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REVIEW ARTICLE

Stimuli-responsive hydrogels in drug delivery and tissue engineering

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Abstract

Hydrogels are the three-dimensional network structures obtained from a class of synthetic or natural polymers which can absorb and retain a significant amount of water. Hydrogels are one of the most studied classes of polymer-based controlled drug release. These have attracted considerable attention in biochemical and biomedical fields because of their characteristics, such as swelling in aqueous medium, biocompatibility, pH and temperature sensitivity or sensitivity towards other stimuli, which can be utilized for their controlled zero-order release. The hydrogels are expected to explore new generation of self-regulated delivery system having a wide array of desirable properties. This review highlights the exciting opportunities and challenges in the area of hydrogels. Here, we review different literatures on stimuli-sensitive hydrogels, such as role of temperature, electric potential, pH and ionic strength to control the release of drug from hydrogels.

Keywords

Hydrogel, pH sensitivity, polymerization, scaffolds, stimuli, swelling

History

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Introduction

The development of drug delivery system is based on the physicochemical and pharmacokinetic properties of the drug. Conventional delivery systems suffer from the limitations of minimal synchronization between the time required to achieve therapeutically effective plasma drug concentration and the actual drug release profile exhibited by the dosage form (Bruguerolle, 1998). With the ongoing research in advanced drug delivery formulations to provide stable and economical drug delivery systems, our focus is on the hydrogel systems which are known to reduce the problems of conventional dosage forms, molecules as small as non-steroidal anti-inflammatory drugs (NSAIDs) or as large as proteins and peptides (Graham & Mc-Neil, 1984; Bajpai & Saggu, 2007).

Initially, hydrogels was described as a colloidal gel of inorganic salts, which were highly different from the hydrogels, we are dealing with nowadays. At that time, the term ''hydrogel'' was used to describe a three-dimensional (3D) network of hydrophilic natural polymers and gums, in which the network is formed by chemical or physical crosslinking. These ordinary hydrogels were used only for swelling–deswelling process depending on the availability of water in the environment (Lee et al., 2013). The hydrogel of new generation was first developed by Witchterle & Lim (1960). Applications of smart hydrogels have been divided into four areas, such as drug delivery, biosensor, bioseparation and tissue engineering. As the time passes, research on hydrogels for drug delivery has been focused on developing advanced drug delivery systems, such as self-regulated insulin delivery systems. With the advancement in the technology, hydrogels having numerous applications in tissue engineering have been developed. These systems are called smart hydrogels as they respond immediately to the environmental changes (Qiu & Park, 2001). A large number of studies based on the applications of smart hydrogels in drug delivery, nanotechnology and tissue engineering have been carried out in the recent decades.

These smart hydrogels are currently being developed as new drug delivery systems for various bioactive molecules due of their unique properties, which resembles to that of the living tissues. These unique properties are due to their high water content, soft and rubbery consistency and low interfacial tension with water and biological fluids (Dagani, 1997). These systems are so designed to ensure zero-order constant drug release over a prolonged period of time (Lowman & Peppas, 1991; Stastny et al., 2002). The characteristics like swelling behavior in aqueous medium, pH sensitivity, temperature sensitivity and zero-order kinetics play important role in the development of hydrogel-based drug delivery system.

They can be divided into two categories based on the chemical or physical nature of the crosslinked interactions. Crosslinking due to chemical interactions leads to permanent junction in the polymer network while physical interactions are either due to polymer chain entanglements or due to the physical interactions such as ionic interactions, hydrogen bonding or hydrophobic interactions (Jen et al., 1996). These structures imbibe water or biological fluids in large amount at least 10–20 times their molecular weight thus becomes swollen (Kim et al., 1992). Hydrogels that exhibit both liquid- and solid-like behavior have a variety of functional properties

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Table 1. Different hydrogel preparation techniques along with their merits and demerits.

Methods	Merits	Demerits	References
Solvent casting/particulate leaching	Control over porosity, pore size and crystallinity.	Limited mechanical properties, residual solvent and porogen material.	Betancourt et al. (2010)
Porogen leaching	Controlled over porosity and pore geometry.	Inadequate pore size and pore geometry.	Beyssac et al. (1996)
Gas foaming	Free of harsh organic solvents, control over porosity and pore size.	Limited mechanical property, inadequate pore interconnectivity,	Beyssac et al. (1996)
Self-assembly	Control over porosity, pore size and fiber diameter,	Expensive material complex design parameters,	Bhattarai et al. (2010)
Electrospinning	Control over porosity, pore size and fiber diameter,	Limited mechanical properties, pore size decrease with fiber thickness.	Blanco et al. (1998)
Phase separation	No decrease in the activity of molecule.	Difficult to control precisely scaffold morphology.	Blumenstein et al. (2012)
Rapid Prototyping	Excellent control over geometry, porosity, no supporting material required.	Limited polymer type, highly expensive equipment.	Blumenstein et al. (2012)
Fibre mesh	Large surface area for cell attachment, rapid nutrient diffusion.	Lack the structural stability.	Borenstein et al. (2002)
Fibre bonding	High surface to volume ratio, high porosity.	Poor mechanical properties, limited applications to other polymers.	Brannon & Peppas (1991)
Melt molding	Independent control over porosity and poor size.	Required high temperature for non amorphous polymer	Brannon-Peppas & Peppas (1990)
Membrane Lamination	Provide 3D matrix.	Lack required mechanical strength, inadequate pore interconnectivity.	Bromberg & Ron (1998)
Freeze drying	High temperature and separate leaching step not required.	Small pore size and long processing time.	Borenstein et al. (2002)

such as swelling, mechanical, permeation, surface and optical properties (Rossi et al., 1991).

In addition, stimuli-sensitive hydrogels have the unique property of undergoing abrupt volume changes from their collapsed and swollen states in response to environmental stimuli, which have both sensor and effector functions. Therefore, various stimuli-sensitive hydrogels that have been studied theoretically and experimentally which can respond to pH, temperature, electric field, ionic strength, solvent composition, pressure and other stimuli (Tanaka et al., 1980). The factors responsible for the drug release from the hydrogels are diffusion coefficient, porosity and tortuosity (Rowley et al., 1999; Liu et al., 2000; Aroca et al., 2007).

Various advantages of hydrogels as drug delivery system come from their good transport properties, ability to protect drugs, proteins and peptides from the environment, biodegradability and can be modified according to the route of administration. The high water content of these materials contributes to their better biocompatibility (Hejazi & Amiji, 2003). Sensor properties of hydrogels are responsible for their sol–gel phase transition behavior depending upon the environmental conditions. Because of having such unique properties, they are also referred to as ''intelligent'' or ''smart'' polymeric systems as they dictate not only the delivery of drugs, but also when and at which time interval it is being released from the system (Soppimath et al., 2002). The stimuli of the hydrogels are physical (temperature, electric fields, light, pressure and magnetic fields), chemical (pH and ions) or biological/biochemical ones, responsible for various responses (Qiu & Park, 2001). Hydrogels have been used in a variety of applications like wound healing, tissue engineering, gene delivery, ocular drug delivery, transdermal delivery and subcutaneous drug delivery in the form of implants. Different hydrogel preparation techniques along with their merits and demerits and various polymer for hydrogels are shown in Tables 1 and 2.

Types of hydrogels

Hydrogels are classified based on the nature of the stimuli responsible for the swelling behavior. Various stimuli-responsive hydrogels also have the ability for controlled and targeted delivery of drug and other bioactive molecules. Stimuli responsible for swelling of hydrogels are shown in Figure 1. These hydrogels are discussed below.

pH-sensitive or ion-sensitive hydrogels

The hydrogels release the drug by changing the pH of the external environment. pH-sensitive polymers, e.g. polyvinyl amine containing either acidic or basic groups (Brannon & Peppas, 1991; Katchalsky & Michaeli, 1955). Poly acrylic acid (PAA; an anionic polymer) dissolves/swell more at high pH due to ionization whereas Poly(*N,N*′-diethylamino ethyl methacrylate (PDEAMA; a cationic polymer) swells more at low pH. The swelling of the polyelectrolyte is mainly due to the electrostatic repulsion between charges present in the polymer chain (Firestone & Siegel, 1991). Ionization on polyelectrolyte's is more difficult due to the electrostatic interactions exerted by the other adjacent ionized groups present on the polymer chain. This can be minimized by using co-monomers like methyl methacrylate, 2-hydroxyethyl methacrylate and maleic anhydride (Kou et al., 1988; Brannon-Peppas & Peppas, 1990; Falamarzian & Varshosaz, 1998). A new kind of pH-sensitive hydrogel based on poly(lactic acid) (PLA), methoxyl poly(ethylene glycol) (MPEG) and itaconic acid (IA) system prepared by heat-initiated free radical polymerization was found as a safe candidate for drug delivery systems (Wang et al. 2012).

Table 2. Various polymer for hydrogels along with their applications.

Applications	Polymers	References
Wound care	Polyurethane, Poly(ethylene glycol), Poly(propylene glycol), Poly(vinylpyrrolidone), Polyethylene glycol and Agar, Xanthan, Methyl cellulose, Carboxymethyl cellulose, Alginate, Hyaluronan and other hydrocolloids	Brownlee & Cerami (1979)
Drug delivery pharmaceutical	Poly(vinylpyrrolidone), Starch, Poly(vinylpyrrolidone), Poly(acrylic acid) Carboxymethyl cellulose, Hydroxypropyl methyl cellulose, Polyvinyl alcohol, Acrylic acid, Methacrylic acid, Chitosan, Glycerophosphate, Carrageenan, Acrylic acid, 2-Acrylamido-2-methylpropanesulfonic acid, Acrylic acid, Carboxymethyl cellulose	Bruguerolle (1998)
Dental material	Hydrocolloids (Ghatti, Karaya, Kerensis gum)	Cahalan et al. (1988)
Tissue engineering implants	Poly(vinylalcohol), Poly(acrylic acid), Hyaluronan, Collagen	Calejo et al. (2012)
Injectable polymeric system	Polyesters, Polyphosphazenes, Polypeptides, Chitosan, β-Hairpin peptide	Chang (1988)
Techanical products (cosmetic, pharmaceutical)	Starch, Gum Arabic, Xanthan, Pectin, Carrageenan, Gellan, Welan, Guar gum, locust Bean gum, Alginate, Starch, Heparin, Chitin and Chitosan	Chang (1988)
Others (agriculture, waste treatment, separation, etc.)	Starch, Xanthan, Polyvinyl alcohol, Poly (vinyl methyl ether), Poly (*N*-isopropyl acrylamide)	Cahalan et al. (1988)

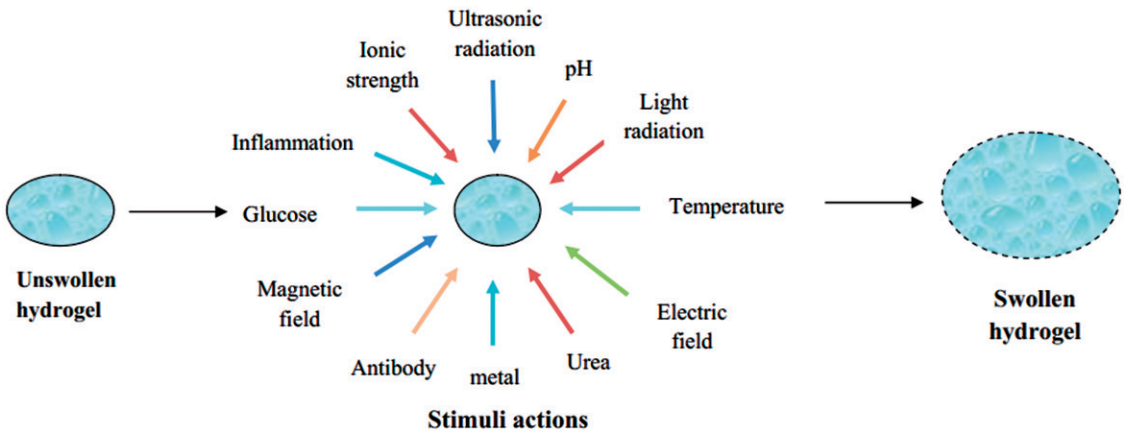

Figure 1. Stimuli responsible for swelling of hydrogels.

Takemoto et al. (2010) performed the work on polyion complex in which first the preparation of poly(*N*-vinylacetamide)-*co*-poly(*N*-vinylformamide) (poly(NVA-*co*-NVF)) hydrogel was carried out, followed by hydrolysis reaction to produce a cationic polyvinyl amine (PVAm) layer on the surface of the hydrogel and then polymerization of polyacrylic acid (PAA) to the surface cationized hydrogel resulted in the formation of polyionic complex (PIC) hydrogel. Therefore, it can be said that the main determining factor for drug release depends on the thickness of the PIC layer having a continuous polymer network, and possesses different functions for the controlled release of drug molecules (Takemoto et al., 2010). Various drugs delivered through pH-responsive hydrogels are summarized in Table 3.

Temperature-sensitive hydrogels

The mechanical characteristics of the hydrogel and of the drugs from the hydrogels are altered with the change in the temperature of external environment (Bromberg & Ron, 1998). The common characteristics of thermo-sensitive polymer are the presence of different hydrophobic groups (methyl, ethyl and propyl). Poly(*N*-iso-propylacrylamide) (PNIPAAm) and poly(*N,N*-diethylacrylamide (PDEAAm) are widely used polymers for temperature-sensitive hydrogel because of their lower critical solution and controlled drug delivery which is based on sol–gel phase conversion at the body temperature (Soppimath et al., 2002).

Negative thermo-sensitive hydrogels contract when heated to above their lower critical solution temperature (Bae et al., 1991). These hydrogels obtain on–off drug release profile from matrices with on at a lower temperature and off at a higher temperature (Katono et al., 1991). Positive thermo-sensitive hydrogels show swelling at higher temperature while shrinking at lower temperature (Schild, 1992). The lower critical solution temperature (LCST) or lower consolute temperature is the critical temperature below which the components of a mixture are miscible in all compositions. At temperatures below LCST, the system is completely miscible in all proportions, whereas above LCST partial liquid miscibility occurs.

If any hydrophobic group is present in the polymer chain then LCST becomes lower while if any hydrophilic group is present in the polymer, then LCST becomes higher (Feil et al., 1992).

The LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segments of the polymer or by forming co-polymers of hydrophobic (e.g. NIPAAm)

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Table 3. Various drugs delivered through pH-responsive hydrogels for drug delivery.

S. No.	Drug	Polymer	Application	Conclusion	References
1.	Methyl prednisolone	Carboxymethyl chitosan and Carbopol 934	Intestinal drug delivery	Hydrogel release minimum amount in acidic pH but sustained and high drug release in the basic pH of intestine.	Choi & Park (2005)
2.	Clarithromycin	Chitosan and *N,N′*-Methylenebisacrylamide	*Helicobacter pylori* infection treatment	Drug release at lower value of pH in stomach maintained for longer period of time	Chudzik (2012)
3.	Indomethacin	Poly (hydroxyethyl methacrylate-*co*-acrylic acid)	Enteric drug delivery	Swelling control mechanism is suggested for peculiar release of drug.	Chung et al. (2008)
4.	Terbinafine	Poly(acrylamide/maleic acid)	*Candida albicans* infection treatment	Terbinafine adsorption capacity depends on parameters like pH of the solution and maleic acid content of hydrogel	Cohen et al. (1997)
5.	Vitamin B12 and Salicylic acid	Polyvinyl alcohol	Colon targeted drug delivery	Maximum drug release in simulated intestinal fluid where swelling pattern varied with ratio of PVA and maleic acid.	Crabbe & Thompson (2001)
6.	Insulin	Poly(*N*-isopropylacrylamide-cobutyl-methacrylate-*co*-acrylic acid)	Polypeptide drug carrier	Drug was released in a pH-dependant manner	Creque et al. (1980)
7.	Doxorubicin	Poly(*N*-isopropylacrylamide)	Showed anticancer activity	Release of drug occurred in controlled manner	Dagani (1997)
8.	Proteins	Poly(itaconic acid-*g*-ethylene glycol)	Applications in oral delivery of bioactive agents (proteins).	Maintained a collapsed configuration at acidic pH, also confirmed the cytocompatibility (up to 5 mg/mL), although toxicity was observed at 10 mg/mL.	Dong et al. (1991)
9.	Insulin	Ethylene-*co*-vinyl acetate (EVAc)	Sustained release of insulin from the polymer	Provide sufficient mechanical strength in physiological environment.	Drury & Mooney (2003)
10.	Calcitonin	Poly(*N*-isopropyl acrylamide-*co*-butyl methacrylate-*co*-acrylic acid)	Useful for the delivery of human calcitonin	Provide maximum release of drug in less time while maintaining structural integrity.	Dufresne et al. (2004)

and hydrophilic (e.g. acrylic acid) monomers (Hirotsu, 1993; Irie, 1993; Nazar et al., 2011). Recently, the potential use of arginine-based surfactants and ethyl(hydroxyethyl) cellulose produced low toxicity thermoresponsive hydrogel for pharmaceutical and biomedical applications. Thermosensitive hydrogels for nasal drug delivery was developed using *N*-trimethyl chitosan chloride as polymer. Poly(ethylene glycol) and glycerophosphate showed promising role, particularly in rheological and mucoadhesive behavior, and a sol–gel transition was achieved at 32.5 °C within 7 min (Langer, 1998). Various drugs delivered through temperature-responsive hydrogel are summarized in Table 4.

Glucose-sensitive hydrogels

These hydrogels are sugar sensitive and shows variable response depending upon the level of glucose. Glucose-sensitive hydrogels are useful for development of self-regulated delivery systems which can deliver the necessary amount of insulin in response to blood glucose concentration (Ishihara & Matsui, 1986; Albin et al., 1987). This can be achieved by incorporating glucose oxidase (GOD)-loaded hydrogels, lectin-loaded hydrogels and hydrogels with phenyl boronic acid moieties (Brownlee & Cerami, 1979).

Horbett and coworkers (Lowman & Peppas, 1991; Bajpai & Saggu, 2007) were the first to investigate system consisting of immobilized GOD in a pH-responsive polymeric hydrogel, enclosing a saturated insulin solution. In GOD-loaded hydrogels, GOD is combined with pH-sensitive hydrogels. An increase in the blood glucose level causes the glucose to diffuse into the membrane where glucose is converted into the gluconic acid, which lowers the pH resulting in swelling of hydrogels and the release of insulin. This system is gaining interest due to its release pattern which is similar to that of the endogenous release of insulin (Seminoff et al., 1989). Insulin release from glucose-sensitive hydrogels are shown in Figure 2.

In lectin-loaded hydrogels, the unique carbohydrate-binding properties of lectins are very useful for the fabrication of glucose-sensitive systems. Such systems are developed by synthesizing the glycosylated insulin derivative to form complex with concanvalin A (lectin possessing four binding sites). The glycosylated insulin derivative is then released from its complex with Con A in the presence of free glucose, based on the competitive and complementary binding properties of glycosylated insulin and glucose to Con A. Another approach includes the use of phenylboronic acid moiety which forms complex with polyol compounds like glucose in aqueous solutions (Kim et al., 1990; Kitano et al., 1991; Takemoto et al., 2010). One of the types of phenylboronic acid moiety can be prepared by copolymerization of *N*-vinyl-2-pyrrolidone (NVP) and 3-(acrylamido) phenylboronic acid (PBA; Kitano et al., 1992). Due to the reversible complex formation between phenylboronic acid of poly (NVP-*co*-PBA) and poly(vinyl alcohol) the competitive binding of phenylboronic acid with glucose and PVA could be utilized to construct a glucose-sensitive system. The formation and dissociation of the poly(NVP-*co*-PBA)/PVA complex could be investigated by observing the change in the viscosity. It was observed that poly(NVP-co-PBA) formed a complex with PVA in the absence of glucose, however the complex dissociated in the presence of glucose. Thus, such systems can sensitize the glucose level and release the insulin. In other studies, self-assembled multilayered films were fabricated to modulate insulin release from the positively charged poly [2-(dimethylamino) ethyl methacrylate] (PDMAEMA) star polymer and negatively charged insulin and GOD (Yin et al., 2011). Glucose-responsive microhydrogels based on methacrylate derivatives of dextran and concanavalin A have been prepared for self-regulated insulin delivery without destroying the tertiary structure of insulin (Kataoka & Matsumoto, 1998).

Kataoka & Matsumoto (1998) worked on a matrix of glucose-responsive gel using PNIPAAm and fraction of a phenylboronic acid group and it could cause a remarkable glucose-dependant change in swelling of hydrogel. It was observed that on–off regulation of insulin release from the gel was achieved through a drastic change in the solute transport property which was a result of the formation and disruption of the surface barrier layer of the gel (Matsumoto et al., 2012).

Matsumoto et al. (2012) while working with 2,2′-azobisisobutyronitrile (AIBN) as an initiator in the presence of *N,N*′-methylene-bis (acrylamide) (MBAAm) as a cross-linking agent in DMSO reported that surface-controlled release of insulin can be achieved as gel can form a skin layer which provide a rationale for glucose-sensitive release under glucose homeostasis conditions (Podual et al., 2000a,b). Various polymers used for glucose-sensitive drug delivery are summarized in Table 5.

Alginate-calcium ion hydrogels

Sodium alginate forms ionic hydrogel upon contact with divalent cations, e.g. calcium due to the physical crosslinking (chelation) between the carboxylate anions of guluronate units in alginate and the calcium ions. Kikuchi et al. (1997) proposed that alginate dissolution is due to the calcium ion release from the hydrogels and integrated this concept with the pulsatile release of macromolecular dextran. Further different parameters like alginate concentration, alginate molecular weight or alginate gel bead diameter influences the onset time for the release of dextran (Okor et al., 1991; Iskakov et al., 2002).

Isakov and group worked on fluorescein isothiocyanate (FITC) dextran (MW 9400, 71 200, 145 000) pulsatile release from alginate-calcium ion beds coated with poly(carboxy-*n*-propylacrylamide-*co*-dimethyl acrylamide) of varying thickness (25–125 μm), and found that FITC-dextran release is strongly dependant on copolymer coat thickness and molecular weight, which effect the onset release time which got modulated from 2 to 60 h for dextran (MW 145 000) having 125-mm thick copolymer coated beads (Kuo & Ma, 2001).

Later on, Kuo and group worked on ionically crosslinked alginate hydrogels and control the alginate gelation rate. Both (higher or lower) gelation rate have their impact as faster gelation rate is preferable for better cell encapsulation, while lower gelation rate results in uniform structural and

Table 4. Various drugs delivered through temperature-responsive hydrogels for drug delivery.

S. No.	Drug	Polymer	Application	Conclusion	References
1.	Nalbuphine	Poly(*N*-isopropylacrylamide) and Chitosan	Injectable opioid analgesic	The gelation temperature of hydrogel is well below body temperature which make it ideally suited to function as injectable drug depots.	Geisse (2009)
2.	Human growth hormone	Pluronic F127 and *N*-(3-amino-propyl) methacrylamide	Anabolic cell and tissue growth	Hydrogels exhibit swelling and collapse behavior in aqueous solution with the increase in temperature.	Gong & Osada (2004)
3.	Recombinant multiblock human copolymers growth hormone (rhGH)	Pluronic	Controlled protein delivery	Multi-block hydrogels showed enhanced gel stability, linear mass erosion rates, mechanical strength and zero-order hGH release profile was observed.	Gorgieva & Kokol (2012)
4.	Diclofenac sodium and procaine HCL	1-vinyl-2-pyrrolidinone and *N*-isopropylacrlyamide	Controlled analgesic drug delivery	The hydrogels were designed to achieve phase transition temperature near body temperature and further active component got released at a slower rate at temperature above LCST.	Graham & Mc-Neil (1984)
5.	Mucin	Chitosan, Polyethylene glycol and Polyacrylic acid	Nasal drug delivery	Hydrogel exhibit sol–gel transition at 32.5 °C and hydrogel forms rheologically synergy.	Gupta et al. (2010)
6.	Plasmid DNA (pDNA)	*N*-isopropylacrylamide and *N,N*-dimethylaminoethyl methacrylate (PNIPAm-*co*-PDMAEMA)	Delivery of DNA	Improved gene delivery and effective gene transfection	Harasaki et al. (2001)
7.	Doxorubicin	Poly[(2-ethoxy) ethoxy ethyl vinyl ether] (poly(EOEOVE))	Provide tumor-specific chemotherapy	Temperature-sensitive properties providing controlled drug release	Hejazi & Amiji (2003)
8.	Plasmid DNA	Polyethylenimine (PEI)-plasmid DNA complexes	Improved transfection efficacy	Acid-labile temperature-responsive sol–gel reversible polymer were prepared for enhanced gene delivery to the myocardium and skeletal muscle cells.	Hench & Jones (2005)
9.	BSA	poly(*N*-isopropylacrylamide) (PNIPAAm),	Hydrogel with improved controllability and specificity were prepared using photo crosslinking agent poly(ethylene glycol) diacrylate (PEGDA).	Hydrogel network provide controlled drug release because of their temperature sensitivity and ability of *in situ* photopolymerization to localize at the specific region in the body.	Hennink & Nostrum (2002)
10.	Plasmid DNA	Multiblock copolymers(MBCPs) synthesized from pluronic and di-(ethylene glycol) divinyl ether (DEGDVE)	Used as delivery vehicle for controlled and sustained release of plasmid DNA	Acid-labile temperature-responsive sol–gel reversible polymer enhanced gene delivery to the myocardium and skeletal muscle cells	Hinrichs & Suhuurmans (1999)

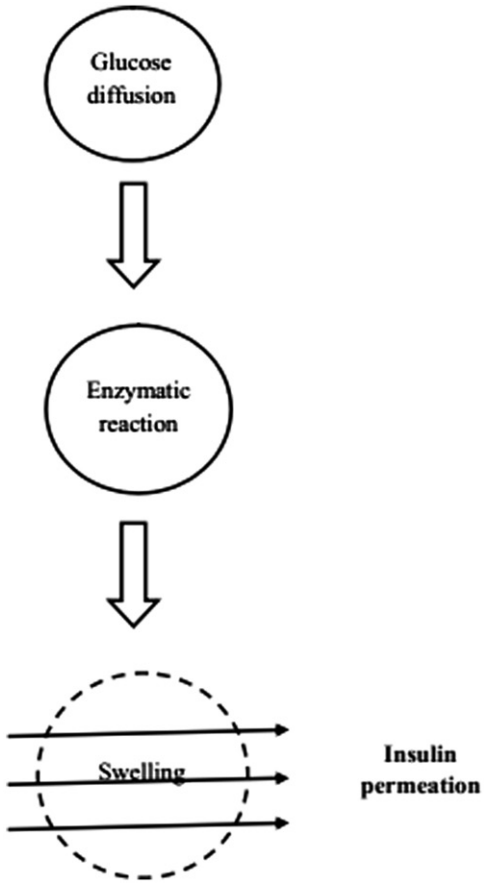


Figure 2. Schematic representation of glucose-sensitive hydrogels.

mechanical integrity. Further, it was found that the gelation rate of hydrogel can be controlled by various factors such as calcium content, polymer concentration and gelation temperature (Chen et al., 1997).

Chen et al. (2011b) developed a novel natural semi-interpenetrating polymer network (semi-IPN) composed of chitosan crosslinked with glutaraldehyde and silk fibroin. They investigated the pH and ion sensitivity of this network on the system. The FTIR spectra of the semi-IPN showed that the chitosan and silk fibroin had a strong H-bond interaction and formed an interpolymer complex. This chitosan/silk fibroin semi-IPN showed good ion sensitivity. The semi-IPN exhibited good swelling when put alternatively into different pH buffer solutions, which is due to the formation and dissociation of H-bonding within the network. Due to the reversible behavior of semi-IPN, it can also be used as an ''artificial muscle'' because of its swelling–shrinking nature at different pH (Park & Hoffman, 1993). Park and co-workers determined the swelling behavior of non-ionic PNIPAAm) hydrogel in various salts solutions. This non-ionic poly(NIPAAm) gel exhibited a sharp volume phase transition at a critical concentration of sodium chloride in aqueous solution. The critical concentration depends on the temperature changes, however, other salts tested did not cause such an abrupt volume change, which may be due to the reason that NIPAAm exhibits a LCST phenomenon in aqueous solution. This gel collapses and shrinks above the LCST and re-swells and expands below that critical temperature (Balasubramaniam et al., 2003). Thus, it was observed that hydrogels exhibit a different degree of swelling in response to different types of salts along with their concentrations. Balasubramaniam and group developed ion-activated *in situ* gelling systems for sustained ophthalmic delivery of ciprofloxacin HCl and concluded that the formulated systems provided sustained release of the drug over a period of 8 h *in vitro* (Sultana et al., 2006). Sultana and co-workers developed an ion-activated, gelrite based *in situ* ophthalmic gels of pefloxacin mesylate and compared with conventional eye drops and concluded that this system was capable of effective and controlled management of conjunctivitis (Liu et al., 2010). Liu et al. in 2010 investigated *in situ* gelling Gelrite/Alginate formulations as vehicles for ophthalmic delivery and found that the optimum concentration of gelrite solution for *in situ* gel-forming delivery systems was 0.3% (w/w) and that for alginate solution was 1.4% (w/w; Vodithala et al., 2010). The (mixture of 0.2% Gelrite and 0.6% alginate) solution showed a significant enhancement in gel strength at physiological condition. Vodithala et al. (2010) developed ion-activated ocular *in situ* gels of ketorolac tromethamine using gelrite as a polymer and concluded that the developed formulations showed sustained release of drugs for up to 6 h. The formulations were found to be non-irritating with no ocular damage (Khoylou & Naimian, 2009).

Preparation of hydrogels

The most common method of preparation of hydrogel-based drug product has been showed in Figure 3. The various crosslinked networks of synthetic polymers such as polyethylene oxide (PEO) (Razzak et al., 2001), polyvinyl pyrrolidone (PVP; Palumbo et al., 2006), polylactic acid (Onuki et al., 2008), polyacrylic acid (PAA; Yang et al., 2009), polymethacrylate (Singh & Vashishth, 2008) polyethylene glycol (PEG; Peppas & Khare, 1993) or natural biopolymers, such as hyaluronic acid, pectin, chondroitin sulfate, alginic acid, carrageenan have been prepared using different techniques like solution polymerization or crosslinking (Fei et al., 2000), irradiation crosslinking (Hennink & Nostrum, 2002; Liu et al., 2002), physical crosslinking (Yoshii & Kume, 2003), suspension polymerization and grafting polymerization (Witchterle & Lim, 1960).

Solution polymerization/crosslinking

In solution polymerization, ionic or neutral monomers are mixed with multifunctional crosslinking agent. Polymerization can be initiated thermally by UV light or by redox initiators. Solvents are incorporated to serve as heat sink and to minimize the temperature control problems. Unreacted monomers, initiators and crosslinking agent are removed by the use of distilled water (Morishta et al., 2002). This method can be used for preparing either pH-sensitive or temperature-sensitive hydrogels using methacrylic acid (Zhang & Wu, 2002) or *N*-isopropylacrylamide (Lugao & Malmonge, 2001), respectively, as the monomer.

Table 5. Various glucose sensitive drug delivery systems along with their applications.

S. No.	Polymer	Application	Conclusion	References
1.	Poly(diethylaminoethyl methacrylate) and Poly ethylene glycol	Modulated insulin release	Enzymes in the hydrogel tend to cause reversible swelling in an acidic environment in response to different glucose concentration.	Junginger (1991)
2.	2-Hydroxyethyl methacrylate and *N,N*-dimethylaminoethyl methacrylate	Glucose-responsive insulin release systems.	Hydrogels without crosslinking agents and with catalase was found to possess higher sensitivity towards pH and glucose than chemically crosslinked hydrogels.	Kang & Bae (2003)
3.	PEGylated concanvalin A, 3-sulfopropylacrylate, *N*-vinyl pyrrolidone and acrylamide	Sol–gel phase reversible insulin release	The membrane and the matrix insulin delivery system were more efficient than erodible system and modulated insulin release is observed in physiological glucose concentration (1–4 mg/dl).	Kataoka & Matsumoto (1998)
4.	*N,N*-dimethylacrylamide (DMAAm) sulfadimethoxine monomer	Sulfonamide based glucose-responsive hydrogels	Sulfonamide based hydrogel shows reversible swelling ranging from 12 to 8 as function of glucose concentration (0–300 mg/dl) in buffered saline solution (pH 7.4 at 37 °C).	Katchalsky & Michaeli (1955)
5.	Poly(methacrylic acid-*g*-ethylene glycol) (poly(MAAc-*g*-EG)	Useful in the development of self-regulated insulin delivery systems	Hydrogels showed a glucose-sensitive behavior with the help of enzyme glucose oxidase from the combination of the catalytic reaction of glucose oxidase and pH-sensitive complex.	Katono et al. (1991)
6.	Poly(*N*-isopropylacrylamide) (pNIPAM) and pNIPAM-coacrylamidophenylboronic acid (pNIPAM-*co*-APBA)	Development of glucose-responsive microgels.	Glucose-responsive hydrogel lead to the formation of core shell structure, thus controlled release of insulin from the delivery system achieved.	Kazakia et al. (2006)
7.	Diethylaminoethyl methacrylate (DEAEM), poly(ethylene glycol) monomethacrylate (PEGMA)	pH-sensitive swelling behavior of the hydrogels were studied.	Showed pulsatile swelling behavior.	Kheirandish et al. (2009)
8.	Poly(*N,N*′-diethylaminoethyl methacrylate) PDEAEM	Preparation of pH-sensitive hydrogels for modulated insulin delivery.	Glucose oxidase most commonly used enzyme in glucose sensing. It oxidizes glucose to gluconic acid, resulting in a pH change of the environment. Due to swelling of membrane, more drugs is released than the membrane in the less-swollen state.	Khoylou & Naimian (2009)
9.	Phenylborate-poly(vinyl alcohol)	Preparation of Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin in self-regulated manner.	Glucose-responsive gels based on the complexation between polymers and poly(vinyl alcohol) lead to high-glucose sensitivity at physiological pH.	Kidd et al. (2011)
10.	Poly(N-isopropylacrylamide-co-methacrylic acid) (PNIPAm*/mAA)*	Glucose-sensitive, nanoparticle using poly(NIPAm/mAA) developed to prevent diabetes-related cases of Alzheimer's disease.	Dynamic glucose-sensitive insulin delivery systems prepared using poly(NIPAm/MAA) nanoparticle with controlled release pattern.	Kikuchi et al. (1997)

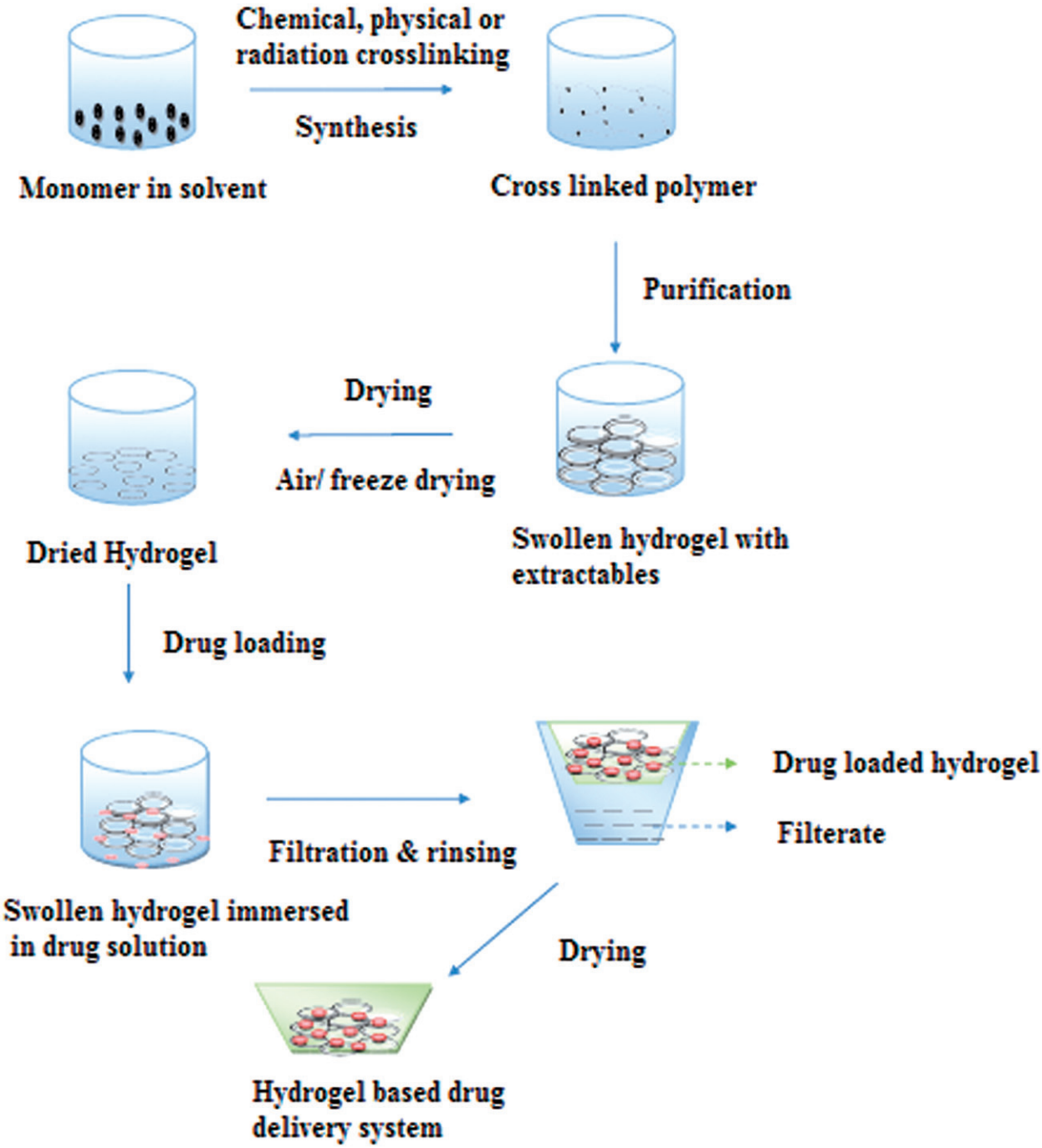


Figure 3. General schematic preparation of hydrogels.

Crosslinking by irradiation

Radiation crosslinking technique is widely used, since it does not involve the use of chemical additives and therefore retains the biocompatibility of the biopolymer (Peppas et al., 1986). The technique mainly relies on producing free radicals in the polymer following the exposure to the high-energy source, such as gamma ray, X-ray or electron beam. The radiolysis of water molecules using radiations results in the formation of hydroxyl radicals, which attacks the polymer chain to form macroradicals. Recombination of macroradicals on different chains results in the formation of covalent bonds that ultimately leads to crosslinking (Shu & Zhu, 2002). This whole procedure is carried out in the presence of inert atmosphere or nitrogen as macroradicals can interact with oxygen.

Physical crosslinking

Limitations of covalent crosslinking can be overcome by reversible ionic crosslinking (Torre et al., 2003). Ionic polymers can be crosslinked by the addition of di- or trivalent counter ions. This method relies on the principle of gelling a polyelectrolyte solution (e.g. Na^+ alginate) with a multivalent ion of opposite charge (e.g. Ca^{2+} $2Cl^-$), e.g. chitosan polycationic polymer can form complex with

poly(acrylic acid). This polyelectrolyte complex undergoes slow erosion, which produce a more biodegradable material than covalently crosslinked hydrogels (Noble et al., 1999; Berger et al., 2004). In contrast to covalent coupling, there is no additional requirement of catalyst (Spinelli et al., 2008).

Grafting polymerization

Grafting involves the polymerization of a monomer on the backbone of a preformed polymer and these polymer chains are activated by the action of various chemical reagents and high-energy irradiations. The production of functional monomers on these activated macroradicals leads to branching and then to crosslinking (Figure 4). Starch grafted with acrylic acid by using *N*-vinyl-2-pyrrolidone is an example of chemical grafting (Said et al., 2004) whereas the preparation of hydrogel of CMC by grafting CMC with acrylic acid in the presence of electron beam in aqueous solution is an example for the formation of hydrogels using high-energy radiation. The electron beam in radiation treatment is used to initiate the free radical polymerization of acrylic acid on the backbone of CMC. The water radiolysis product can also be helpful to abstract proton form macromolecular backbones. Irradiation of both CMC and monomer leads to produce free radicals, which combine to produce hydrogels (McMullan, 2005).

Characterization of hydrogels

Morphological characterization

Scanning electron microscopy

Hydrogels can be characterized for their morphology by the use of scanning electron microscopy (SEM). It provides the two-dimensional images which are six-order magnified images of a sample under vacuum (Zworykin et al., 1942; Omidian et al., 2005). SEM is also used to determine the surface topology, composition and electrical conductivity of the dried samples. SEM has significance as it can determine the pore size and pore structure of building block which affects swelling and further allows controlled release of the bioactive material from the hydrogels.

Atomic force microscopy

It is a very high-resolution type of scanning probe microscopy having an advantage over scanning electron microscopy as it provides 3D surface profile (Janshoff et al., 2002). The mechanism involves the approaching of the tip of the probe to the surface of the material results in a decrease in amplitude of the oscillation due to increased interaction between the surface and the tip. This oscillation can be compared with an external reference which provides information on the surface characteristics of the material (Harasaki et al., 2001; Geisse, 2009). Atomic force microscopy can work well with an ambient air and even in a

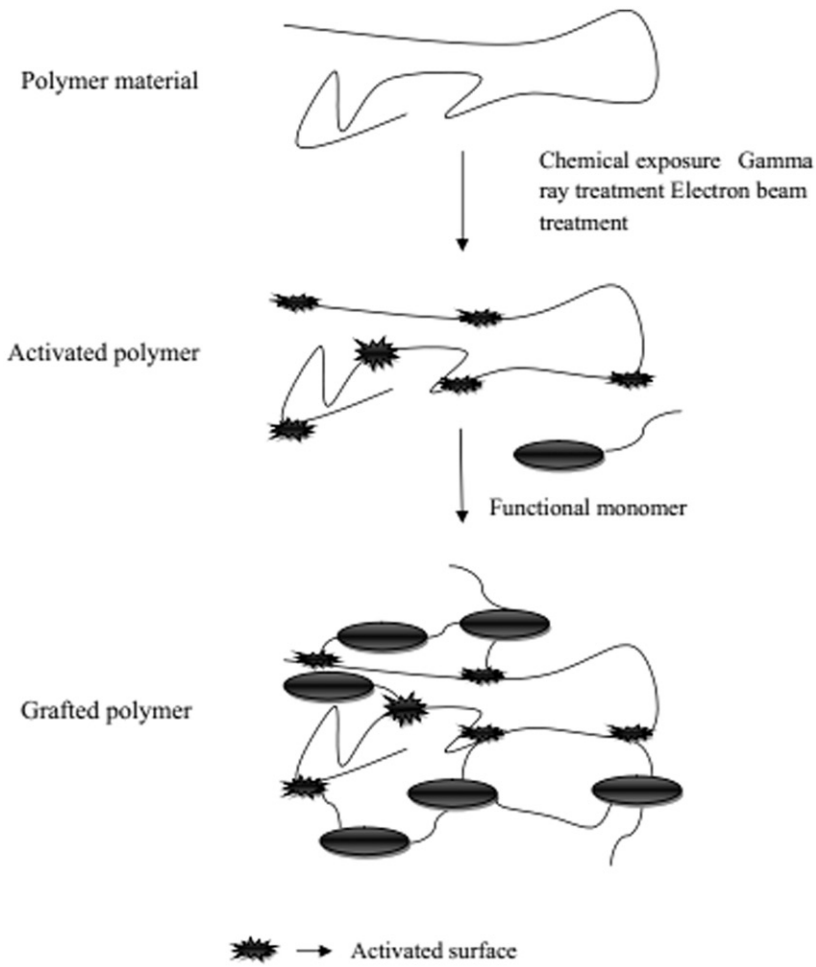


Figure 4. Grafting of a monomer on performed polymer backbone leading to branching and crosslinking.

liquid environment which makes it possible to study biological macromolecules and even living organisms (Alarcon et al., 2005).

Chemical/physical characterization

The functional groups play a significant role in the water holding capacity of the hydrogel. By modification of functional groups, the properties of hydrogels can be improved. The characterization based on these groups can be carried out using techniques like UV–visible spectroscopy, infrared (IR) spectroscopy, mass spectrometry and nuclear magnetic resonance (NMR; Mansur et al., 2008). Mansur and co-workers carried out Fourier transform infrared spectroscopy (FTIR) for characterization of Polyvinyl alcohol–glutaraldehyde crosslinked hydrogels and found vibrational band between 2840 and 3000 cm^{-1} which refer to the stretching C–H from alkyl groups and the peaks between 1750–1735 cm^{-1} are due to the stretching of C=O and C–O from acetate group. The considerable reduction of the intensity of the O–H peaks from the hydrogel indicates the formation of acetal bridges (Kumar et al., 2007).

Swelling characterization

The polymer chains in a hydrogel interact with the solvent molecule (usually water) and tend to expand to the fully solvated state, while the crosslinked structure applies a retractive force to pull the chains inside (Wang et al., 2010). Equilibrium is achieved when these expanding and retracting forces counter balance each other. Swelling studies can be carried out by immersing completely dried hydrogels in swelling medium and latter the hydrogel is removed from the solution and weighed after an excessive solution on the surface is blotted (Bhattarai et al., 2010). The swelling characteristics are crucial to the use of hydrogels in biomedical and pharmaceutical applications since the equilibrium-swelling ratio influences the solute diffusion coefficient, surface mobility, optical and mechanical properties of the hydrogel (Tang et al., 2007). The swelling properties are determined by many factors, including the type and composition of monomers, crosslinking density and other environmental factors (temperature, pH and ionic strength; Nicodemus & Bryant, 2008).

The swelling ratio is calculated by the following equation:

$$Q = (M_s - M_d)/M_d$$

where Q is the swelling ratio, M_s and M_d are the mass of hydrogel in the swollen state and in the dried state, respectively.

The water content of the hydrogels can be determined as the water loss of fully swollen polymer at different time intervals as a function of the time of exposure at 37 °C (Serafim et al., 2013).

The water content is determined as a function of time by this equation:

$$\text{Water content} = \frac{W_w}{(W_w + W_g)}$$

where W_w is the weight of water and W_g is the weight of gel.

Rheological characterization

The rheological properties are very much dependant on properties of hydrogels like association, entanglement and crosslinking agent present in hydrogels (Kheirandish et al., 2009). Viscous polymer solutions follow the law $G' \sim \omega^2$ and $G'' \sim \omega$ where G' and G'' represents shear storage modulus and shear loss modulus, respectively, while ω represents the angular velocity. Elasticity dominates in case when $G' > G''$ which represents the Maxwell-type behavior having single relaxation time and this behavior increases with the increase in concentration (Weng et al., 2007). Weng et al. carried out rheological measurements for *in situ* crosslinking hydrogels formulated from oxidized dextran and *N*-carboxyethyl chitosan and characterized the network structure in hydrogel (Zhang & Ma, 1999).

Porosity and density characterization

The solvent replacement is the main method for determination of porosity, which involves the immersion of dried hydrogels overnight in absolute ethanol and weighed after blotting of excess ethanol on the surface (Shi et al., 2002; Polnok et al., 2004).

The porosity can be calculated from the following equation:

$$\text{Porosity} = \frac{(M_2 - M_1)}{\rho V}$$

where M_1 and M_2 are the mass of the hydrogel before and after immersion in absolute ethanol, respectively, ρ is the density of absolute ethanol and V is the volume of the hydrogel.

The solvent displacement method is used to carry out the density determination of dried hydrogels, which actually show the apparent densities of the hydrogels. This method involves the weighing of dried hydrogels and then these hydrogels are immersed in a predetermined volume of hexane and the increase in the hexane volume was measured as the volume of the polymer (Chang, 1988).

The density can be calculated using the following equation:

$$\text{Density} = M_h/V$$

where M_h is *m*ass of hydrogels and V is the volume of solvent displaced by hydrogels.

Determination of void fraction

Void fraction can be defined as the measure of empty void spaces in the hydrogel. It is a fraction of the volume of voids over the total volume of hydrogels (Chen et al., 2000). The void fraction inside hydrogels can be determined by immersing the hydrogels in swelling media up to equilibrium and this volume can be determined as the dimensional volume. Total volume of pores can be determined by subtracting the weight of dried hydrogel from the weight of swollen hydrogel (Gorgieva & Kokol, 2012).

The void fraction can be calculated using the following formula:

$$\text{Void fraction} = V_d/V_t$$

where V_d is dimensional volume of the hydrogel and V_t is the total volume of pores.

In vitro weight loss profile

In vitro weight loss profile of the hydrogels describes the change in weight as a function of time. Dried hydrogels in the desired swelling medium are used for sampling which firstly includes washing with distilled water, and then drying in vacuum oven until constant weight is obtained (Chiu et al., 2013). The percentage weight loss can be calculated using this formula:

$$\text{Percent weight loss} = \text{Wt}_{(i)} - \text{Wt}_{(t)}/\text{Wt}_{(t)} \times 100$$

where $\text{Wt}_{(i)}$ is the initial weight of hydrogel at time zero and $\text{Wt}_{(t)}$ is the weight of the hydrogel at time t.

Mechanical characterization

The mechanical strength mainly depends on the composition and structure of the hydrogels. These hydrogels possess weak mechanical strength in fully swollen state due to the high water content (Nicodemus & Bryant, 2008). The mechanical properties of the hydrogels are affected by the degree of swelling, co-monomer composition, polymerization conditions and crosslinking density (Mauck et al., 2006). Bench compactor can be used for testing the mechanical properties of the hydrogels (Jaiswal & Koul, 2011). Mechanical characterization can also be used to determine the multi-components of the hydrogels (Kazakia et al., 2006).

Most common methods used to determine the mechanical properties of hydrogels include tensile testing or strip extensiometry. In strip extensiometry technique, tensile force is applied to the strips of material held between two grips. In ring extensiometry, tensile force can be applied to a ring instead of a single strip. Thus, the shear-strain chart can be obtained between the applied force and elongation of the material. This chart can be used to find out different mechanical properties of the hydrogels, including Young's modulus, yield strength and ultimate tensile strength. Extensiometry can also be used to examine the viscoelastic nature of a hydrogel material by elongating the material strip to a particular length and examining the stress relaxation response over time at a constant strain. Compression is another technique used to examine the mechanical properties of hydrogel. It involves placing the material between two plates and compressing it. Pressure is applied to the hydrogel surface to calculate the mechanical properties of the hydrogel using a theoretical model. The main advantage of compression test over extensiometry is that it does not limit the hydrogel geometry to strips or rings (Svensson et al., 2005).

Mechanical properties of the hydrogels could be affected by the type of crosslinking agent and density (Drury & Mooney, 2003). Zhang and co-workers worked on the development of collagen–chondroitin sulfate–hyaluronic acid hybrid hydrogel (CCH) scaffolds. Their results showed that the compressive modulus of the crosslinked hydrogels increased from 44.93 to 53.67 kPa with the increase in concentration of genipin (crosslinking agent) up to 1 mM. Results of compression showed that the compressive modulus of non-crosslinked CCH hydrogels was slightly greater than that of collagen hydrogels, which may be due to the compressive behavior of the negatively charged glycosaminoglycans (GAGs). It is based on the theory that water molecules attracted more towards the negative charges of the GAGs, which leads to the increase in compressive capabilities of the tissue (Almarza & Athanasiou, 2004; Chao et al., 2007). In addition, the concentration of genipin greatly affects the compressive modulus and shows a slow increase in compressive modulus from 44.93 to 53.67 kPa with the increase of genipin concentration. They also found that pure collagen was sufficient to provide mechanical strength to hydrogel. Thus, biological and mechanical properties of collagen hydrogel could be increased by blending hydrogel with suitable polymers [i.e. poly(glycolic acid), poly(lactic-*co*-glycolic acid) and chitosan], and by adding a suitable chemical crosslinking agent, which simultaneously affect the swelling properties of the hydrogels (Zhang et al., 2011). In the market, a large number of hydrogel-based products are being used (Table 6).

Applications

Hydrogels are being used in a variety of applications ranging from drug delivery to tissue engineering applications. They have gained importance due to their ability to be delivered through different routes like transdermal, subcutaneous, implantable, ocular, rectal, vaginal, pulmonary, dermal and nasal routes (Junginger, 1991; Nagai & Machida, 1993; Park & Park, 1996).

Wound healing

Hydrogels act as a moist wound dressing material and have ability to absorb and retain the wound exudates along with the foreign bodies (bacteria etc.) within its network structure. In addition, hydrogels have been found to promote fibroblast proliferation by reducing the fluid loss from the wound surface and protect the wound from external impurities which have great impact for rapid wound healing and maintains the microclimate for biosynthetic reactions which is necessary for normal cellular activities (Lopez & Bodmeier, 1997).

Hydrogels carry out fibroblast proliferation and keratinocyte migration which are necessary for the epithelialization of the wound. Hydrogel sheets are generally applied over the wound surface with backing of fabric or polymeric film and are secured at the wound surface by the use of adhesives or bandages (Ueno et al., 2001). Dextran-based hydrogels are prepared to promote neovascularization and skin regeneration in a third-degree burn wounds (Sun et al., 2011). The covalently bound heparin (heparin sulfate proteoglycan) is a multivalent biomaterial which can be used for controlled release of basic fibroblast growth factor (bFGF; Figure 5).

Tissue engineering

Tissue engineering (TE) is a multidisciplinary approach for the development of biological substitutes. The principles of TE have been used extensively to restore functions of the traumatized/malfunctioning tissues or organs by combining the patient's cells with a scaffold for generating new tissues (Hoffman, 2002; Hench & Jones, 2005). The pore size of the scaffolds should be optimized, as it is necessary for the cell

Table 6. Currently available hydrogels based products in the market.

S. No.	Products	Company name	Hydrogel composition	Application
1	SQZ Gel™ oral controlled release system	Macromed (Sandy, UT, USA)	Chitosan and polyethylene glycol	Hypertension
2	Hycore-V™ and HYcore R™	CeNeS Drug Delivery (Irvine, UK)		Vaginal and rectal infections, localized delivery of metronidazole
3	Cervidil vaginal insert	Controlled therapeutics, UK; marketed by Forest Pharmaceuticals (St Louis, MO, USA)	Poly(ethylene oxide) and urethane	Cervidil Vaginal Insert (dinoprostone, 10 mg) is indicated for the initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor.
4	Smart Hydrogel™	MedLogic Global (Plymouth, UK)	Poly(acrylic acid) and poly(oxyethylene-*co*-oxyethylene) glycol	Ophthalmic, Buccal, nasal, Vaginal, Transdermal, Injectable, Implantable and non-aerosol pulmonary drug, provide stimuli-responsive drug delivery
5	Aquamere™	Hydromer (Somerville, NJ, USA)	Interpolymers of PVP and PVP-grafted copolymers with urethane	Skin care, topical and oral drug delivery
6	Aquatrix™ II	Hydromer	Chitosan-PVA	Skin adhesive gels, wound and burn dressing, implants and drug delivery matrices
7	Hypan	Hymedix International (Dayton, NJ, USA)	Hydrophilic acrylate derivatives with a unique multiblock structure	Used in the manufacture of soft contact lenses and moisturizing wound gels and dressings
8	Gelrite™	Merck & Co., Inc.	Deacetylated gellan gum, Gelrite, alginate	Used for ocular delivery of drugs. It is converted into gel in the presence of sodium ions in tears, leads to sustained release of drugs.
9	Lutrol®	BASF SE-Care Chemicals Division-Pharma Ingredients & Services-67117 Limburgerhof	Lutrol FC-127 and Poloxamer 407	Used for ocular delivery using phase transition mechanism. They increase the viscosity of gel in system at 37 °C.
10	WOULGAN Biogel	Biotec BetaGlucans	Carboxymethyl-cellulose (CMC) and beta-glucan (SBG)	Used as wound healing product
11	MEDIHONEY	Derma Sciences	Leptospermum honey (i.e. Manuka)	Used in first and second degree burns dressing
12	AQUATRIX II hydrogels	Hydromer Inc.	PVP/Chitosan, PVP/Polyethyleneimine	Drug delivery and in burn application
13	AQUAMERE S-SERIES	Hydromer Inc.	PVP/Dimethyiconylacrylate/Polycarbamyl/ Polyglycol Ester	Cosmetic products (sun and hair care and skin treatment)
14	DERMASEAL allergen-blocker	Hydromer Inc.	Hydroxypropylcellulose/Methyl Gluceth-20	Skin protectant
15	COLLAGRAFT	Nuecoll Inc., Zimmer Inc.	Bovine type I collagen	Used in long bone fracture cases
16	CollapatII©	Biomet Inc.	Bovine type I collagen	Used intact or after proteolytic removal of the small non-helical telopeptides, which reduces possible antigenicity.
17	ZATAMIL®	Zatamil® Ego Pharmaceuticals Pvt Ltd	MOMETASONE FUROATE 0.1% w/w	For the treatment of psoriasis and atopic dermatitis
18	VISCOAT	Visco Vision Inc., Taiwan	Silicone and biphasic chitosan	Used as surgical aid in anterior segment procedure
19	GELFOAM®	Baxter U.S.	absorbable gelatin sponge	Used in hemostatic device
20	BIOPOL®	Chemipol S.A. Espana	Poly(vinyl alcohol)	Used in cardiac tissue engineering
21	PURILON™	Southwest Medical	Comfeel Purilon Gel	Used as wound dressing material
22	CORPLEX™	Corium International	Polysiloxanes, polyacrylates, ethylene vinylacetate and polyisobutylenes and other rubber-based PSAs	Used for optimal application in mucosal or dermal drug delivery
23	Pure Vision Bifocal	Bausch & Lomb, Japan	Polymer with silicone	Used in the development of soft contact lenses

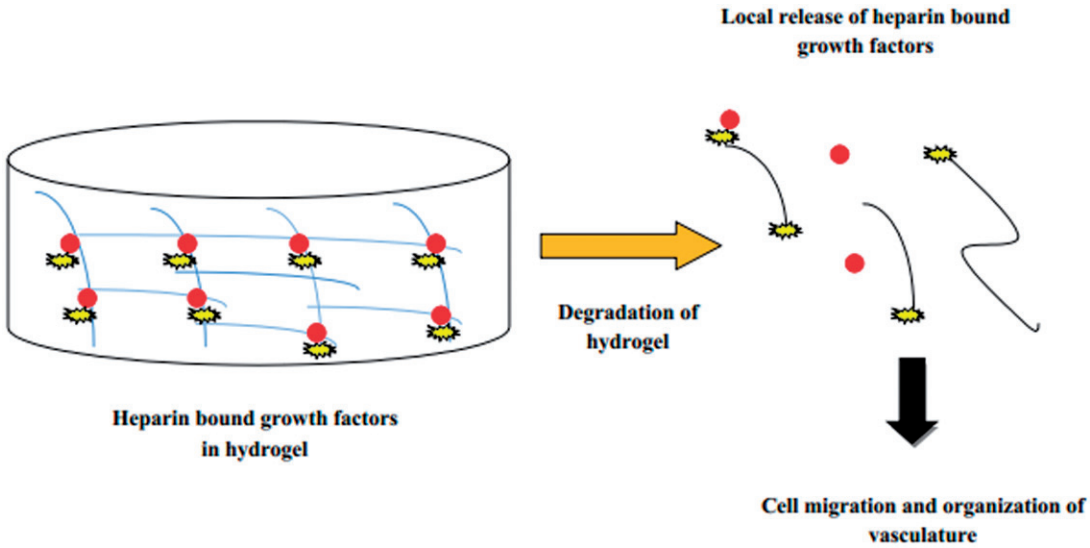
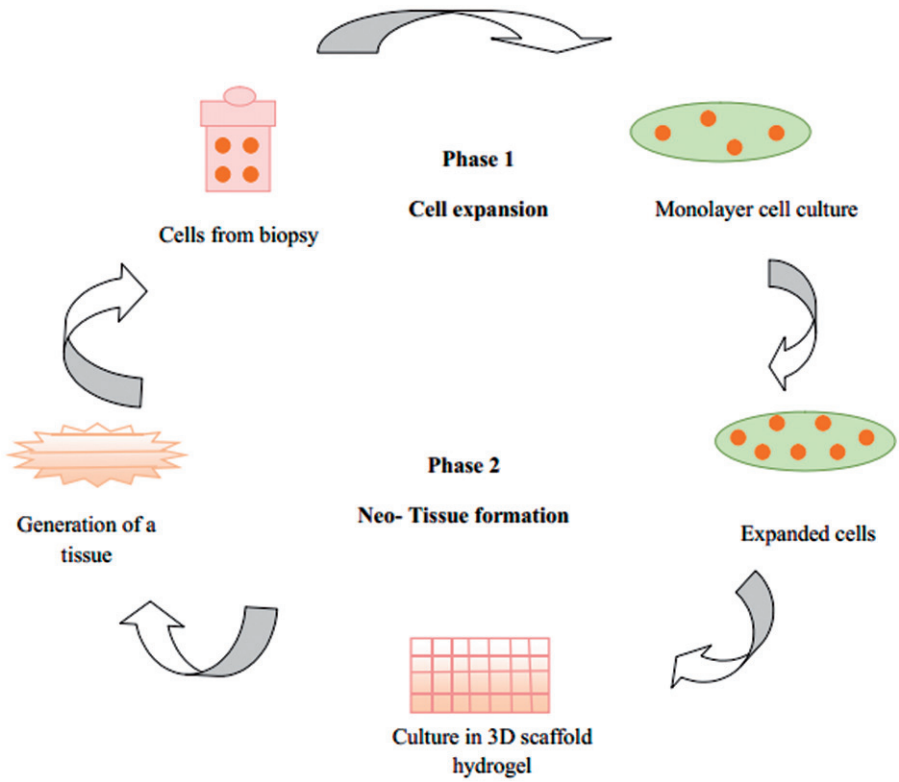


Figure 5. Release of heparin bound growth factors from hydrogels in wound healing.

Figure 6. Schematic flow chart of basic principle of tissue engineering using hydrogels as extracellular matrix.



migration into the core of the scaffolds, angiogenesis and supply of nutrients to the cells and to take away the metabolic products away from the cells (Pal et al., 2008). By tissue engineering, ideally, patient-derived cells can be cultured *in vitro* and combined with hydrogel matrix to form a 3D scaffold, fabricated by simple molding technique or more advanced bioprinting procedures (Figure 6).

Microfabrication techniques are potentially powerful tools in tissue engineering since they can be used to replicate structures which are in the order of 0.1–10 mm. Microengineered hydrogels are classified as either ''top down'' or ''bottom up''. Top down approach utilizes microengineering approaches to control the microscale features of relatively large pieces of hydrogels. This approach includes designing and micromolding of the shapes of the scaffolds (Borenstein et al., 2002; Fidkowski et al., 2005). In the bottom-up approach, fabrication by the assembly of smaller building blocks is carried out. This approach mimics much of the native biology that is often made from repeating functional units.

For example, the sinusoid is the repeating functional unit found in the liver. Bottom-up approaches can be used to generate functional units that can be assembled in a modular approach to generate larger scaffolds (McGuigan & Sefton, 2006).

Tissue printing is an emerging approach that can also be used to form tissues from smaller building blocks. Using tissue printing, it is possible to generate microvasculature and

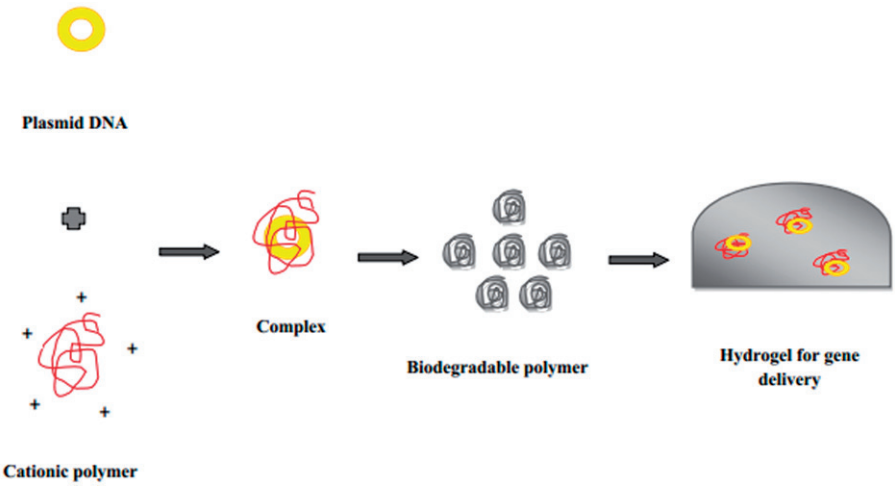


Figure 7. Gene delivery of hydrogels incorporating biodegradable polymer.

desired architecture in tissues (Mironov et al., 2003). Although a number of challenges (ejector clogging and poor tissue mechanics) have limited the current applications of this technology. It is anticipated that through further research the tissue printing will become a powerful ''bottom-up'' approach to engineer complex 3D tissues.

Colon specific drug delivery

Colon specific hydrogels of polysaccharides have been specifically designed because of the presence of high concentration of polysaccharidase enzymes in the colon region of GI (gastrointestinal) tract. Drugs loaded in such hydrogels show tissue specificity and change in the pH or enzymatic actions causes the release of the drugs (Calejo et al., 2012). Stomach-specific antibiotic delivery for the treatment of *Helicobacter pylori* infection in peptic ulcer is a good example of such system (Patel & Amiji, 1996).

Gene delivery

Most plasmid DNA delivery systems based on synthetic polymers can lead to *in vitro* degradation of biodegradable polymer for more than 30 days (Figure 6). Gene delivery generally mediated by viral and non-viral methods. But, viral vectors are quite limited as they can produce immunogenic reactions or mutagenesis of transfected cells therefore, after the relevance of non viral approaches scientist put interest to involve the use of polymers viz. poly-L-lysine (PLL), PGA, PLA and PLGA for gene delivery (Choi & Park, 2005). The use of PEG–PLGA–PEG hydrogel for the delivery of plasmid-beta 1 gene increased the wound healing process in a diabetic mouse model (Lee et al., 2003).

Further, researchers reported the use of recombinant silk-elastin like polymer hydrogels (SELP) for the delivery of pRL-CMV for the treatment of human breast cancers (Mageed et al., 2004). These results suggest that an increase in the transfection efficiency when SELP hydrogels were used. Inclusion of basic fibroblast growth factor (BFGF), insulin growth factor II (IGF-II) and collagen within the microcapsules showed proliferation and differentiation of encapsulated C2C12 myoblasts cell lines. When tested against tumor induced by B16-Fo/neu tumor cells in mice, the alginate polylysine alginate (APA) microcapsules showed 80% reduction in tumor volume at day 21 (Li et al., 2006). Lentiviral gene therapy vectors can be entrapped within fibrin hydrogels alone or in complex form with hydroxylapatite (HA) nanoparticles, which provides an opportunity to enhance the bioactivity of fibrin hydrogels for a wide range of applications in regenerative medicine (Kidd et al. 2011). Gene delivery of hydrogels incorporating biodegradable polymer is shown in Figure 7.

Ocular drug delivery

In conventional ocular drug delivery, there are various constraints like effective drainage by tear, blinking and low permeability of the cornea, short-term retention of the drugs and in suspensions and ointments, the unpleasant irritation feeling made scientists to take interest on the hydrogels for ocular drug delivery. The *in situ* gelling system is prepared using alginate with high gluronic acid content for the ophthalmic delivery of pilocarpine. This system significantly extended the duration of action of pilocarpine to 10 h compared to pilocarpine nitrate as solution which was only 3 h of duration of action (Cohen et al., 1997). Nowadays, silicone hydrogel therapeutic lenses are considered a place for their use in recurrent corneal erosions, irregular corneas, keratoconus as bandage lenses (Stapleton et al., 2006).

Transdermal delivery

The possible benefits of hydrogels in transdermal drug delivery include (a) drugs can be delivered for a long duration at a constant rate, (b) can be easily interrupted on demand by simply removing the devices and (c) can by-pass hepatic first-pass metabolism and also due to higher water content, swollen hydrogels can provide a better environment for the skin in comparison to conventional ointments and patches. The hydrogels obtained from the copolymerization of bovine serum albumin (BSA) and PEG succeeded as transdermal hydrogels due to their high water content (over 96%) which allow the release of both hydrophilic and hydrophobic drugs. Their use as novel drug formulation in the field of wound dressing was proposed as the potential application of the BSA–PEG hydrogels (Gayet & Fortier, 1996). The experimentation was carried out to design a practically controlled-release transdermal system for selegiline using thermo-sensitive hydrogels using copolymers of alginate and

pluronic F127 which lead to the reduction in the intersubject variability of skin permeation (Chen et al., 2011a).

Subcutaneous delivery

Hydrogels show their applications in implantable therapeutics. Subcutaneous exogenous inserted materials may evoke undesirable responses, such as inflammation, carcinogenicity and immunogenicity. Hydrogels are considered as biocompatible materials due to their high water content. They also provide several promising properties such as (i) minimal mechanical irritation upon *in vivo* implantation, due to their soft, elastic properties; (ii) prevention of protein adsorption and cell adhesion due to low interfacial tension between water and hydrogels; (iii) broad acceptability for individual drugs with different hydrophilicity and molecular sizes; and (iv) unique possibility (crosslinking density and swelling) to manipulate the release of incorporated drugs (Sinha & Khosla, 1998). Several hydrogel formulations for the subcutaneous delivery of anticancer drugs have also been proposed, e.g. PHEMA in crosslinked form when applied with cystabine (Ara-C) and methotrexate showed good biocompatibility (Beyssac et al., 1996; Teijon et al., 1997). Poly(AAm-co-monomethyl or monopropylitaconate) developed by Blanco's group was employed for the controlled release of Ara-C and 5-fluorouracil (Blanco et al., 1998). The subcutaneous reservoir hydrogel implant were prepared using copolymer of 2-hydroxyethyl methacrylate (HEMA) and are of great interest due to biocompatibility, reversible swelling in aqueous environment, resistance to biodegradation and microbial growth (Kuzma et al., 2011).

Biomedical applications of stimuli-responsive polymers in novel drug delivery

Stimuli-responsive polymers are those that respond sharply to small changes in physical or chemical conditions. These polymers are also known as ''environmentally sensitive'', ''smart'' or ''intelligent'' polymers. They have numerous biomedical applications, especially in the field of drug delivery, cell culture surfaces and in diagnosis. These stimuli-responsive polymers may also be combined with a variety of bioactive molecules, such as nucleic acids, proteins and peptides, small organic molecules and carbohydrates, e.g. poly(ethylene glycol) (PEG) may be conjugated to with the poly(lactic-*co*-glycolic acid) [PLGA] to provide ''stealth'' properties. The example of most common smart polymer is poly(*N*-isopropyl acrylamide), or PNIPAAm which is thermally responsive smart polymer. Some of these polymers may respond to more than one stimulus, such as a copolymer of NIPAAm and acrylic acid (AAc), which is responsive to both temperature and pH. Similarly, copolymers of pH-sensitive methacrylic monomers such as methacrylic acid (MAAc) and hydrophobic methacrylate monomers, such as methyl methacrylate (MMA) are used to prepare enteric-coated tablets. They released the drug in the intestine where the pH rises to physiologic pH levels. These polymeric coatings are useful for protecting ''fragile'' drugs from stomach acid and gastric enzymes (Hoffman, 2013). Vernon and group developed tri-block copolymers, mixed them with drugs and injected sub-cutaneously or intra-muscularly to form phase separated, degradable, drug depot masses at body conditions. These tri-block copolymers were composed of alternating ABA or BAB blocks such as PLGA–PEG–PLGA or PEG–PLGA–PEG blocks and were thermally gelling, hydrolytically degradable in nature. These tri-block polymers released the drug slowly by dissolution and diffusion of the drug (Vernon et al., 2000). These smart polymers have also been designed to escape intracellular uptake by the macrophage. Ethyl acrylic acid (EAAc) and propyl acrylic acid (PAAc) form pH-sensitive polymers and copolymers which become sharply hydrophobic as the pH is lowered through their p*K*s, which is within the pH range of early endosomes. When Ethyl acrylic acid (EAAc) and propyl acrylic acid (PAAc) that form pH-sensitive polymers are conjugated or complexed with drugs and endocytosed into target cells, they can disrupt the lipid bilayer of the endosome as pH drops within the endosome, enhancing the escape of the polymer–drug carrier into the cytosol (Yin et al., 2006).

These stimuli-responsive polymers are steadily increasing attention of many scientists in the biomedical applications, especially in the fields of controlled and self-regulated drug delivery due to their close resembles with the normal physiological process of the disease state, thus ensuring optimum drug release as per physiological need (Bawa et al., 2009). These polymers have many advantages in drug delivery because they experience rapid changes in their structure triggered by small changes in the outer environment. One of the polymer named poly(NIPAAm-*co*-AAm) copolymers was used by Li and group to develop Gold (Au) nanocages for the controlled release using high-intensity focused ultrasound (HIFU). They modified the surface of gold nanocages using thermally responsive copolymer, poly(NIPAAm-*co*-AAm) (NIPAAm: *N*-isopropylacrylamide; AAm: acrylamide) by means of gold-thiolate linkage. These copolymers lead to conformational changes in response to temperature changes at a transition point known as LCST. This conformational change with temperature change control the drug release by altering the duration in which the polymer chains are kept in the high-temperature state. When a significant amount of acoustic energy is applied to the focus using HIFU, the temperature in the focal volume of the sample increases rapidly. As the temperature rises beyond the LCST of the copolymer, the polymer chains change from a stretched conformation to a collapsed state. This leads to the opening of the pores of the gold nanocages resulting in the drug release. However, when HIFU is turned off, the temperature drops to its original state and the polymer chains relax back to their extended conformation, blocking their pores and thus terminating the drug release. Thus, they successfully developed a platform for HIFU-induced, localized and controlled drug release from the Au nanocages covered with thermally responsive polymers (Li et al., 2011).

In the recent years, stimuli-responsive nanogels also known as polymeric nanoparticles are reported by many researchers that are capable of responding to external stimuli by changing their physico-chemical properties, such as volume, water content, refractive index, permeability and hydrophilicity–hydrophobicity. As compared to other polymeric nanoparticles, these stimuli-responsive nanogels

provide advantages of high stability, prolonged circulation time in the blood stream, high encapsulation efficacy, controlled as well as site-specific drug release modulated by environment stimuli. These applications of stimulus-responsive nanogels make them an active participant, rather than a passive carrier for drug delivery (Zha et al., 2011).

With the advancement in drug delivery application, self-folding polymeric containers are introduced recently to encapsulate a variety of therapeutic cargos such as small molecules, peptides, proteins, bacteria, fungi and mammalian cells. These self-folding polymeric containers contain a thin film or interconnected planar templates curve, roll-up or fold into 3D structures such as cylindrical tubes, spirals, corrugated sheets or polyhedra. These self-folding polymeric containers are important for drug delivery applications since they provide a means to realize 3D, biocompatible, well-tailored composition, size, shape, wall thickness, porosity, surface patterns and chemistry (Fernandes & Gracias, 2012).

Recently, Malachowski et al. (2014) proposed a thermo-responsive multi-fingered drug eluting devices. Their aim was to design such tissue gripping drug delivery devices that offer an effective strategy for sustained release of drugs with immediate applicability in the gastrointestinal tract. These were prepared using rigid poly(propylene fumarate) segments and stimuli-responsive poly(*N*-isopropylacrylamide-*co*-acrylic acid) hinges and are referred to as theragrippers. The stimuli-responsive polymer allows them to close above 32 °C thus provide a spontaneously gripping onto tissue when introduced from a cold state into the body. They studied the release potential of theragrippers loaded with fluorescent dyes and commercial drugs such as mesalamine and doxorubicin and found an enhanced release as compared to a control batch (Malachowski et al. 2014).

Yang et al. (2014) developed a new type of triple-stimuli-responsive (ultrasound/pH/GSH) biodegradable nanocapsules for intravenous drug delivery, which is filled with perfluorohexane, and the DOX-loaded PMAA with disulfide crosslinking. These soft biodegradable nanocapsules with uniform size of 300 nm can easily enter the tumor tissues by ensuring diagnostic and image-guided therapeutic applications using Ultrasound contrast agents (UCAs), thus provide applications in echogenic intravenous drug delivery (Yang et al., 2014). If such stimuli-responsive polymers could show significantly enhanced delivery of drugs such as siRNA, they might be utilized in clinical testing in the near future.

Limitations of hydrogels as drug delivery systems

(a) Low mechanical strength is the main problem with the use of hydrogel based drug delivery systems. In some cases, leaching of the drug may result (Patil et al., 2011).
(b) They are difficult to handle (Peppas & Colombo, 1997).
(c) Drug is very difficult to load in hydrogel-based drug delivery systems (Amsden, 1998).
(d) Sterilization is the main problem with the use of these delivery systems (Arndt et al., 2004).
(e) Swelling of temperature-sensitive hydrogels affected greatly by changes in the temperature of swelling medium (Mason et al., 2001).
(f) Polymer complex can be broken or the network can be swollen as a result of changes in external environment (Bromberg & Ron, 1998).
(g) Monomers and crosslinkers used in the synthesis of the hydrogels are not biocompatible, i.e. they may be toxic, carcinogenic or teratogenic (Chiu et al., 1999).
(h) One of the major limitation of pH-sensitive polymers is their non-biodegradability. Hydrogels made of non-biodegradable polymers have to be removed from body after use. Non-biodegradability is a serious issue in case of implantable drug delivery agents or implantable biosensors (Beckert & Al, 1970).
(i) Glucose-sensitive hydrogel systems do not retain their original states fast enough after responding to the change in glucose concentration (Qiu & Park, 2001).
(j) Hydrogel suffers from problem of reproducibility (Qiu & Park, 2001).
(k) Electro-sensitive hydrogel-based drug delivery systems cannot work properly under physiological conditions and cannot modulate the drug release in a manner in which it is required (Qiu & Park, 2001).
(l) Reaction of hydrogels in response to stimulus (light) is very slow. In many cases, the conversion of light into thermal energy must precede the restructuring of polymer chains upon temperature change, which leads to leaching of content during swelling–deswelling cycles (Qiu & Park, 2001).

Clinical trials based on hydrogel-based drug delivery

A short-term clinical trial for the prevention of Peristomal Infection after Percutaneous Endoscopic Gastrectomy (PEG) was done by Blumenstein and group which was based on the development of glycerin-based wound dressing hydrogel. Glycerin hydrogel (GHG) wound dressing system has been proposed with more effective antimicrobial properties. The main purpose of this study was to check the superiority of GHG regarding the incidence of peristomal wound infections during a 30-day post-procedure follow-up. Sixty-eight patients with cancer undergoing PEG were selected from one university and two general hospitals between January 2007 and December 2008. Patients were randomized into the following groups: group 1 includes 34 patients who received GHG and group 2 includes 34 patients who received a traditional wound dressing. In group 1, dressing were changed at day 1 and weeks 1, 2 and 4. In group 2, dressings were changed daily during the first week and at weeks 2 and 4. Infectious site (PEG site) was assessed using two different infection scores. A statistically significant reduction in the mean infection score was observed in patients of group one (first week: 1.64 ± 1.6 versus 3.12 ± 2.69, $p < 0.008$; second week: 1.37 ± 1.11 versus 2.53 ± 2.37, $p < 0.02$). After 1 week, 14.7% wound reactions occurred in group 1 as compared to 47.05% wound reactions in group 2, i.e. traditional group ($p < 0.005$). It was observed that GHG wound dressing significantly reduced the peristomal wound infections and proved itself as convenient, cost-effective alternative for wound management following PEG (Blumenstein et al., 2012) and favored approximately five times less frequent dressing change. Another clinical trial was done on a patient-operated

Table 7. Recent patent on stimuli-responsive hydrogels for drug delivery applications.

S. No.	Title	Patent No.	Conclusion	References
1	PVA hydrogel	Publication no. US7235592. 26 June 2007	Provides methods of making covalently crosslinked vinyl polymer hydrogels having advantageous physical properties, and covalently crosslinked vinyl polymer hydrogel compositions made by such methods, as well as articles of manufacture comprising such covalently crosslinked vinyl polymer hydrogel compositions. The physical properties of the produced hydrogels can be adjusted by varying controlled parameters such as the proportion of physical associations, the concentration of polymer and the amount of radiation applied. Such covalently crosslinked vinyl polymer hydrogels can be made translucent, preferably transparent or opaque depending on the processing conditions. The stability of the physical properties of the produced vinyl polymer hydrogel can be enhanced by controlling the amount of covalent crosslinks.	Weng et al. (2007)
2	Composite hydrogel drug delivery systems	Publication no. US 6632457 B1. 14 Oct 2003	Compositions and methods are provided to control the release of relatively low molecular weight therapeutic species through hydrogels by first dispersing or dissolving such therapeutic species within relatively hydrophobic rate-modifying agents to form a mixture. The mixture is formed into micro particles that are dispersed within bioabsorbable hydrogels, to release the water soluble therapeutic agents in a controlled fashion. Methods of using the compositions of the present invention in therapeutic systems are also provided.	Witchterle & Lim (1960)
3	Silicone hydrogel contact lens	Publication no. US6861123 B2. 1 Mar 2005	The invention provides molds and mold inserts useful in the production of contact lenses. In particular, the invention provides high optical quality molds and inserts which are useful for the manufacturing silicone hydrogel contact lenses.	Yan et al. (2010)
4	Low friction hydrogel having straight chain polymers and method for preparation	Publication no. US20040116305 A1. 17 June 2004	A low friction hydrogel, wherein a linear chain polymer is admixed with or graft-polymerized to a polymer gel; and a method for preparing the hydrogel. The hydrogel exhibits improved low friction property over a conventional material.	Yang et al. (2009)
5	Method of manufacturing hydrogel dressings	Publication no. US4871490 A. 3 Oct 1989	A method of manufacturing hydrogel dressings from synthetic and natural polymers by polymerization and crosslinking involves pouring aqueous solutions of synthetic polymers, such as polyacrylamide and polyvinyl pyrrolidone, their monomers or their mixtures, natural polymers, such as gelatin or agar, or their mixtures and, possibly, plasticizing agents, such as poly/ethylene glycol/, poly/propylene glycol/and silicone oils, of the following composition: 2–20% by weight of synthetic polymers, not more than 5% by weight of natural polymers, not less than 75% by weight of distilled water and 1–3% by weight of plasticizing agent, into a mold imparting a shape to the dressing, tightly closing in that mold and subjecting to an ionizing radiation dose not smaller than 25 kGy.	Yang et al. (2014)
6	Hydrogel-based joint repair system and method	Publication no. US8242179 B2. 14 Aug 2012	The invention provides a system and method for treating an orthopedic condition using a hydrogel-forming composition, which forms a hydrogel *in situ* at a target location and at least bio-mechanically treats the condition. The invention also provides a hydrogel forming composition designed to form a hydrogel with desirable biocompatible and biomechanical properties. In some aspects, the hydrogel is formed in a water-permeable casing, which is delivered to an orthopedic joint in a minimally invasive manner. In particular, the system and method can be used for intervertebral disc replacement or repair.	Yin et al. (2011)
7	Hydrogel adhesive	Publication no. US4768523 A. 6 Sep 1988	An improved hydrogel adhesive, particularly adapted for adhesion and contact to tissue. It is especially useful in attaching electrical leads to tissue, e.g. in attaching pacemaker leads to the heart, interiorly or exteriorly.	Yin et al. (2006)
8	Phase separated, branched, copolymer hydrogel	Publication no. US7919542 B2. 5 Apr 2011	Hydrogel obtained comprises a composition comprising a mixture of a hydrophilic polymer and a polymer chain-modifying agent, wherein the polymer chain-modifying agent is selected from the group consisting of an aromatic tetracarboxylic dianhydride, a titanate, and a polyetherimide. Also provides a method for producing a phase separated, branched, copolymer hydrogel comprising a mixture of a hydrophilic polymer and a polymer chain-modifying agent. Provides an implantable medical device comprising a phase separated, branched, copolymer hydrogel wherein the phase separated, branched; copolymer hydrogel is formed of a hydrophilic polymer and a polymer chain-modifying agent.	Yong-Hee et al. (1994)
9	Crosslinked hydrogel compositions with improved mechanical performance	Publication no. US5541305 A. 30 Jul 1996	Provides a method of altering the water content of a hydrogel comprising treatment of said hydrogel with a liquid dehydrating composition. There is further provided a method of altering the water content of a hydrogel-containing medical device. The medical devices of the present invention comprise a hydrogel having a water level *ex vivo* lower than the thermodynamic equilibrium water level when *in vivo*. These medical devices comprise a hydrogel contacted with a liquid dehydrating agent, wherein said medical device has a lower water level *ex vivo* than the thermodynamic equilibrium water level when the medical device is *in vivo*.	Yoshii & Kume (2003)

microwave system based on hydrogel contact lenses. Clinical effects of a patient-operated system of microwave disinfection of soft contact lenses were checked in a prospective pilot trial involving 103 patients who were taken from five optometric practices. Fifty-six subjects used the test system for a period of 1 month and 13 subjects used the test system for a total period of 3 months. Slit-lamp test was used to examine the clinical signs in both test and control subjects. After 1 month, the incidence of all signs reported in the microwave group was not significantly found greater than in the control group ($p = 0.267$), and results were the same after 3 months ($p = 0.214$). There was a significantly greater incidence of edema in the 1-month test group and of staining in the control group. UV spectroscopic examination of worn lenses from test subjects exhibiting significant signs did not show a higher level of deposition than on lenses worn by control ($p = 0.397$) subjects (Crabbe & Thompson, 2001). A clinical trial of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) hydrogel for the treatment of deep second-degree burns was carried out. The efficacy and safety of a rhGM-CSF hydrogel to promote deep-second-degree burn wound healing was evaluated. In this multicenter, randomized, double-blind and placebo-controlled clinical trial, a total of 90 patients with deep second-degree burns were randomly divided into two groups. Complete healing time and percentage of wound healing at different time points was observed and side effects of the developed system were recorded. A statistically significant difference was observed at each time point ($p < 0.01$). However, no side effects were observed. These results showed that rhGM-CSF hydrogel significantly improved and accelerate deep second-degree burn wound healing, thus considered safe for use (Zhang et al., 2009). A number of patents have been compiled on stimuli-responsive hydrogels for drug delivery applications in the last few decades (Table 7).

Future scope

The design and synthesis of ''smart'' hydrophilic polymers and hydrogels has significant potential in biomedical and nanotechnology applications in future. The future success of these materials relies on the development of novel materials that can address specific biological and medical challenges. This development will occur through synthesis of new polymers or by modifying natural polymers. The desired tissue used as model to engineer their desired mechanical, chemical and biological properties into the hydrogel (Lee & Mooney, 2001) for tissue engineering. All over the world, the universities and scientific organizations are currently looking into ways of growing functioning heart cells on the heart to replace the tissue that dies when a heart attack occurs by using scaffolds consisted of materials, such as carbon nanofibers and gold nanowires to grow new heart tissue without the need for surgery (Zhang et al., 2011).

Glucose-sensitive hydrogels have the ability to mimic the normal endogenous insulin secretion that minimizes the diabetic complications like cardiovascular disorders; retinopathy and nephropathy as well as improve patient compliance as it can release the bioactive compound in a controlled manner and when it is required by the body. Therefore, this delivery system may play promising role in future (Obaidat & Park, 1996). Silicone hydrogel lenses have made even further progress towards a lens of first choice. Five silicone hydrogel lens types are now available which are recently launched at the American Academy of Optometry (AAO). Moreover, number of silicone hydrogel daily wearers over the year, increasing daily confirming that the majority of patients can be refitted from conventional hydrogel lens wear to silicone hydrogel daily wear with excellent results (Dumbleton et al., 2010). Researchers at Stanford have created a new conducting polymer hydrogel that features high electrochemical activity and can be easily deposited onto surfaces using an ink-jet printer or simply sprayed on. Therefore, these electrically conductive hydrogel may open new opportunities for medical sensors and implants (Pan et al., 2012). Hydrogels attached with adhesion molecules like polylysine (polylysine-modified hydrogels) which are brain mimetic materials for neural tissue engineering has a bright future as no any delivery system or natural phenomenon have the ability to regenerate the neurons (Rao et al., 2011). The above examples represent some of the approaches which can improve the efficiency of delivery system and can also involve regenerating the tissues as well as the neurons. The main advantageous feature of the hydrogel is that they can deliver the drugs with controlled rate and can be applied through all of the routes which bring attention to work upon it.

Conclusion

Revolutionary advancement has been done in the last few decades for the development of drug delivery system. With the advancement of novel drug delivery systems, hydrogel drug delivery system has further corroborated the link between therapeutic need and drug delivery. The main critical parameters required to be monitored are hydrophobicity/hydrophilicity of the polymer which have great impact on release rate and dissolution rate. The stimuli responses like pH, temperature and glucose levels are monitored to attain the controlled and site specific delivery which ultimately ensures achievement of better patient compliance. The most significant weakness of all these stimuli-responsive system is that their response time is too slow. Thus, the fast acting hydrogels are necessary and easier way to achieve this goal to make thinner and smaller hydrogels. Further advancement involves the synthesis of new polymers and crosslinking agents ensuring significant controlled release. The main success of hydrogel can be attained by high level of *in vitro–in vivo* correlation between their performance and ability to maintain the structural integrity in biological systems. If the achievements of the past can be extrapolated into future, then there will be high possibility to achieve newer trends in the field of novel drug delivery.

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Declaration of interest

The authors report no conflicts of interest.

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