drug delivery. J Control Release 48:141–148

Hassan CM, Peppas NA (2000) Structure and morphology of freeze/thawed PVA hydrogels. Macromolecules 33:2472–2479

Hennink WE, De Jong SJ, Bos GW, Veldhuis TFJ, van Nostrum CF (2004) Biodegradable dextran hydrogels crosslinked by stereocomplex formation for the controlled release of pharmaceutical proteins. Int J Pharm 277(1–2):99–104

Hiemstra C, Zhong ZY, Li LB, Dijkstra PJ, Jan FJ (2006) In-situ formation of biodegradable hydrogels by stereocomplexation of PEG-(PLLA) and PEG-(PDLA) star block copolymers. Biomacromolecules 7(10):2790–2795

Hoare TR, Kohane DS (2008) Hydrogels in drug delivery: progress and challenges. Polymer 49:1993–2007

Hoffman AS (2002) Hydrogels for biomedical applications. Adv Drug Deliv Rev 43:3–12

Hunkeler D (1992) Synthesis and characterization of high molecular weight water-soluble polymers. Polym Int 27:23–33

Ichikawa H, Fukumori Y (2000) Novel positively thermosensitive controlled-release microcapsule with membrane of nano-sized poly(N-isopropylacrylamide) gel dispersed in ethylcellulose matrix. J Control Release 63:107–119

Iizawa T, Taketa H, Maruta M, Ishido T, Gotoh T, Sakohara S (2007) Synthesis of porous poly (N-isopropylacrylamide) gel beads by sedimentation polymerization and their morphology. J Appl Polym Sci 104:842–850

Janes KA, Fresneau MP, Marazuela A, Fabra A, Alonso MJ (2001) Chitosan nanoparticles as delivery systems for doxorubicin. J Control Release 73:255–267

Jeong B, Choi YK, Bae YH, Zentner G, Kim SW (1999) New biodegradable polymers for injectable drug delivery systems. J Control Release 62:109–114

Jeong B, Bae YH, Kim SW (2000) Drug release from biodegradable injectable thermosensitive hydrogel of PEG–PLGA–PEG triblock copolymers. J Control Release 63:155–163

Jhan MS, Andrade JD (1973) Water and hydrogels. J Biomed Mater Res 7(6):509–522

Katono H, Maruyama A, Sanui K, Okano T, Sakurai Y (1991) Thermo-responsive swelling and drug release switching of interpenetrating polymer networks composed of poly(acrylamide–co-butyl methacrylate) and poly(acrylic acid). J Control Release 16:215–227

Kesavan K, Kant S, Pandit JK (2015) Therapeutic effectiveness in the treatment of experimental bacterial keratitis with ion-activated mucoadhesive hydrogel. Ocul Immunol Inflamm 19:1–4

Khare AR, Peppas NA (1993) Release behavior of bioactive agents from pH-sensitive hydrogels. J Biomater Sci Polym 4:275–289

Khare AR, Peppas NA (1995) Swelling/deswelling of anionic copolymers gels. Biomaterials 16:559–567

Klouda L, Mikos AG (2008) Thermoresponsive hydrogels in biomedical applications—a review. Eur J Pharm Biopharm 68(1):34–45

Kubinova S, Horak D, Kozubenko N, Vanecek V, Proks V, Price J (2010) The use of superporous Ac-CGGASIKVAVS-OH-modified PHEMA scaffolds to promote cell adhesion and the differentiation of human fetal neural precursors. Biomaterials 31:5966–5975

Kuijpers AJ, van Wachum PB, van Luyn MJA, Engbers GHM, Krijsveld J, Zaat SAJ, Dankert J, Feijen J (2000) In vivo and in vitro release of lysozyme from crosslinked gelatin hydrogels: a model system for the delivery of antibacterial proteins from prosthetic heart valves. J Control Release 67:323–336

Leda K (2015) Thermoresponsive hydrogels in biomedical applications: a seven-year update. Eur J Pharmac Biopharma 97(B):338–349

Lim DW, Park TG (2000) Stereocomplex formation between enantiomeric PLA–PEG–PLA triblock copolymers: characterization and use as protein delivery microparticulate carriers. J Appl Polym Sci 75:1615–1623

Lim DW, Nettles DL, Setton LA, Chilkoti A (2007) Rapid cross-linking of elastin-like polypeptides with (hydroxymethyl)phosphines in aqueous solution. Biomacromol 8(5):1463–1470

Limón D, Amirthalingam E, Rodrigues M, Halbaut L, Andrade B, Garduño-Ramírez ML, Amabilino DB, Pérez-García L, Calpena AC (2015) Novel nanostructured supramolecular hydrogels for the topical delivery of anionic drugs. Eur J Pharm Biopharm 96:421–436

Liu JH, Lin SQ, Li L, Liu E (2005) Release of theophylline from polymer blend hydrogels. Int J Pharm 298(1):117–125

Mansur HS, Orefice RL, Mansur AAP (2004) Characterization of poly(vinyl alcohol)/poly (ethylene glycol) hydrogels and PVA-derived hybrids by small-angle X-ray scattering and FTIR spectroscopy. Polymer 45:7193–7202

Mehvar R (2000) Dextran for the targeted and sustained delivery of therapeutic and imaging agents. J Controlled Release 69:1–25

Minhas M, Ahmad M, Ali L, Sohail M (2013) Synthesis of chemically cross-linked polyvinyl alcohol-co-poly (methacrylic acid) hydrogels by copolymerization; a potential graft-polymeric carrier for oral delivery of 5-fluorouracil. DARU J Pharm Sci 21:44

Misra GP, Singh RS, Aleman TS, Jacobson SG, Gardner TW, Lowe TL (2009) Subconjunctivally implantable hydrogels with degradable and thermoresponsive properties for sustained release of insulin to the retina. Biomaterials 30(33):6541–6547

Mocanu G, Mihaï D, Dulong V, Picton L, Le Cerf D (2012) New anionic crosslinked multi-responsive pullulan hydrogels. Carbohyd Polym 87:1440–1446

Mohamadnia Z, Zohuriaan-Mehr MJ, Kabiri K, Jamshidi A, Mobedi H (2007) pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery. J Bioact Compat Polym 22:342–356

Okuyama Y, Yoshida R, Sakai K, Okano T, Sakurai Y (1993) Swelling controlled zero order and sigmoidal drug release from thermo-responsive poly(N-isopropylacrylamide-co-butyl methacrylate) hydrogel. J Biomater Sci Polym 4:545–556

Owens DE, Jian Y, Fang JE, Slaughter BV, Chen Y-H, Peppas NA (2007) Thermally responsive swelling properties of polyacrylamide/poly(acrylic acid) interpenetrating polymer network nanoparticles. Macromolecules 40(20):7306–7310

Patel VR, Amiji MM (1996) Preparation and characterization of freeze-dried chitosan–poly (ethylene oxide) hydrogels for site-specific antibiotic delivery in the stomach. Pharm Res 13:588–593

Peppas NA, Mikos AG (1986) Preparation methods and structure of hydrogels. In: Peppas NA (ed) Hydrogels in medicine and pharmacy, vol I. CRC Press, Boca Raton

Percec V, Bera TK, Butera RJ (2002) A new strategy for the preparation of supramolecular neutral hydrogels. Biomacromolecules 23:272–279

Qiu Y, Park K (2012) Poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO) Pluronics® (or Poloxamers®) and Tetronics® environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 64:49–60

Rowley J, Madlambayan G, Faulkner J, Mooney DJ (1999) Alginate hydrogels as synthetic extracellular matrix materials. Biomaterials 20:45–53

Ruixin L, Chang S, Wei W, Xiaoliang W, Hui L, Danke X, Wenying Z (2015) Encapsulation of 10-hydroxy camptothecin in supramolecular hydrogel as an injectable drug delivery system. J Pharm Sci 104(7):2266–2275

Saboktakin RM, Tabatabaei RM (2015) Supramolecular hydrogels as drug delivery systems. Int J Biol Macromol 75:426–436

Sahu NK, Gils PS, Ray D, Sahoo PK (2012) Hydrogels: Rev Adv Polym Sci Tech: Int J 2(4): 43–50

Said HM, Alla SGA, El-Naggar AWM (2004) Synthesis and characterization of novel gels based on carboxymethyl cellulose/acrylic acid prepared by electron beamirradiation. React Funct Polym 61:397–404

Schild HG (1992) Poly(N-isopropylacrylamide): experiment, theory and application. Prog Polym Sci 17:163–249

Schuetz YB, Gurny R, Jordan O (2008) A novel thermoresponsive hydrogel of chitosan. Eur J pharmBiopharm 68:19–25

Shin B-K, Baek EJ, Choi SG, Davaaa E, Nhoc Y-C, Limc Y-M, Parkc J-S, Huh KM, Park J-S (2013) Preparation and irradiation of Pluronic F127-based thermoreversible and mucoadhesive hydrogel for local delivery of naproxen. Drug Dev Ind Pharm 39(12):1874–1880

Siegel RA, Falamarzian M, Firestone BA, Moxley BC (1998) pH-controlled release from hydrophobic/polyelectrolyte copolymer hydrogels. J Control Release 8:179–182

Smetana K (1993) Cell biology of hydrogels. Biomaterials 14:1046–1050

Starodoubtsev SG, Khokhlov AR, Sokolov EL, Chu B (1995) Evidence for polyelectrolyte/ionomer behavior in the collapse of polycationic gels. Macromolecules 28:3930–3936

Stringer JL, Peppas NA (1996) Diffusion in radiationcrosslinked poly(ethyleneoxide) hydrogels. J Control Release 42:195–202

Suda K (2007) Superabsorbent polymers and superabsorbent polymer composites. Sci Asia 33(Suppl):139–143

Szepes A, Makai Z, Blumer C, Mader K, Kasa P, Revesz PS (2008) Characterization and drug delivery behaviour of starch based hydrogels prepared via isostatic ultrahigh pressure. Carbohyd Polym 72:571–575

Takashima Y, Yuting Y, Otsubo M, Yamaguchi M, Harada A, Beilstein (2012) J Org Chem 8:1594–1600

Takigami M, Amada H, Nagasawa N, Yagi T, Kasahara T, Takigami S, Tamada M (2007) Preparation and properties of CMC gel. Trans Mater Res Soc Jpn 32(32):713–716

Tan HL, Tan LS, Wong YY, Muniyandy S, Hashim K, Pushpamalar J (2016) Dual crosslinked carboxymethyl pulp/pectin hydrogel beads as potential carrier for colon-targeted drug delivery. J Appl Polym Sci 133(19)

Telitel S, Dumur F, Faury T, Graff B, Tehfe M-A, Gigmes D, Fouassier J-P, Lalevée J (2013) New core-pyrene π structure organophotocatalysts usable as highly efficient photoinitiators. Beilstein J Org Chem 9:877–890

Tong Q, Zhang G (2005) Rapid synthesis of a superabsorbent from a saponified starch and acrylonitrile/AMPS graft copolymers. Carbohyd Polym 62:74–79

Toshikazu T, Hisahiko K, Kenji U, Toshiro M (1992) Structure and mechanical properties of poly (vinyl alcohol) gels swollen by various solvents. Polymer 33(11):2334–2339

Vakkalanka SK, Brazel CS, Peppas NA (1996) Temperature- and pH-sensitive terpolymers for modulated delivery of streptokinase. J Biomater Sci Polym 8:119–129

Van Tomme SR, van Steenbergen MJ, De Smedt SC, van Nostrum CF, Hennink WE (2005) Biomaterials 26(14):2129–2135

Vemula PK, Li J, George J, Am J (2006) Chem Soc 128:8932–8938

Wang C, Stewart RJ, Kopecek J (1999) Hybrid hydrogels assembled from synthetic polymers and coiled-coil protein domains. Nature 397:417–420

Watanabe N, Hosoya Y, Tamura A, Kosuge H (1993) Characteristics of water-absorbent polymer emulsions. Polym Int 30:525–531

Watanabe T, Ohtsuka A, Murase N, Barth P, Gersonde K (1996) NMR studies on water and polymer diffusion in dextran gels. Influence of potassium ions on microstructure formation and gelation mechanism. Magn Reson Med 35:697–705

Wichterle O, Lim D (1960) Hydrophilic gels for biological use. Nature 185:117–118

Wu J, Su ZG, Ma GH (2006) A thermo- and pH-sensitive hydrogel composed of quaternized chitosan/glycerophosphate. Int J Pharm 315(1–2):1–11

Wu X, He C, Wu Y, Chen X (2016) Synergistic therapeutic effects of Schiff's base cross-linked injectable hydrogels for local co-delivery of metformin and 5-fluorouracil in a mouse colon carcinoma model. Biomaterials 75:148–162

Xu X, Weng Y, Xu L, Chen H (2013) Sustained release of avastin® from polysaccharides cross-linked hydrogels for ocular drug delivery. Macromolecules 60:272–276

Yin Y, Yang Y, Xu H (2002) Swelling behavior of hydrogels for colon-site drug delivery. J Appl Polym Sci 83:2835–2842

Yin Y, Ji X, Dang H, Ying Y, Zhing H (2008) Study of the swelling dynamics with overshooting effect of hydrogels based on sodium alginate-g-acylic acid. Carbohyd Polym 71:682–689

Yokoyama F, Masada I, Shimamura K, Ikawa T, Monobe K (1986) Morphology and structure of highly elastic poly-(vinyl alcohol) hydrogel prepared by repeated freezing-and-melting. Colloid Polym Sci 264

Yoshida M, Asano M, Kumakura M, Kataki R, Mashimo T, Yuasa H, Yamanaka H (1991) Thermo-responsive hydrogels based on acryloyl-L-proline methyl ester and their use as long-acting testosterone delivery systems. Drug Des Deliv 7:159–174

Yu H, Xiao C (2008) Synthesis and properties of novel hydrogels from oxidized Konjac glucomannan cross linked gelation for in-vitro drug delivery. Carbohyd Polym 72:479–489

Zhang JT, Bhat R, Jandt KD (2009) Temperature-sensitive PVA/PNIPAAm semi-IPN hydrogels with enhanced responsive properties. Acta Biomat 5(1):488–497

Zhang Z, He Z, Liang R, Ma Y, Huang W, Jiang R, Shi S, Chen H, Li X (2016) Fabrication of a micellar supramolecular hydrogel for ocular drug delivery. Biomacromolecules 17(3):798–807

Zheng X, Li X, Lin Z, Lin G (2016) Injectable micellar supramolecular hydrogel for delivery of hydrophobic anticancer drugs. J Mater Sci Mater Med 27(4):73

Zu Y, Zhang Y, Zhao X, Shan C, Zu S, Wang K, Li Y, Ge Y (2012) Preparation and characterization of chitosan-polyvinyl alcohol blend hydrogels for the controlled release of nano-insulin. Int J Biol Macromol 50(1):82–87