

Review

Hydrogels as potential drug delivery systems

Saima Amin*, Saeid Rajabnezhad and Kanchan Kohli

Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi-110062, India.

Accepted 18 September, 2009

Hydrogels, the swellable polymeric materials, have been widely investigated as the carrier for drug delivery systems. These biomaterials have gained attention owing to their peculiar characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli. Hydrogels being biocompatible materials have been recognized to function as drug protectors, especially for peptides and proteins, from *in vivo* environment. Also these swollen polymers are helpful as targetable carriers for bioactive drugs with tissue specificity. This article presents an overview to the advances in hydrogel based drug delivery that have become the interest of most researchers.

Key words: Hydrogels, pH sensitivity, temperature sensitivity, glucose sensitivity, biodegradable.

INTRODUCTION

With ongoing research in advanced drug delivery formulations to provide stable and economical drug delivery systems, the focus is on hydrogels which are known to reduce the problems of not only conventional dosage forms but also of novel drug delivery systems which require a biocompatible, convenient and stable drug delivery system for molecules as small as NSAIDs (Non-steroidal anti-inflammatory drugs) or as large as proteins and peptides (Graham and Mc-Neil, 1984; Bajpai and Sonkusley, 2002). There are a number of evidences when such drug delivery devices are imperative such as delivery of insulin at elevated blood sugar levels where it is required to constantly provide the drug in the system. These controlled drug delivery systems are designed for zero order release kinetics which ensure constant drug release over a prolonged period of time. Drug targeting is achieved by using biocompatible polymers along with drug in micronized form and then attaching certain "homing devices" like antibodies. It leads to exposure of drug to diseased cells while the normal cells are protected (Stastny et al., 2002; Lowman and Peppas, 1991). All these approaches of dosage form designs require a carrier which should be biocompatible and biosensitive like hydrogels which are hydrophobic polymeric network of three dimensional structures consisting of single chain of polymers (monomers) being cross-

linked or chains of co-polymers being cross-linked. The cross linking renders these structures insoluble in water due to ionic interaction and hydrogen bonding (Peppas et al., 2000). These structures imbibe water or biological fluids in large amount at least 10-20 times their molecular weight thus become swollen (Kim et al., 1992). Cross-linked hydrogels have sufficient mechanical strength and physical integrity. If water is removed from these swollen biomaterials they are called xerogels, which are the dried hydrogels. When these dried hydrogels absorb 10-20 times weight of water they become super absorbent. Dehydrated hydrogels are called aerogels as their water is removed without causing structural deformation. Microgels are, however, those having small particles with a diameter of 100 nm and also swell in water.

The network structure of hydrogels can be macroporous, microporous or nonporous. Macroporous hydrogels are having large pores of dimension 0.1 to 1 μm . These hydrogels release the drug entrapped inside the pores through mechanism dependent on drug diffusion coefficient. Porosity and tortuosity of the gel network (Rowley et al., 1999; Aroca et al., 2007; Liu et al., 2000). Microporous hydrogels are having small pore size of the gel network, usually in the range of 100-1000 \AA . The drug releases by molecular diffusion and convection. However, when drugs and polymers are thermodynamically compatible, partitioning of drug through the hydrogel walls is predominant. Nonporous hydrogels are the mesh-like structures of macromolecular dimension (10–100 \AA) and are formed due to cross linking of monomer chains. The release of drug is only by diffusion mecha-

*Corresponding author. E-mail: daneshyarsaima@yahoo.com.
Tel: 011 26059676, ext 5663.

nism (Mc-Neill and Graham, 1993; Jhan and Andrade, 1973).

CHARACTERIZATION OF HYDROGELS

Generally hydrogels are characterized for their morphology, swelling property and elasticity. Morphology is indicative of their porous structure. Swelling determines the release mechanism of the drug from the swollen polymeric mass while elasticity affects the mechanical strength of the network and determines the stability of these drug carriers (Khare and Peppas, 1995). Some of the important features for characterization of hydrogels are as follows:

Morphological characterization

Hydrogels are characterized for morphology which is analyzed by equipment like stereomicroscope. Also the texture of these biomaterials is analyzed by SEM to ensure that hydrogels, especially of starch, retain their granular structures (Szepes et al., 2008).

X-ray diffraction

It is also used to understand whether the polymers retain their crystalline structure or they get deformed during the processing pressurization process (Szepes et al., 2008; Yu and Xiao, 2008; Pal et al., 2008).

In-vitro release study for drugs

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 (Szepes et al., 2008; Yu and Xiao, 2008).

FTIR (Fourier Transform Infrared Spectroscopy)

Any change in the morphology of hydrogels changes their IR absorption spectra due to stretching and O-H vibration. Formation of coil or helix which is indicative of cross linking is evident by appearance of bands near 1648 cm^{-1} (Yu and Xiao, 2008; Pal et al., 2008).

Swelling behavior

The hydrogels are allowed to immerse in aqueous medium or medium of specific pH to know the swellability of these polymeric networks. These polymers show increase in dimensions related to swelling (Yu and Xiao,

2008; Yin et al., 2008; Kim et al., 1992).

Rheology

Hydrogels are evaluated for viscosity under constant temperature of usually 4°C by using Cone Plate type viscometer (Schuetz et al., 2008).

PREPARATION OF HYDROGELS

Hydrogels are prepared by various methods. Some of the important methods are discussed below:

Isostatic ultra high pressure (IUHP)

Here the suspension of natural biopolymers like starch, are subjected to ultrahigh pressure of 300-700 MPa for 5 or 20 min in a chamber which brings about changes in the morphology of the polymer (i.e. gelatinization of starch molecules occur). It is different from heat-induced gelatinization where a change in ordered state of polymer occurs. Usually the temperature within the chamber varies from 40 to 52°C (Szepes et al., 2008).

Use of cross linkers

Since hydrogels are the polymers which swell in presence of water and they entrap drug within their pores; therefore, to impart sufficient mechanical strength to these polymers, cross linkers are incorporated like glutaraldehyde, calcium chloride and oxidized konjac glucomannan (DAK). These cross linkers prevent burst release of the medicaments. Hydrogels of gelatin has been prepared with DAK. Some researchers have reported *in situ* hydrogel formation by incorporating lactose along with sodium azide that results in formation of azide groups along with amino groups in polymers like chitosan and thus a photocrosslinkable chitosan (Az-Ch-LA) is formed which has desired integrity (Ta et al., 2008; Pal et al., 2008; Singh et al., 2007; Tokuyama et al., 2007; Chen et al., 2007b).

Use of water and critical conditions of drying

Aerogels of carbon have been prepared by super critically controlling the drying conditions. Aerogels of resorcinol formaldehyde hydrogels have also been prepared by using water as solvent and sodium carbonate as pH regulator. The final texture of hydrogel is governed by molar ratio of resorcinol to sodium carbonate. This method of preparation leads to porous hydrogels with no shrinkage during drying process. The method is expensive but leads to formation of xerogels with suffi-

cient mechanical strength (Leonard et al., 2008).

Use of nucleophilic substitution reaction

Hydrogels of N-2-dimethylamino ethyl-methacrylamide (DMAEMA), a pH and temperature sensitive hydrogel has been prepared by nucleophilic substitution reaction between methacryloyl chloride and 2-dimethylamino ethylamine. The synthesized hydrogel was characterized for its swelling behaviour (Wang et al., 2007).

Use of gelling agents

Gelling agents like glycerophosphate, 1-2 propanediol, glycerol, trehalose, mannitol, etc, have been used in formation of hydrogels. Usually the problem of turbidity and presence of negative charged moieties which are associated with this method pose problem of interaction with the drug (Schuetz et al., 2008; Guo and Gao, 2007).

Use of irradiation and freeze thawing

Hydrogels prepared by chemical methods (i.e. use of crosslinkers, gelling agents or reaction initiators) are having problems of removal of residue or unnecessary charged moieties present. Irradiation method is suitable and convenient but the processing is costly. The mechanical strength of such hydrogels is less. However with freeze thawing method, the hydrogels so formed have sufficient mechanical strength and stability but are opaque in appearance with a little swelling capacity. However, hydrogels prepared by microwave irradiation are more porous than conventional methods (Yang et al., 2008; Zhao et al., 2008; Wang et al., 2007; Chen et al., 2007a; Mohdy and Safrany, 2008).

TYPES OF HYDROGELS

pH sensitive or ion sensitive hydrogels

These hydrogels respond to changes in pH of the external environment. These gels have ionic groups (which are readily ionizable side groups) attached to impart peculiar characteristics. Some of the pH sensitive polymers used in hydrogels' preparations are polymethyl methacrylate (PMMA), polyacrylamide (PAAm), polyacrylic acid (PAA), poly dimethylaminoethylmethacrylate (PDEAEMA) and polyethylene glycol. These polymers though in nature are hydrophobic but swells in water depending upon the pH prevalent in the external environment. Any change in pH of the biological environment causes changes in the swelling behaviour, for example, the hydrogel of caffeine is prepared with poly-

mer PDEAEMA at pH below 6.6. As the polymer shows high swellability but when pH changes to higher side, the polymer showed shrinkage leading to drug release. The other pH sensitive hydrogels are copolymer of PMMA and polyhydroxyethyl methyl acrylate (PHEMA) which are anionic copolymers, swell high in neutral or high pH but do not swell in acidic medium. It was also observed that pH and ionic strength determines kinetics of swelling of PHEMA and guar gum (Peppas and Peppas, 1990; Das et al., 2006). Other drugs that have been delivered through pH sensitive hydrogels are listed in Table 1.

pH sensitive hydrogels have also been used to encapsulate proteins in acrylamide polymer cross-linked with bisacrylamide acetal cross linkers. At pH of around 5, the pore size of the acetal cross-linked hydrogels increases leading to release of protein. However at neutral pH, the acetal groups remain intact as cross linkers and protein do not diffuse out easily (Murthy et al., 2002; Gupta et al., 2002).

Temperature sensitive hydrogels

The hydrogels being cross-linked polymers are temperature sensitive. These hydrogels are pharmaceutically well accepted owing to large number of temperature sensitive drugs being delivered in these dosage forms. The release as well as mechanical characteristics of drug and hydrogels are altered with the change in the temperature of external environment (Prabaharan and Mano, 2006). Negative thermo-sensitive hydrogels contract upon heating above their low critical solution temperature. Positive thermo-sensitive hydrogels contract upon cooling above their upper critical solution temperature (Soppimath et al., 2002). In general, these hydrogels are hydrophobic polymers which show variable network in response to temperature thus modulate the drug release. These thermo-sensitive gels are specific, controllable and biocompatible drug delivery devices. They could be biodegradable also. The drugs which are widely been explored for such devices are usually from category of anticancer, antidiabetic, hormones or proteins and peptides. Sometimes these gels are formed within the system and are particularly beneficial for tissue targeting to inflamed or diseased areas (Ramanan et al., 2006; Ruel and Leroux, 2004; Bae et al., 1991). Drugs like insulin, heparin and indomethacin have been delivered using these types of hydrogels. Tanaka (1978) developed the thermo-sensitive hydrogels of PNIPAAm (polyisopropylacrylamide). The cross-linked polymers containing 75% NIPAAm (N-isopropyl acrylic amide) and rest of MAA (methacrylic acid) showed temperature dependent swelling. However, the combined effect of temperature and pH controls the drug release only when hydrogel gets swollen (Peppas et al., 2000; Kim and Park, 2002).

Thermo-sensitive macrocapsules of nanoparticles have been developed recently where the matrix consists of

Table 1. Various drugs delivered through pH responsive hydrogels for drug delivery.

Therapeutic moieties	Polymers	References
Insulin	Tri polymer of N-vinyl 2- pyrrolidone methacrylamide and itaconic acid.	Bajpai and Saggi (2007).
Caffeine	Poly dimethylaminoethylmethacrylate.	Peppas and Peppas (1990).
Camptothecin	Polyethyleneglycol.	Laloo et al. (2006).
Calcitonin	Copolymer of polymethacrylic acid and polyethylene glycol.	Serres et al. (1996) ; Torres and Peppas (1999).
Ketoprofen	Copolymer of cationic guar gum and acrylic acid monomer.	Takayama and Nagai (1991).

temperature sensitive ethylcellulose polymer being coated with thermo-sensitive membrane prepared by cross linking poly NIPAAm hydrogel. The drug release is expected to be high when high temperature causes collapsing of the membrane leading to large void formation. These polymers exhibit phase separation at lower critical solution temperature of about 32°C in aqueous solution (Sershen et al., 2000). A novel thermo-sensitive hydrogel of PNIPBAm {poly (N-isopropyl- 3-butenamide)} was synthesized by Xu et al. (2007). The synthesized gel showed smaller pore size with the increase in concentration of cross linker but the swelling ratio was high with a gel containing low concentration of cross linker. Another thermo-sensitive hydrogel of poly organophosphazene polymers bearing alpha-amino-omega- methyl-poly ethylene glycol (AMPEG) and hydrophobic L-isoleucine ethyl ester side groups so synthesized showed variable physical appearance from transparent sol to translucent gel depending upon temperature and was utilized to entrap natural insulin source for prolonged release (Park and Song, 2005). The same polymer has been used for controlled release of an anticancer drug-doxorubicin. The drug showed sustained release over a period of 20 days with no effect on gel characteristics like viscosity or gel strength and thus could be injected for its depot therapy (Kang et al., 2006). Some of temperature sensitive hydrogels having pharmaceutical applicability have been listed in Table 2.

These hydrogels are not having thermo-sensitive response only, but they are biodegradable also. That is why they are preferred for oral drug delivery. One such example is novel biodegradable, thermo-sensitive hydrogel of poly (epsilon-caprolactone-co-lactide-polyethylene glycol) copolymer (Shim et al., 2006) used for injectable drug delivery systems for proteins and peptides.

Glucose sensitive hydrogels

These hydrogels are sugar sensitive and show variability in response depending upon the presence of glucose. One of such pharmaceutical hydrogel system is the cross linked poly (methacrylamido phenylboronic acid)- co-acylamide hydrogel which liberates the drug in a controlled manner only when the concentration of glucose is high in the surrounding environment causing swelling of the hydrogel (Pluta and Karolwicz, 2004;

Eddington and Beebe, 2004). Usually glucose sensitive hydrogels are based on implantable sensor which is sensitized to glucose concentration from 0-20 mM (Lie et al., 2006). Insulin loaded hydrogels of cross-linked copolymers of polyethyleneglycol and methacrylic acid have been prepared by partitioning the insulin concentration. The micro particles of hydrogels showed no leakage under acidic conditions while the release was highest at pH 7.4 (Kumar et al., 2006). A similar glucose sensitive hydrogel was prepared by photopolymerization of 2- hydroxyethyl methacrylate and 3- acrylamido phenyl boronic acid. The liberation of insulin was glucose concentration dependent (Lee et al., 2004).

The hydrogels based on sulfonamide chemistry, where the hydrogel showed maximum swelling at pH 7.4 in a local glucose environment of 0-300 mg/dl (Kang and Bae, 2003) for delivery of insulin, was an enzymatic approach. The hydrogel of poly (2-hydroxyethyl methacrylate-co- N, N-dimethylaminoethyl methacrylate or poly HEMA-co-DMAEMA polymer entrapped the insulin, glucose oxidase and catalase enzymes. Under the environment of glucose, the glucose diffuses in the hydrogel from blood and gets converted to gluconic acid which raises the pH thus causes swelling of the hydrogel. Swelling of hydrogel leads to liberation of insulin which controls the glucose level in the blood. Through such controlled release devices not only the insulin release is controlled (by varying the concentration of cross linking agent) but also, the morphology of the hydrogel is regulated by oxygen uptake (Traitel et al., 2000).

Based on a similar approach of stimuli sensitive hydrogels, a conjugated polymer of monomethoxy poly (ethylene glycol) with glucose containing polymer showed reversible gel to sol phases depending on the concentration of glucose in the external environment. The viscosity of the hydrogel decreased with the addition of glucose (Kim, 1999). Apart from gel to sol approach for glucose sensitive hydrogels, the other approach is competitively binding insulin to concanavalin A, which is a lectin protein that reacts with specific sugar residues present at terminals so that in the presence of glucose, insulin is displaced (Obaidat and Park, 1997; Masteikova et al., 2003; Kim and Park, 2001). Thus, in general, glucose sensitive hydrogels are formed by immobilizing glucose oxidase enzyme which catalyses beta D-glucose to gluconic acid and hydrogen peroxide. The release of gluconic acid decreases pH of the external environment

Table 2. Temperature sensitive hydrogels for drug delivery.

Therapeutic moieties	Polymers	References
Human Growth Hormone	Poly organophosphazene with α -amino omega-methylpolyethylene glycol.	Kim and Park (2002); Kang and Song (2008).
Adrenochrome (Blood coagulating agent)	Copolymer of gelatin and PVA	Mukherjee and Banthia, (2006).
5-Fluorouracil	Co-polymer of poly-PNIPA and poly-PNIPA-Co-AA	Chen et al. (2007); Li et al. (2008).
Insulin	NIPAAm-Co.AAm	Bikram et al, (2007); Wanf et al. (2008).
Vaginal Microbicide	NIPAAm-Co-AAm	Gupta et al. (2007).
Proteins and Peptide	Polyepsilon caprolactone-co-lactide-polyethylene glycol; Chitosan	Shim et al. (2007); Lee et al. (2004); Klouda and Mikas, (2008) ; Sun et al., 2007.

PNIPA is poly N-isopropyl acrylamide; PNIPA-Co-AA is poly N-isopropyl acrylamide- co- acrylic acid; NIPAAm is N-isopropylacrylamide.

causing decrease in swelling behaviour. This enzyme can be present in bound form or it could be attached to the polymer chain (Yoshioka and Calvert, 2002). The conducting behavior of gels which gives the idea of swelling vary with the ions liberated due to formation of gluconic acid or by ionization of amines present in the polymer (usually acrylates) used for preparation of hydrogels. Therefore, these smart biomaterials show controlled delivery of solute usually proteins like insulin, lysozyme or BSA (Bovine serum albumin) in response to external environment (Tang et al., 2003).

Apart from temperature, pH, glucose sensitive hydrogels, other stimuli like light, electric field, chemicals and ions have been utilized in formulation of responsive hydrogels (Suzuki and Tanaka, 1990; Lam et al., 2006; Zhang et al., 2005; He et al., 2008b). But these have not gained considerable attention in the field of drug delivery.

Nanohydrogels

Nanohydrogels are the hydrogels which are prepared in water by self aggregation of polymers of natural origin like dextran. These types of hydrogels are formed from natural polysaccharides like dextran, pullulan, or cholesterol-containing polysaccharide. The cholesterol-containing polysaccharide is stirred at 50°C for 12 h in aqueous buffer which leads to swelling of the cholesterol containing polysaccharide. After sonication at 25°C for 10 min, nanoparticles of hydrogels are formed. The size and density of hydrogel nanoparticles can be controlled by changing the degree of substitution of cholesterol groups of such polysaccharides (Akiyoshi et al., 1998; Kim et al., 2000). These hydrogels are of nano dimensions usually of 20-30 nm and are used for cell targeting as they release the entrapped drug by swelling caused by change in the pH of the surrounding environment. Drugs like adriamycin has been delivered to tumor cells and the drug showed pH dependent release and the highest release was when pH was below 6.8 (Na and Bae, 2004). These nanoparticles of hydrogels have been used for controlled release of proteins like lysozyme, albumin, immunoglobulin. The amount of protein released is

dependent on the square root of time. Hydrogels especially of dextran are made biodegradable by encapsulation of enzyme dextranase (Hennink et al., 1997). The hydrogels of pullulan nanoparticles have been used for cell targeting by encapsulating active drug in aqueous core of Aerosol OT/ n-hexane (Gupta and Gupta, 2004).

Similar hydrogels have been made by self-assembling nanoparticles of linoleic acid modified chitosan. 1.8% linoleic acid substituted chitosan has structural integrity and shows loading capacity of 19.85 to 37.57% of bovine serum albumin. These nanoparticles hydrogels are biocompatible and biodegradable and are ideal for tissue targeting (Chenguang et al., 2007). The nanohydrogel of polysaccharide-mannose from *Saccharomyces cerevisiae* have been prepared or encapsulating insulin or BSA. The incorporation of calcium phosphate prevents the initial burst release thus these hydrogels are used for controlled drug delivery (Yamane and Akiyoshi, 2007).

Pharmaceutical applications of hydrogels

To provide sustained or controlled drug delivery into systems, the hydrogels are designed, modulated and characterized for the expected *in-vivo* results. These hydrogels have gained existence in drug delivery through parenteral, ocular, rectal, vaginal, dermal and nasal routes (Matsuda, 2002; Obaidat and Park, 1997; Kim and Park, 2002). Some of the important pharmaceutical applications of hydrogels are discussed below.

Wound healing

A modified polysaccharide that occurs in cartilage has been used in formation of hydrogels to treat cartilage defects has been developed (Fenglan et al., 2004). The polysaccharide is functionalized with methacrylate and aldehyde group which react with proteins of skin tissues, while the methacrylate cross links with back bone of disaccharide chondroitin; thus, a network is formed from where the chondrocytes cells are released (Baroli, 2007; Netti et al., 1993). Honey hydrogels have been used for

prompt wound healing. These hydrogels have matrix in which honey is cross-linked and most acceptable, easily peeled, and transparent system (Yusof et al., 2007). The hydrogel of gelatin and PVA (polyvinyl alcohol) along with blood coagulant have been formulated. The cell adhesive hydrogel ensured better effect than corresponding gel or ointment in controlling blood coagulation (Mukherjee and Banthia, 2006).

Colon specific drug delivery

Colon specific hydrogels of polysaccharides have been specifically designed because of 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 that cause liberation of drug (Singh et al., 2007). Controlled delivery of Ibuprofen to colon has been achieved through hydrogel of guar gum cross linked with glutaraldehyde as cross linker (Das et al., 2006).

Cosmetology

For aesthetic purpose, hydrogels have been implanted into breast to accentuate them. These hydrogels swell *in-vivo* in aqueous environment and retain water. These breast implants have silicone elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel (Adam et al., 2007).

Topical drug delivery

Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. Instead of conventional creams, the hydrogels have been formulated for better patient compliance. These hydrogels have moisturizing properties therefore scaling and dryness is not expected with this drug delivery system (Trookman et al., 2007; Rowley et al., 1999; Wyhne et al., 2002). Antifungal formulations like cotrimazole has been developed as hydrogel formulation for vaginitis. It has shown better absorption than conventional cream formulations (Chang et al., 2002).

Ocular drug delivery

For ocular drug delivery of pilocarpine and timolol, the polymers which form gel such as xyloglucan have been used for sustained drug delivery. Hydrogels of poly hydroxyethyl methacrylamide (pHEMA), N, N-dimethyl acrylamide (DMAAm) and 2-(N-ethyl per fluorooctane sulfonamide) ethylacrylate (FOSA) have been used for ocular delivery to have complete absorption through cornea. Drugs like diclofenac and phenaramine maleate have been successfully delivered through hydrogels

(Miyazaki et al., 2001; Bugalassi et al., 2000; Ximeng et al., 2007; Nanjawade et al., 2007).

Industrial applicability

Hydrogels have been used as absorbents for industrial effluents like methylene blue dye (Paulino et al., 2006). The other example is the adsorption of dioxins by hydrogel beads. The DNA of Salmon milt adsorbs dioxins which produce health hazards like carcinogenicity, immunotoxicity or endocrine disruption.

Modified dosage forms

An interesting research in this field of drug delivery is of bio-macromolecules like insulin delivered to the site of absorption with hydrogels of poly (methacrylamide-co-N-vinyl-2-Pyrrolidone-co-itaconic acid). The insulin entrapped in this matrix showed release at the desired interval. The swelling behaviour was analyzed in medium containing pepsin which degrades insulin. Thus when an optimized concentration of cross linkers like N, N' - methylene bisacrylamide are used then maximum entrapment efficiency is observed. Thus the release and unwanted degradation of drugs like insulin can be prevented by hydrogel based drug delivery devices (Bajpai and Saggi, 2007; Sato, 1984).

Tissue engineering

The micronized hydrogels (microgels) have been used to deliver macromolecules like phagosomes into cytoplasm of antigen-presenting cells. The release is because of acidic conditions (Murty et al., 2002; Jain et al., 2007). Such hydrogels mold themselves to the pattern of membranes of the tissues and have sufficient mechanical strength. This property of hydrogels is also used in cartilage repairing (Park et al., 2007; Gyenes et al., 2007).

Protein drug delivery

Interleukins which are conventionally given as injection are now given as hydrogels. These hydrogels have shown better patient compliance. The hydrogels form *in-situ* polymeric network and release proteins slowly. These are biodegradable and biocompatible also (Hiemstra et al., 2007; Klouda and Mikos, 2008; Patil et al., 1996; Sutter et al., 2007).

Miscellaneous applications

Hydrogels are also used in other forms of drug delivery

like pulsatile drug delivery or oral drug delivery (He et al., 2008a; Guo and Gao, 2007; Gazzaniga et al., 2008). Injectable hydrogels are also been investigated for cancer drug delivery. *In situ* gel-forming hydrogels for prolonged duration have also been reported (Ta et al., 2008; Fang et al., 2008).

Conclusion

There are enough scientific evidences for the potentiality of hydrogels in delivery of drug molecules to a desired site by triggering the release through an external stimulus such as temperature, pH, glucose or light. These hydrogels being biocompatible and biodegradable in nature have been used in the development of nano biotechnology products and have marvelous applications in the field of controlled drug delivery as well. That is why these turn-able biomedical drug delivery devices are gaining attention as intelligent drug carriers.

REFERENCES

- Adams TST, Crook T, Cadier MAM (2007). A late complication following the insertion of hydrogel breast implants. *J. Plast. Reconstr. Aesthet. Surg.* 60: 210-212.
- Akiyoshi K, Kobayashi S, Schichibe S, Mix D, Baudys M, Kim SW, Sunamoto J (1998). Self assembled hydrogel nanoparticle of cholesterol-bearing pullulan as a carrier of protein drugs: Complexation and stabilization of insulin. *J. Control Rel.* 54 (3):313-320.
- Aroca AS, Ribelles JL, Pradas MM, Garayo AV, Anton JS (2007). Characterization of macroporous polymethyl methacrylate coated with plasma polymerized poly 2- hydroxyethyl acrylate. *Eur. Polym. J.* 43: 4552-4564.
- Bae YH, Okano T, Kim SW (1991). On-off thermo control of solute transport II. Solute release from thermo sensitive hydrogels. *Pharm. Res.* 8(5): 624-628.
- Bajpai SK, Saggi SS (2007). Insulin release behaviour of poly (methacrylamide-co-N-vinyl-2-pyrrolidone –co-itaconic acid) hydrogel: An interesting probe. Part II. *J. Macromol. Sci. A: Pure Appl Chem* 44: 153-157.
- Bajpai SK, Sonkusley J (2002). Hydrogels for oral drug delivery of peptides: Synthesis and characterization. *J Appl Polym Sci* 83: 1717-1729.
- Baroli B (2007). Hydrogels for tissue engineering and delivery of tissue-inducing substances. *J. Pharm. Sci.* 96: 2197-2223.
- Bikram M, Gobin AM, Whitmire RE, West JL (2007). Temperature sensitive hydrogels with SiO₂ –Au nanoshells for controlled drug delivery. *J. Control Res.* 123 (3): 219-227.
- Bugalassi S, Chetoni P, Panichi L, Boldrini E, Saettone MF (2000). Xyloglucan as a novel vehicle for timolol: pharmacokinetics and pressure lowering activity in rabbits. *J. Ocul. Pharmacol. Th.* 16: 497-509.
- Chang JY, Oh YK, Kong HS, Kim EU, Jang DD, Nam KT (2002). Prolonged antifungal effects of clotrimazole containing mucoadhesive thermosensitive gels on vaginitis. *J. Control Rel.* 82: 39-50.
- Chen H, Gu Y, Hub Y, Qian Z (2007a). Characterization of pH and temperature sensitive hydrogel nano-particles for controlled drug release. *PDA J. Pharm. Sci. Tech.* 61 (4):303-313.
- Chen J, Sun J, Yang L, Zhang Q, Zhu H, Wu H, Hoffman AS, Kaetsu J (2007b). Preparation and characterization of a novel IPN hydrogel membrane of poly (N-isopropyl acrylamide carboxymethyl chitosan (PNIPAAm/CMCS). *Radiat. Phys. Chem.* 76: 1425-1429.
- Chenguang L, Goud DK, Xiguang C, Jin PH (2007). Preparation and characterization of self- assembled nanoparticles based on linolenic acid modified chitosan. *J. Ocean. Uni. China* 4(3): 234-239.
- Das A, Wadhwa S, Srivastava AK (2006): Cross-linked guar gum hydrogels discs for colon-specific delivery of ibuprofen: formulation and *in-vitro* evaluation. *Drug Del.* 13: 139-142.
- Eddington DT, Beebe DJ (2004). Flow control with hydrogels. *Adv Drug Deliver Rev.* 56(2): 199-210.
- Fang J, Chen J, Leu Y, Hu J, (2008). Temperature sensitive hydrogels composed o chitosan and hyaluronic acid as injectables carriers for drug delivery. *Eur. J. Pharm. Biopharm.* 68: 626-636.
- Fenglan X, Yubao L, Jiang WX (2004). Preparation and characterization of nano- hydroxyl apatite polyvinyl alcohol hydrogel biocomposite. *J. Mater. Sci.* 39: 5669-5672.
- Gazzaniga A, Palugan L, Oppoli A, Sangalli ME (2008). Oral pulsatile delivery systems based on swellable hydrophilic polymers. *Eur. J. Pharm.* 68: 11-18.
- Graham NB, Mc-Neil ME (1984). Hydrogels for controlled drug delivery. *Biomaterials* 5 (1): 27-36.
- Guo BL, Gao QY (2007). Preparation and properties of a pH/ temperature responsive carboxy methyl chito-san/poly (N-isopropyl acrylamide) hydrogel for oral delivery of drugs. *Carbohydr. Res.* 342: 2416-2422.
- Gupta KM, Barner SR, Tangaro RA, Roberts MC, Owen DH, Katz DF, Kiser PF (2007). Temperature and pH sensitive hydrogels: an approach towards smart semen-triggered vaginal microbicidal vehicles. *J. Pharm. Sci.* 96 (3): 670-681.
- Gupta M, Gupta AK (2004). In-vitro cytotoxicity studies of hydrogels pullulan nanoparticles prepared by AOT/n-hexane micellar system. *J. Pharm. Pharm. Sci.* 7 (1): 38-46.
- Gupta, Vermani and Garg (2002). Hydrogels: From controlled release to pH-responsive drug delivery. *Drug Discov. Today* 7: 569-579.
- Gyenes T, Torma V, Zringi M (2007). Swelling properties of aspartic acid based hydrogels. *Colloid. Surface A.* (In press). www.elsevier.com/locate/colsurfa.
- He C, Kim SW, Lee DS (2008a). In situ gelling stimuli sensitive block copolymer hydrogels for drug delivery. *J Control Rel.* (In press). www.elsevier.com/locate/jcr.
- He H, Li L, Lee LJ (2008b). Photo polymerization and structure formation of methacrylic acid based hydrogels. The effect of light intensity. *React. Funct. Polym.* 68:13-113.
- Hennink WE, Franssen O, Wolthuis WNE, Talsma H (1997). Dextran hydrogels for the controlled release of proteins. *J Control Rel.* 48 (2-3):107-114.
- Hiemstra C, Zhong Z, Jomme SR, Steenbergen MJ, Jacobs JJ, Otter WA, Hennink WE, Feijen J (2007). *In-vitro* and *in-vivo* protein delivery from in-situ forming poly (ethylene glycol)- polylactide hydrogels. *J. Control Rel.* 119: 320-327.
- Jain SK, Jain A, Gupta Y, Ahirwar M (2007): Design and development of hydrogel beads for targeted drug delivery to the colon. *AAPS Pharm. Sci. Tech.* 8(3): E56.
- Jhan MS, Andrade JD (1973). Water and hydrogels. *J Biomed. Mater. Res.* 7(6): 509-522.
- Kang GD, Cheon SH, Song SC (2006). Controlled release of doxorubicin from thermosensitive poly (organophosphazene) hydrogels. *Int. J. Pharm.* 319 (1-2): 29-36.
- Kang GD, Song Sc (2008). Effect of chitosan on the release of protein from thermo sensitive poly organophosphazene hydrogels. *Int. J. Pharm.* 349: 188-195.
- Kang SI, Bae YH (2003). A sulfonamide based glucose responsive hydrogel with covalently immobilized glucose oxidase and catalase. *J. Control Rel.* 86 (1): 115-121.
- Khare AR, Peppas NA (1995). Swelling/deswelling of anionic copolymer gels. *Biomaterials* 16: 559-567.
- Kim IS, Jeong Y, Kim SH (2000). Self assembled hydrogel nanoparticles composed of dextran and poly (ethylene glycol) macromer. *Int. J. Pharm.* 205 (1-2): 109-116.
- Kim JJ (1999). Phase- reversible glucose sensitive hydrogels for modulated insulin delivery. PhD dissertations, Purdue University, Indiana, USA.
- Kim JJ, Park K (2001). Modulated insulin delivery from glucose-sensitive hydrogel dosage forms. *J Control Rel.* 77 (1-2): 39-47.
- Kim MR, Park TG (2002). Temperature- responsive and degradable

- hyaluronic acid/ pluronic composite hydrogels for controlled release of human growth hormone. *J Control Rel.* 80 (1-3): 69-77.
- Kim SW, Bae YH, Okano T (1992). Hydrogels: Swelling, drug loading and release. *Pharm Res* 9(3): 283-290.
- Klouda L, Mikos AG (2008). Thermoresponsive hydrogels in biomedical applications. *Eur. J Pharm. Biopharm.* 68: 34-45.
- Kumar A, Lahiri SS, Singh H (2006). Development of PEGDMA: MAA based hydrogel microparticles for oral insulin delivery. *Int. J. Pharm.* 323 (1-2): 117-124.
- Laloo A, Chao P, Hu P, Stein S, Sinko PJ (2006). Phar-macokinetic and pharmacodynamic evaluation of a novel insitu forming polyethylene glycol-based hydrogel for the controlled delivery of camptothecins. *J. Control Res.* 112: 333-342.
- Lam Y, Li H, Ng TY, Luo R (2006). Modeling and stimulation of the deformation of multistate hydrogels subjected to electrical stimuli. *Engg. Anal. Bound Elem.* 30(11): 1011-1017.
- Lee YJ, Pruzinsky SA, Braun PV (2004). Glucose sensitive inverse opal hydrogels: analysis of optical diffraction response. *Langmuir* 20(8): 3096-3106.
- Lei M, Baldi A, Nuxoll E, Siegel RA, Ziaie B (2006). A hydrogel based implantable micromachined transponder for wireless glucose measurement. *Diabetes Technol Ther* 8(1): 112-122.
- Leonard A, Blacher S, Crine M, Jomaa W (2008). Evolution of mechanical properties and final textural properties of resorcinol-formaldehyde xerogels during ambient air drying. *J. Non-Cryst.* 354: 831-838.
- Li X, Wu W, Liu W (2008). Synthesis and properties of thermo-responsive guar gum/ poly N-isopropyl-acrylamide interpenetrating polymer network hydro-gels. *Carbohydr. Polym.* 71: 394-402.
- Liu Q, Hedberg EL, Liu Z, Bahulekar R, Meszlenyl R, Mikos AG (2000). Preparation of macroporous poly 2-hydroxyethylmethacrylate hydrogels by enhanced phase separation. *Biomaterials* 21:2163-2169.
- Lowman AM, Peppas NA (1991). Hydrogels. In: *Encyclopedia of Controlled Drug Delivery*. Mathiowitz E (Ed). Wiley, New York. pp 397-418.
- Masteikova R, Chalupova Z, Sklublalova Z (2003). Stimuli-sensitive hydrogels in controlled and sustained drug delivery. *Medicina* 39:19-24.
- Matsuda T (2002). Device- directed therapeutic drug delivery systems. *J. Control Rel.* 78:125-131.
- McNeill ME, Graham NB (1993): Properties controlling the diffusion and release of water soluble solutes from poly(ethyloxide) hydrogels 1. Polymer composition. *J. Biomater. Sci. Polym. Ed.* 4(3): 305-322.
- Miyazaki S, Suzuki S, Kawasaki A, Endo K, Takahashi A, Attwood D (2001). In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. *Int. J. Pharm.* 229: 29-36.
- Mohdy HLA, Safrany A (2008). Preparation of fast response superabsorbent hydrogels by radiation polymerization and cross linking of N-isopropylacrylamide in solution. *Radiat. Phys. Chem.* 77: 273-279.
- Mukherjee D, Banthia AK (2006). Preparation of adrenochrome hydrogel patch, gel ointment and the comparison of their blood coagulating and wound healing capability. *Mater. Manuf. Process* 21: 297-301.
- Murthy N, Thng YX, Schuck S, Xu MC, Frecher JMJ (2002). A novel strategy for encapsulation and release of proteins: Hydrogels and microgels with acid-labile acetal cross linkers. *J. Am. Chem. Soc.* 124: 12398-12399.
- Na K, Bae YH (2004). Self assembled hydrogel nanoparticles responsive to tumor extracellular pH from pullulan derivative/sulfonamide conjugate: Characterization, aggregation and adriamycin release *in-vitro*. *Pharm. Res.* 19(5):681-688.
- Nanjawade BK, Manvi FV, Manjappa AS (2007). In situ forming hydrogels for sustained ophthalmic drug delivery. *J. Control Rel.* 122: 119-134.
- Netti PA, Shelton JC, Revella, Pirie C, Smith S, Ambrosio L, Nicolais L, Bonfield W (1993): Hydrogels as an interface between bone and an implant. *Biomaterials* 14 (14): 1098-1104.
- Obaidat AA, Park K (1997). Characterization of protein release through glucose sensitive hydrogel membranes. *Biomaterials* 18: 1801-806.
- Pal K, Banthia AK, Majumdar DK (2008). Effect of heat treatment of starch on the properties of the starch hydrogels. *Mater. Lett.* 62: 215-218.
- Park H, Temenoff JS, Tabata Y, Caplan AI, Mikos AG (2007). Injectable biodegradable hydrogel compositions for rabbit marrow mesenchymal stem cell and growth factor delivery for cartilage tissue engineering. *Biomaterials* 28: 3217-3227.
- Park KH, Song SC (2005). A thermosensitive poly (organo phosphazene) hydrogel used as an extra-cellular matrix for artificial pancreas. *J. Biomater Sci. Polym. Ed.* 16(11):1421-1431.
- Patil NS, Dordick JS, Rethwisch DG (1996). Macroporous poly (sucrose acrylate) hydrogel for controlled re-release of macromolecules. *Biomaterials* 17: 2343-2350.
- Paulino AT, Guilherma MR, Reis AV, Campese GM, Muniz EC, Nozaki J (2006). Removal of methylene blue dye from an aqueous media using superabsorbent hydrogel supported on modified polysaccharide. *J. Colloid Interf. Sci.* 301: 55-62.
- Peppas LB, Peppas NA (1990). Dynamic and equilibrium behavior of pH sensitive hydrogels containing 2-hydroxy ethyl methacrylates. *Biomaterials* 11: 635-644.
- Peppas NA, Burer P, Leobandung W, Ichikawa H (2000). Hydrogels in pharmaceutical formulations. *Eur J Pharm Biopharm* 50: 27-46.
- Pluta J, Karolewicz B (2004). Hydrogels: properties and application in the technology of drug form I. The characteristics hydrogels. *Polym. Med.* 34 (2): 3-19.
- Prabakaran M, Mano JF (2006). Stimuli responsive hydrogels based on polysaccharides incorporated with thermo responsive polymers as novel biomaterials. *Macromol. Biosci.* 6 (12): 991-1008.
- Ramanan RM, Chellamuthu P, Tang L, Nguyen KT (2006). Development of a temperature- sensitive composite hydrogel for drug delivery applications. *Biotechnol. Prog.* 22 (1): 118-125.
- Rowley J, Madlambayan G, Faulkner J, Mooney DJ (1999). Alginate hydrogels as synthetic extracellular matrix materials. *Biomaterials* 20: 45-53.
- Ruel GE, Leroux JC (2004). In-situ forming hydrogels- A review of temperature sensitive systems. *Eur. J. Pharm. Biopharm.* 58 (2): 409-423.
- Sato S (1984): Self regulating insulin delivery systems. *J Control Rel.* 1: 67-77.
- Schuetz YB, Gurny R, Jordan O (2008). A novel thermoresponsive hydrogel of chitosan. *Eur. J. Pharm. Biopharm.* 68:19-25.
- Serres A, Baudys M, Kim SW (1996). Temperature and pH sensitive polymers for human calcitonin delivery. *Pharm. Res.* 13:196-201.
- Sershen SR, Westcott SL, Halas NJ, West JL (2000). Temperature sensitive polymer nanoshells composite for photothermally modulated drug delivery. *J. Biomed. Mater. Res.* 51 (3): 293-298.
- Shim WS, Kim JH, Kim K, Kim YS, Park RW, Kim IS, Kwon IC, Lee DS (2007). pH and temperature sensitive injectable, biodegradable block copolymer hydrogels as carriers for paclitaxel. *Int. J. Pharm.* 331 (1): 11-18.
- Shim WS, Kim SW, Lee DS (2006). Sulfonamide based pH and temperature sensitive biodegradable block copolymer hydrogels. *Biomacromole* 7(6): 1935-1941.
- Singh B, Sharma N, Chauhan N (2007). Synthesis, characterization and swelling studies of pH responsive Psyllium and methacrylamide based hydrogels for the use in colon specific drug delivery. *Carbohydr. Polym.* 69: 631-643.
- Soppimath KS, Aminabhavi TM, Dave AM, Kumbhar SG, Rudzinski WE (2002). Stimulus-responsive smart hydrogels as novel drug delivery systems. *Drug Dev. Ind. Pharm.* 28(8): 957-974.
- Stastny M, Plocova D, Etrych T, Kova M, Ulbrich K, Rihova B (2002). HPMA- hydrogels containing static drugs kinetics of the drug release and *in-vivo* efficacy. *J Control Rel.* 81: 101-111.
- Sun G, Zhang XZ, Chu CC (2007). Formulation and characterization of chitosan based hydrogel films having both temperature and pH sensitivity. *J. Mater. Sci. Mater. Med.* 18(8):1563-1577.
- Sutter M, Siepmann J, Hennink WE, Jiskoot W (2007). Recombinant gelatin hydrogels for the sustained release of proteins. *J Control Rel.* 119: 301-312.
- Suzuki A, Tanaka T (1990). Phase transition in polymer gels induced by visible light. *Nature* 346: 345-347.
- 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. *Carbohydr. Polym.* 72:571-575.
- Ta HT, Dass CR, Dunstan DE (2008). Injectable chitosan hydrogels for localized cancer therapy. *J Control Rel.* 126: 205-216.
- Takayama K, Nagai T (1991). Simultaneous optimization for several characteristics concerning percutaneous absorption and skin damage of Ketoprofen hydrogels containing d-limonene. *Int. J. Pharm.* 74: 115-126.
- Tanaka T (1978). Collapse of gels and the critical endpoint. *Phys. Rev. Lett.* 40: 820-823.
- Tang M, Zhang R, Bowyer A, Eisenthal R, Hubble J (2003). A reversible hydrogel membrane for controlling the delivery of macromolecules. *Biotechnol. Bioengin.* 82 (1): 47-53.
- Tokuyama H, Ishihara N, Sakohora S (2007). Effects of synthesis-solvent on swelling and elastic properties of poly N-isopropylacrylamide hydrogels. *Eur. Polym. J.* 43: 4975-4982.
- Torres LM, Peppas NA (1999). Molecular design and *in-vitro* studies of novel pH sensitive hydrogels for the oral delivery of calcitonin. *Macromole* 32: 6646-6651.
- Traitel T, Cohen Y, Kost J (2000). Characterization of glucose sensitive insulin release systems in simulated *in- vivo* conditions. *Biomaterials* 21(16): 1679-1687.
- Trookman N, Rizer R, Stephens T J, Trancik R (2007). Atopic dermatitis advantages of a novel hydrogel vehicle. *J. Am. Acad. Dermatol.* P730, pg AB 75.
- Wanf B, Xu X, Wang Z, Cheng S, Zhang X, Zhuo R (2008). Synthesis and properties of pH and temperature sensitive P(NIPAAm-Co-D MAEMA) hydrogels. *Colloids Surface B: Biointerface* (In press). www.elsevier.com/locate/CSB.
- Wang M, Xu L, Hu H, Zhai M, Peng J, Nho Y, Li J, Wei G (2007). Radiation synthesis of PVP/ CMC hydrogels as wound dressing. *Nucl. Instrum. Meth. B* 265: 385-389.
- Wyhne A, Whitefield M, Dixon AJ, Anderson S (2002): An effective, cosmetically acceptable, novel hydrogel emollient for the management of dry skin conditions. *J. Dermatol. Treat.* 13(2): 61-66.
- Xinmeng L, Yingde C, Liyod AW, Mikhalovsky SV, Sandeman S, Howel CA, Liewen L (2007). Polymeric hydrogels for novel contact lens based ophthalmic drug delivery systems. *Rev. Contact. Lens. Ant. Eye* (In press). www.elsevier.com/locate/cla.
- Xu X, Zhang X, Wang B, Cheng S, Zhuo R, Wang Z (2007). Fabrication of a novel temperature sensitive poly (n-isopropyl-3-butenamide) hydrogel. *Colloid Surface B* 59: 158-163.
- Yamane S, Akiyoshi K (2007). Nanogel- inorganic hybrid; Synthesis and characterization of polysaccharide calcium phosphate nanomaterials. *Eur. Cells Mater.* 14(3):113.
- Yang X, Liu Q, Chen X, Yu Feng, Zhu Z (2008). Investigation of PVA/ WS-chitosan hydrogels prepared by combined γ radiation and freeze thawing. *Carbohydr Polym* (In press). www.elsevier.com/locate/carbpol.
- Yin Y, Ji X, Dong H, Ying Y, Zhing H (2008). Study of the swelling dynamics with overshooting effect of hydrogels based on sodium alginate-g-acrylic acid. *Carbohydr. Polym.* 71: 682-689.
- Yoshioka Y, Calvert P (2002). Epoxy-based electro active polymer gels. *Exp. Mech.* 42: 404-408.
- Yu H, Xiao C (2008). Synthesis and properties of novel hydrogels from oxidized Konjac glucomannan cross linked gelation for *in-vitro* drug delivery. *Carbohydr. Polym.* 72: 479-489.
- Yusof N, Hafiza AHA, Zohdi RM, Bakar ZA (2007). Development of honey hydrogel dressing for enhanced wound healing. *Radiat. Phys. Chem.* 76: 1767-1770.
- Zhang XZ, Lewis PJ, Chu CC (2005). Fabrication and characterization of a smart drug delivery systems. *Biomaterials* 26(16): 3299-3309.
- Zhao ZX, Li Z, Xia Q, Bajalis E, Xi H, Lin YS (2008). Swelling/deswelling kinetics of PNIPAAm hydrogels synthesized by microwave irradiation. *Chem Eng* (In press). www.elsevier.com/locate/cej.