Int J Pharm Bio Sci 2012 July; 3(3): (P) 586 - 597

Review Article **Biomaterial Sciences**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

BIOMATERIAL HYDROGELS FOR DIFFERENT BIOMEDICAL APPLICATIONS

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ABSTRACT

Biomaterials are biologically compatible materials or formations that can be used to treat, augment or replace tissues in physiological environment. Biomaterials are hybrid structures or may be derived exclusively from synthetic and natural materials. Hydrogels on the other hand are three dimensional crosslinked polymeric networks and can imbibe large amount of water or biological fluids. Hydrogels are extensively used in biomedical areas for a range of unique properties like environment responsiveness, bioadhesive properties, biocompatibility and biodegradability. Biocompatable hydrogels are particularly advantageous in a number of areas like drug delivery, wound management, tissue engineering and organ transplant. This review make an attempt to present a systematic understanding on diverge chemistry and applications of biomaterial hydrogels as applied in pharmaceutical and biomedical arena.

KEY WORDS : Hydrogels; Drug delivery device; Environment responsive; Wound healing; Tissue engineering scaffold; gene delivery

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INTRODUCTION

Biomaterials are chemical formations that can be used as a facilitator in physiological contact without a direct therapeutic or toxicology consequence. These are generally applied for a specified period of time to treat, supplement, or replace cells and tissues *in vivo*. Currently, regenerative therapy, tissue specific drug delivery and life support facilities are heavily dependent upon biomaterials and devices [1,2]. Materials in biological applications were traditionally comprised of ceramics, polymer composites and metals. Traditional materials that are applied in biomedical areas were however severely constrained due to a variety of reasons like tissue rejection, cellular toxicity, inflammatory rejections etc. Optimization of material properties and directed therapy were often used as a compromise in supportive and regenerative applications. Three dimensional structures of hydrophilic polymers, commonly known as hydrogels, are a class of biomaterials that have demonstrated a great potential in pharmaceutical and biomedical applications[3].

Hydrogels can be defined as crosslinked water-swollen polymeric materials[4]. They were the first used clinically as biomaterials in early 1960s. One of the early application was crosslinked poly (hydroxyethyl methacrylate) hydrogels as soft contact lenses[5]. Nowadays, synthetic methods are used to design tailor able polymers as self-assemble and environment sensitive hydrogels with controlled degradation and mechanical properties. Apart from the synthetic polymers like poly hydroxyethyl methacrylate and poly methyl methacrylates, natural polymers have also gained significant importance in different biocompatible hydrogel applications. Alginate and chitosan are the two biopolymers available from natural sources that were extensively applied in biomedical and devices applications.

Water activity is one of the primary considerations for hydrogel structure and properties. The ability of natural and synthetic hydrogels to absorb water appear due to the presence of hydrophilic groups such as –OH, -CONH, -$CONH_2$, -COOH, -SO_3H etc.[6] Hydrogels generally degrade and eventually disintegrate or get dissolved. To retard this degradation, controlled chemical crosslinking is introduced within the hydrogel structure. Depending on the pendent functional groups along the polymer chains, hydrogels have the ability to respond to their environmental changes such as pH, ionic strength or temperature. Stimuli sensitive hydrogels have proved to be important in development of delivery devices[7]. The pH sensitive hydrogels were used since long in the pharmaceutical industry as enteric delivery materials. The enteric hydrogels are used to protect acid-labile drugs like penicillin G or erythromycin or to safeguard stomach mucosa from irritant compounds like aspirin[8]. Different pH sensitive hydrogels have also been used in blood-glucose sensing and insulin delivery[9]. Temperature sensitive hydrogels are useful in nasal, ophthalmic and in tissue applications. Electric field sensitive hydrogels on the other hand are used in artificial muscles, and controlled drug delivery devices[10].

Hydrogels were extensively applied in the delivery of proteins and peptides, tissue engineering, microfluidics, gene delivery and in nanotechnology. The success of hydrogels originates from their well known biocompatibility due to their high water content and soft nature. These properties render hydrogels similar to biological tissues and consequently minimize cell adherence and inflammation once implanted or injected in body[11,12]. Furthermore, their water absorbing capacity facilitates the accommodation of cells or hydrophilic molecules such as proteins and peptides within the polymeric network[13].

Besides biocompatibility, the biomaterials need to be biodegradable so that after serving it degrades into soluble and biocompatible products that can be eliminated. A relative ease in production, structural stability, cytocompatibility, material flexibility,

and minimally invasive administration are useful characteristics of hydrogels for biomedical applications. This review focuses on drug delivery and related biomaterials applications of hydrogels.

1. Hydrogels as drug delivery devices

1.1 Peroral drug delivery

Oral delivery of drug is cheap and allows maximum patient compliance. Through this route one can target mouth, stomach, small intestine and colon[14]. The bioadhesive hydrogels could deliver drugs to the oral cavity or at the specific sites of gastro-intestinal tract. When administered locally these hydrogels can treat periodontal diseases, fungal & viral infections and oral cavity cancers. The main challenge in the local treatment of diseases of the oral cavity is to keep the delivery system at the site of infection for a long period of time. Drugs susceptible to first pass metabolism can also be delivered systemically by sub-lingual/buccal route using hydrogel. Pitaressi and co-workers investigated the release pattern of amoxicillin from a bioadhesive hydrogel in simulated buccal and gastric conditions[15]. The hydrogel increases the gastric residence time of the delivery system. This ensures the release of drugs at the specific site and hence increases in the bioequivalence. Lectin is one of the polymers that have been used for long in such type of delivery systems.

1.2 Drug delivery in the Gastrointestinal (GI) tract

The environment sensitive hydrogels have effectively been used to deliver drug at specific sites of the GIT. The enteric polymers like eudragit are used for long either to protect the acid-labile drugs (e.g. peptides and penicillin-G) from the harsh environment of the stomach or to avoid the contact of the gastric mucosa with the gastric-irritant drugs (e.g. ibuprofen, indomethacin), which may lead to gastric mucosa perforations. Akiyama *et al*. developed an enteric system using poly (acrylic acid), which inhibited the hydrolytic activity of trypsin[16]. In an attempt to deliver insulin orally, Hari *et al*. developed alginate-chitosan microparticle for the controlled delivery of the bioactive peptide. In this study, insulin was dispersed in the crosslinked alginate matrix with a subsequent layer of chitosan over this core[17].

Hydrogel synthesized by thermal crosslinking of poly (vinyl alcohol) and poly (γ-glutamic acid) was found to be pH-sensitive in nature and compatible with the 3T3 fibroblast cell line. The drug diffusion character of the hydrogel indicates its probable use for the oral delivery of the bioactive agent[18]. A controlled and pH dependent release of nifedipine was observed from the hydrogel consisting of N-succinyl chitosan and alginate prepared by ionic gelation method. The hydrogel was able to release the drug in the intestine[19]. Microspheres prepared from the crosslinking of interpenetrating networks of poly(methacrylic acid) and poly(vinyl alcohol) with glutaraldehyde were able to deliver ibuprofen into the intestine[20]. Cationic hydrogels have the potential to deliver drugs specifically in the stomach. Similar kind of delivery system was developed by Patel and his co-workers for the treatment of *H. Pylori* with an antibiotic[21]. Due to lower proteolytic activity in the colonic region, it is becoming a hot spot to deliver peptide drugs. Administration of bioadhesive hydrogel through the rectal route to the colonic region have reduced the chances of delivery system migration and thereby increased the bioavailability of propranolol[22].

1.3 Drug delivery in the oral cavity

Buccal or oral mucosal routes have various advantages for the administration of drugs which undergo severe first-pass metabolism. Hydrogel seemed an appropriate material for the buccal delivery because of its mucoadhesiveness, sustained-release property, comfortable feeling in the buccal cavity and safety.

Topical delivery of antimicrobial agents is widely accepted for prolonging drug concentrations in the oral cavity. Most

antifungals do not posses inherent ability to bind with the oral mucosa which can be achieved using hydrogels. Chitosan hydrogel containing antifungal agent, chlorhexidine gluconate was synthesized with the aim to prolong the adhesion time of oral gel followed by drug release from it[23].

1.4 Ocular Delivery

Instillation of aqueous drops is the preferred way to administer drug in the ocular cavity. But most of the drug is removed from the cavity due to tear drainage and blinking. In addition to this, the low permeability of the cornea worsens the situation. Though the use of suspension and ointments increase the ocular retention time, they produce a gritty feeling thereby reducing the patient compliance. The use of *in-situ* forming gels can increase the ocular retention time and availability of the drug to a greater extent. The advantage of this kind of delivery system lies in the fact that it is liquid while dispensing and instillation, but forms a drug depot after it is administered in the ocular cavity. Pilocarpine entrapped alginate hydrogel is the classic example of this kind[24].

1.5 Nasal Delivery

A new thermosensitive hydrogel was prepared by mixing *N*-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride and poly(ethylene glycol) with a small amount of *α-β*-glycerophosphate. The obtained formulation underwent thermal transition from solution below or at room temperature to non-flowing hydrogel around 37°C in few minutes. It can be dropped or sprayed easily into nasal cavity and spread on the nasal mucosa in solution state. After being administered into nasal cavity, the solution transformed into viscous hydrogel at body temperature, which decreased nasal mucociliary clearance rate and release drug slowly. In another case, quaternized chitosan has been studied as absorption enhancer and proved its non-toxicity, mucoadhesivity and the capacity to open the tight junctions between epithelial cells. A hydrophilic macromolecular drug like insulin was entrapped in this type of hydrogel which show improved absorption[25].

In situ gelling inserts has been prepared from hydrophilic bioadhesive polymers like carrageenan, Carbopol, chitosan, hydroxypropyl methylcellulose, sodium alginate, sodium carboxy methylcellulose, polyvinyl pyrrolidone and xanthan gum. The polymers were dissolved in demineralized water containing oxymetazoline-HCl and then lyophilized into small inserts. A sponge-like inserts were formed with amorphous nature during the freeze-drying process. It was observed that the drug release decreased with higher polymer content and increased drug loading. These bioadhesive nasal inserts thus produced have high potential for extended drug delivery[26].

1.6 Transdermal Delivery

Human skin is having a large surface area which makes it a potential site for administering drugs, both locally and systemically. Systemic delivery by this route helps in bypassing the first–pass metabolism and prolongs the release of drugs[27]. In addition to the above advantages, the hydrogels provide a soothing effect when compared with the occlusive/oily feeling caused by the application of ointments. Drugs like nitroglycerin and hydrocortisone are administered via this route[28]. Hydrogels are also proposed as a delivery system to the wound surface. *In situ* forming hydrogels are preferred due to relative ease of application and increased contact between the hydrogel and wound surface. Hydrogels obtained by the copolymerization of bovine serum albumin and PEG are used as a controlled release devices for hydrophilic and hydrophobic drugs in the field of wound dressing[29].

Currently research is focused to increase the drug permeation through the keratinized layer using either electrical force (iontophoresis) or physical force of ultra-sound (sonophoresis). The drugs whose permeability can be increased by iontophoresis include luteinizing hormone, sodium nonivamide

acetate, nicotine and enoxacin while the permeability of insulin and vasopressin can be increased using sonophoresis. Sun *et al*. proposed the use of diisocyanate cross-linked poly(2-hydroxyethyl methacrylate) hydrogel as composite membrane. It was observed that the membranes can be tailored to give permeation flux in the range of 4 to 68 micrograms cm^{-2}/h for nitroglycerin[30].

1.7 Subcutaneous delivery

Hydrogels are ideal implantable material. Their high water content creates the environment similar to biological tissue, making them relatively biocompatible. Thus hydrogels could be used in the subcutaneous delivery for anticancer drugs. In a study, crosslinked PHEMA was used for the delivery of cyratabine[31]. Yu Liu *et al*. investigated thermo-sensitive Pluronic F127 hydrogel for the controlled release of antithrombotic polypeptide, recombinant hirudin variant-2 when injected subcutaneously. Drug release followed zero-order kinetics at 37°C[32].

1.8 Ear Delivery

The delivery of drug to the ear cavity is mainly carried out by the use of aqueous or oil drops. The main limitation of ear drops is the retention time in the cavity while the person is standing. Hydrogels could be used successfully for the delivery of drugs to the ear cavity. Lee and co-workers were successful in delivering recombinant human insulin-like growth factor- I (rhiGF-I) using gelatin hydrogel. The group found that by delivering the rhiGF-I by this method could be useful in the treatment of noise-induced hearing loss[33].

Hyaluronic acid hydrogel provides a sustained dexamethasone release that might be utilized to treat sudden sensor neural hearing loss. This could potentially reduce the morbidity and costs associated with intratympanic steroids treatment[34].

Injectable chitosan based hydrogels were characterized for their potential as drug delivery matrix to be applied as sealant after ear–nose–throat surgery. Genipin crosslinked chitosan hydrogels showed slower gelling, sufficient gel strength and controlled delivery of dexamethasone. This hydrogel shows excellent antimicrobial properties towards *Staphylococcus aureus*[35].

1.9 Rectal Delivery

Rectal route has been used to deliver drugs for the treatment of disease associated with the rectum, such as hemorrhoids. Rich blood flow to this region can improve the systemic availability of drugs and also helps to bypass first pass metabolism. Drawbacks like discomfort arising from the given dosage forms and substantial variability of treatment depending on patient's acceptance are associated with this route. In addition to that drugs diffusing out of the suppositories in an uncontrolled manner or it are unable to be retained at a particular position in the rectum and tend to migrate upwards to the colon, leads to variation of availability of drugs, especially those that undergo extensive first-pass elimination. Today, hydrogels are seen to be a suitable answer to these drawbacks.

Miyazaki *et al*. investigated the potential application of xyloglucan gels with thermal gelling property for rectal delivery of indomethacin in rabbits[36]. The formulation provided a broader absorption peak and longer residence time. It shows no evidence of tissue damage.

Cylinder shaped hydrogels are synthesized from the crosslinking of hydroxyethyl methacrylate polymer with ethylene glycol dimethacrylate using radical polymerization method at the temperature of 70°C. These hydrogels are loaded with antipyrine and theophylline which exhibit controlled release profile when tested *in-vivo*[37].

2. Hydrogels as wound healing devices

The hydrogels are used successfully as a wound healing device. It has the ability to absorb and hold water in its network structure. It acts as a wound dressing material and has the ability to absorb and retain the wound exudates along with the foreign bodies, such

as bacteria, within its network structure. Hydrogels can be applied either as an amorphous gel or as elastic solid sheet or film. To prepare the film, the polymers are crosslinked so that they physically entrap water. These films can absorb and retain significant volumes of water upon contact with suppurating wounds. When gels are applied to the wound, hydrogel dressings usually require a secondary covering such as gauze and need to be changed frequently[38]. The films however, do not need a secondary dressing as a semi permeable polymer film backing, with or without adhesive borders, controls the transmission of water vapour through the dressing. In addition the films can be cut to fit around the wound due to their flexible nature. The gels are used as primary dressings whereas the hydrogel films may be used as primary or secondary dressings.

Hydrogels are suitable for cleansing of dry, sloughy or necrotic wounds by rehydrating dead tissues and enhancing autolytic debridement. Hydrogel dressings are nonreactive with biological tissue, permeable to metabolites and are nonirritant. Hydrogels also promote moist healing, are nonadherent and cool the surface of the wound, which may lead to a marked reduction in pain and therefore have high patient acceptability. A case studied by Moody[39] reports the use of a hydrogel dressing to treat a chronic leg ulcer for a patient who could not tolerate even reduced compression therapy due to pain, and the hydrogel helped reduce the pain considerably. Hydrogels also leave no residue, are malleable and improve re-epithelisation of wounds[38]. Morgan[40] has stated that hydrogels are suitable for use at all four stages of wound healing with the exception of infected or heavily exuding wounds.

Calcium alginate being a natural haemostat, alginate based dressings is indicated for bleeding wounds. The gel forming property of alginate helps in removing the dressing without much trauma, and reduces the pain experienced by the patient during dressing changes. It provides a moist environment that leads to rapid granulation and re-epithelialization. In a controlled clinical trial, significant number of patients dressed with calcium alginate was completely healed at day 10 compared with the members of paraffin gauze group. Calcium alginate dressings provide a significant improvement in healing split skin graft donor sites[41]. In another study with burn patients, calcium alginate significantly reduced the pain severity. The combined use of calcium sodium alginate and a bio-occlusive membrane dressing in the management of split-thickness skin graft donor sites, eliminated the pain and the problem of seroma formation and leakage seen routinely with the use of a bio-occlusive dressing alone[42]. Flexible, thin, transparent, novel chitosan–alginate polyelectrolyte complex (PEC) membranes caused an accelerated healing of incision wounds in a rat model compared with conventional gauze dressing. Application of the photo-crosslinkable chitosan hydrogel on full-thickness skin incisions made on the backs of mice significantly induced wound contraction and accelerated wound closure and healing compared with the untreated controls[43].

3. Hydrogels as tissue engineering scaffolds

Biomaterials like alginate, fibrin and gelatin based hydrogels were utilized earlier as tissue engineering scaffolds[44]. Now-a-days, polymers of synthetic origin like poly-Nisopropylacrylamide (NIPAAm), PEO–PPO–PEO triblock copolymers (Pluronic), PLGA–PEO–PLGA tri-block copolymers and polyphosphazenes are widely used for the synthesis of hydrogels[45]. These hydrogels exhibit temperature dependent sol–gel phase transition behavior. Above the critical concentration, these hydrogels show sol state at room temperature but transform into gel state at body temperature. An example of this category is the injectable polyNIPAAm physical hydrogels encapsulating cells that have been prepared for cartilage and nerve regeneration[46]. The PEO–PPO–PEO tri-block

copolymer (Pluronic) is popularly used as an *in-situ* forming gel for drug delivery[45]. Pluronic copolymers at a concentration of 20% w/v have been used to encapsulate chondrocytes and produce engineered cartilage[47]. Injected physical hydrogels of pluronics dissolves rapidly at the site when they are diluted with the body fluid. To confer the gel stability, grafted copolymers of PLGA and PEG were synthesized. The synthesized PLGA-g-PEG and PEG-g-PLGA hydrogels are capable of cartilage repair and sustained delivery of insulin[48]. Generally physical hydrogels, when injected with cells, do not exhibit sufficient mechanical strength to hold the proliferation and differentiation of cells along with a structural support for a desired period as the tissue is regenerated. To maintain the structural shape and dimension in a better way, photo-crosslinkable chemical hydrogels were introduced recently. Hyaluronic acid hydrogel encapsulating cells have been prepared by photo-polymerization of functionalized precursor macromers in the presence of fibroblasts[49]. Photo-crosslinked PEG based hydrogels have also been utilized for delivery of chondrocytes, osteoblasts, and mesenchymal stem cells[50,51]. Pluronic/heparin composite hydrogels delivering growth factor have also been studied to induce angiogenesis[52]. Hydrogels mimicking the extracellular environment were prepared by incorporating protease sensitive peptide sequences into photo-crosslinkable PEG hydrogels to facilitate cell invasion and migration[53]. Quite recently, a new class of *in-situ* formed scaffolds by self-assembly of synthetic polypeptides also emerged. The peptide based hydrogel could form stable and unique secondary structures in physiological condition[54]. Moreover, poly(aldehydes guluronate) or poly(organophosphazene) has been shown to form injectable, biodegradable, thermosensitive matrices which are promising materials for cell delivery[55,56].

4. Hydrogels as gene delivery device

Gene delivery is the incorporation of foreign DNA into the host cell and this can be mediated by viral and non-viral methods. The viral method utilizes the capability of a virus to incorporate its DNA into the host cells. For this purpose retroviruses and adenoviruses have widely been used. These viral vectors provide efficient transduction and high gene expression but their use is quite limited as they can produce immunogenic reactions or mutagenesis of transfected cells. The non-viral techniques include the use of a gene gun, electroporation and sonication.

Recently researchers are using polymers like poly-L-lysine, polyamidoamine dendrimer (PAMAM), polyethylenimmine (PEI), PGA, PLA and PLGA, for gene delivery[57]. PAMAM and PEI can provide high transfection efficiency but they suffer from poor degradability. This is why the use of biodegradable polymers, viz. PLA, PLGA and PGA, has gained importance. The use of PEG-PLGA-PEG hydrogel for the delivery of plasmid-beta 1 gene increased the wound healing process in diabetic mouse model[58]. Lin and co-workers reported similar results with agarose hydrogels. They concluded that agarose gels can be useful in the wound-healing and tissue engineering applications[59]. Mageed and co-workers reported the use of recombinant silk-elastin like polymer hydrogels (SELP) for the delivery of 'pRL-CMV' for the treatment of human breast cancers. Their results suggested an increase in the transfection efficiency when SELP hydrogels were used[60]. A recent study describes encapsulation of C2C12 myoblasts in a biocompatible permselective hydrogel of alginate –poly-L–lysine- alginate (APA) to protect the cell from host immune response while allowing diffusion of gene products. Inclusion of basic fibroblasts growth factor, insulin growth factor-II and collagen in the microcapsules showed proliferation and

differentiation of encapsulated C2C12 myoblasts. When tested against tumor induced by B16-F0/neu tumor cells in mice[61], the APA microcapsules had an 80% reduction in tumor volume at day 21.

5. Hydrogel as the replacement of nucleus pulposus

There is potential benefit in the replacement of dehydrated nucleus while preserving the annulus fibrosus and endplates. The approach could entail a less invasive posterior surgery as well as a return of the annulus to its healthy natural tension. Hydrogels are swellable 3D polymer networks that have the ability to hold large amounts of water. They can be tailored to have consistencies similar to those of natural soft tissues, which have made them materials of great interest for nucleus pulposus replacement. In addition, their swelling properties could potentially be utilized to make insertion of an artificial nucleus pulposus by a minimally invasive procedure.

'Neudisc' is an implant composed of two grades of hydrolyzed polyacrylonitrile and polyester mesh that is being developed at Replication Medical, Inc.[62]. The material is designed to be implanted in the dehydrated state and become 80% hydrated once in the position. The polyester mesh layers within the implant act to resist radial deformation or bulging of the implant. Bertagnoli *et al*. reported that unconfined compressive fatigue up to 10 million cycles did not change the hydration level or stiffness of the implant 14 days post fatigue[63].

Bao and Higham developed poly(vinyl alcohol) (PVA) based nucleus pulposus to replace & restore the function of intervertebral disc by mimicking both the mechanical and physiological properties[64]. The hydrogel consists of 70% water & acts similarly to the nucleus in that it absorbs and releases water depending on the applied load. The report reveals that PVA nucleus substitutes have a compressive modulus and compressive strength greater than 4 MPa and 1 MPa respectively. A baboon test model of the PVA nucleus showed no adverse local or systematic tissue reaction[65].

Stammen *et al*.[66] have proposed the use of physically crosslinked PVA hydrogel in cartilage replacement and spine disc replacement. The hydrogel prepared by freezing-thawing method was tested in compression and found an increase in tangent compressive modulus between 1-18 MPa from 10-60% strain. They also found shear tangent modulus in the range of 0.1-0.4 MPa, depending on strain magnitude.

Allen *et al*. has investigated PVA hydrogel with water content of 80% as a nucleus replacement material[67]. The material has been tested in fatigue up to 40 million cycles. When PVA is utilized alone as a prosthetic implants it become unstable within the physiological environment. The instability results from the fact that PVA is a semicrystalline, hydrophilic polymer that can undergo dissolution. The dissolution process involves an unfolding of PVA crystal chains that join the amorphous region of the polymer, disentangle, and eventually dissolve with decreased mechanical stiffness. On the contrary, when the blends of PVA and polyvinyl pyrrolidone (PVP) have been investigated by Marcolongo and Lowman[68,69], they found PVA/PVP hydrogels have enhanced the *in vitro* stability over pure PVA hydrogels. During mechanical testing of lumbar anterior column units, they found that implantation of PVA/PVP hydrogels restored the compressive stiffness of the spinal unit to its original intact values.

CONCLUSION

This review has considered different routes of administration and the utility of hydrogel biomaterials. To achieve the goal certain hydrogels undergo sol-gel phase transition in response to physiological temperature while pH and ion sensitive hydrogels are found to

deliver drugs and other macromolecules like peptides to specific sites of the GI tract. Biocompatibility, biodegradability and absorption of biological fluids translated the hydrogels for use in tissue engineering, gene delivery, wound dressing and as nucleus pulposus replacement material.

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