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Review Article

Synthesis, Characterization, and Advanced Biomedical Applications of Hydrogels: A Current Review

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ABSTRACT

The development of hydrogel technologies has been the focus of various pharmaceutical and medical fields, including tissue engineering, controlled drug delivery, wound management, cell separation, and biological materials. Hydrogels, which are biodegradable and biocompatible materials, have been known to work as drug carriers for controlled and targeted release of bioactive proteins and peptides, are able to protect the drug from harsh environments, and can be used for the encapsulation of living cells. Because of the presence of some biological variables, such as different pHs in the gastrointestinal tract or body temperature, environment-sensitive hydrogels can be used for targeted drug delivery. A wide range of hydrogel-based smart and intelligent carriers for pharmaceutical drugs have been developed and fabricated by various methods to fulfill the needs in biomedical fields. In this review, we summarize and discuss the synthesis of hydrogels by different methods and their classifications, characterizations, and biomedical applications.

INTRODUCTION

With the increasing advancement of research in the field of pharmaceutical technology, hydrogels have received considerable attention as convenient, biocompatible, and stable carriers for a wide range of drugs, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), pharmaceutical proteins, and peptides. Hydrogels are known to decrease the problems of both conventional and novel drug delivery systems [1]. They are extensively used in pharmaceutical and medical fields for the targeted and controlled delivery of drugs, tissue engineering, electrophoresis, and regenerative medicine. They have been designed for site-specific drug delivery by using biodegradable and biocompatible polymers, along with "homing devices" like antibodies. This protects the normal cells and targets the diseased ones [2]. Hydrogels are generally defined as three-dimensional hydrophilic polymeric networks synthesized by various physical and chemical cross-linking methods. Properties of the polymer(s) used can affect the nature and density of the network joints. They can absorb large amounts of water while maintaining the mechanical strength, structure, and integrity. In the equilibrium state, water is much heavier than the polymers in the hydrogel. Their water absorption affinity is attributed to the presence of various hydrophilic groups such as –OH, -CONH, -$CONH_2$, and -SO_3H in the backbone and lateral chains of polymers [3].

Hydrogels can be classified on the basis of the type of cross-linking: physical gels (pseudo gels) and chemical gels (true, permanent). In physical hydrogels, the chains are connected by non-covalent interactions, such as ionic interaction, hydrogen bonds, van der Waals interaction, hydrophobic interaction, and protein interactions. On the other hand, true or permanent hydrogels have covalent bonds between polymers and other small molecule cross-linkers [4]. A variety of synthetic and natural polymers used alone or in combination in the preparation of hydrogels, are discussed in this review article. Presently, a new class of hydrogels, whose swelling and drug release trigger various external physical or chemical stimuli (such as temperature, pH, solvent composition/solvent polarity, light, electric field/magnetic field, specific ionic strength, and sound) are known as environment-sensitive or responsive hydrogels. Because of the sensor property of these hydrogels, they are also known as "intelligent or smart hydrogels" [5]. This review focuses on the synthesis and characterization of many hydrogels available in the market, their recent development in biomedical applications, and their future perspectives as dynamic new dosage forms for drug delivery system.

TYPES OF ENVIRONMENT-RESPONSIVE/SENSITIVE HYDROGELS

pH-Responsive or Ionic Hydrogels

Ionic hydrogels are sensitive to changes in the pH of surrounding medium. They can be anionic or cationic, due to the presence of certain ionic groups. The most common monomer (Table 1) used to fabricate anionic hydrogels is Acrylic Acid (AA) and Methacrylic Acid (MAA) [5,6]. The swelling index of hydrogels of bacterial cellulose and acrylic acid is found to be the highest in neutral or basic pH, and the lowest in acidic medium, due to the anionic nature of copolymers [7,8]. On the other hand, poly-imethylaminoethylmethacrylate (PDEAEMA) [9] and some cellulose derivatives have been used in cationic hydrogel formation (Figure 1). For example, Rodriguez et al. [10] found that hydrogels fabricated with two cationic celluloses with different hydroxyethyl and ammonium group contents work as a site-specific delivery system. This is due to breaking of the hydrophobic bonds between diclofenac sodium and polymers at alkaline pH [10]. The pH-responsive hydrogels have been used in pulsatile drug delivery as biosensors, permeation switches, oral delivery of proteins, and peptides. Casadei et al. [11] reported that pH-sensitive hydrogels of methacrylated and succinic derivatives are potentially helpful for the targeted delivery of an anti-cancer drug (2-methoxyestradiol) used to treat colonic cancer, due to its enzymatic degradability, mucoadhesion and pH-sensitive release [11].

Table 1: Polymers used in hydrogel fabrication [15,16,28].

pH-Sensitive hydrogel	Temperature-sensitive hydrogel	Glucose-sensitive hydrogel
Polymethylmethacrylate Polyacrylamide Polyacrylic acid Polyethylene glycol Polymethacrylic acid Poly(acrylamide (AAm)-coacrylic acid) Poly(*N*,*N*'-diethylaminoethyl methacrylate) Poly(*L*-glutamic acid) Poly(tertiary amine methacrylate) Poly(2-(dimethylamino) ethyl methacrylate) Poly(2-vinylpyridine)	Poly(*N*-isopropylacrylamide) P(NIPAAm–co-BMA) Pluronics(or Poloxamers) Tetronics Poly(*N*,*N*-diethylacrylamide) Poly(*N*-ethylmethacrylamide) Poly(methyl vinyl ether) Poly(2-ethoxyethyl vinyl ether) Poly(*N*-vinylcaprolactam Poly(*N*-vinylisobutyramide) Poly(*N*-vinyl-*n*-butyramide)	Glucose oxidase immobilized onto PDEAEM Glucose oxidase immobilized onto poly (2-hydroxythyl methacrylate – co- N,N-dimethylaminoethyl methacrylate Concanavalin A - poly[3-(acrylamido)phenylboronic acid] complex poly-(glucosyloxyethylmethacrylate)–Con A complexes poly (methacrylamido phenylboronic acid)-coacylamide complex of 2-hydroxyethyl methacrylate and 3- acrylamido phenyl boronic acid

Temperature-Responsive Hydrogels

These temperature-sensitive hydrogels show a significant change in volume as a result of temperature variation due to the change in intra and inter hydrogen bonds and hydrophobic forces. Thermo-responsive hydrogels have led to dramatic

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advances in the bioengineering, biomedical, and biotechnological research areas [5]. They have gained considerable attention for delivering a large number of temperature-sensitive drugs. The release and mechanical properties of both drugs and hydrogels are altered with changes in the temperature of the surrounding media [12]. A hydrogel made with *N*-Isopropylacrylamide (NIPAAm) and Acrylamide (AAm) showed temperature-dependent transition between transparent solution to translucent gel, and this system was utilized to encapsulate insulin for a sustained release delivery system [13]. Another thermo-sensitive hydrogel comprising of chitosan incorporated with silica nanoparticles was formulated for delivery of a vaccine [14]. Many polymers show signs of a temperature-responsive sol-gel phase transition, if the polymers in the hydrogel are not covalently linked. Generally, these hydrogels contain hydrophobic groups on their backbone. The most commonly used polymers are listed in (Table 1). They can be sub-categorized into negative, positive, and inverse thermo-sensitive gels on the basis of critical solution temperature. Negative thermo-responsive hydrogels shrink in temperatures above their Low Critical Solution Temperature (LCST) due to hydrophilic to hydrophobic transition. On the other hand, positive thermo-sensitive gels exhibit the opposite transition (Figure 2).

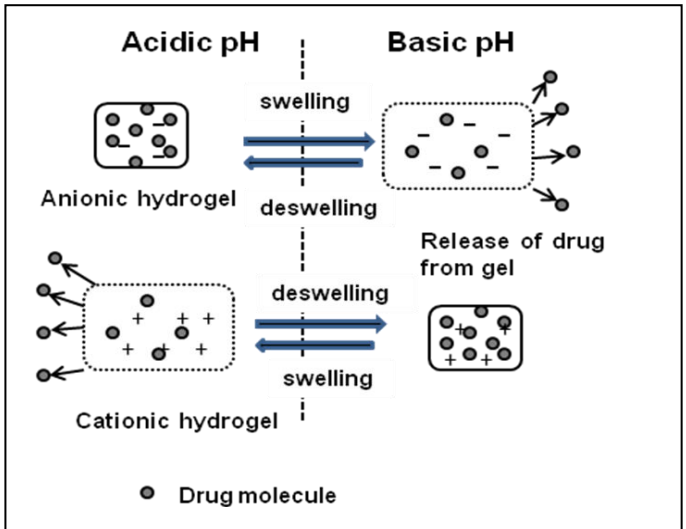

Figure 1: Swelling behaviour of ionic hydrogel as a function of pH.

The poly *N*-isopropylacrylamide (PNIPAAm) hydrogel is a well-known thermo-sensitive hydrogel for pharmaceutical and medical applications because of its LCST at around 32°C, which is near to physiological range. When solution temperature is below LCST, the network expands; it appears transparent because of its high solubility in water, but as temperature increases above its LCST, polymeric chains shrink and dehydrate. At this point, opaque polymers precipitate out from the aqueous media [12,15].

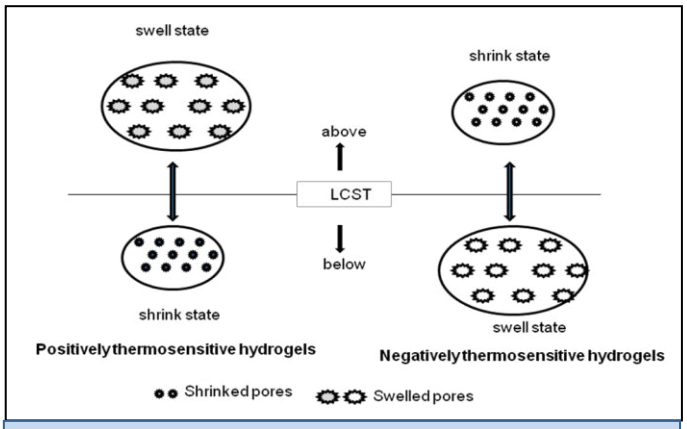

Figure 2: Swelling of thermosensitive hydrogel in response to temperature.

Glucose-Sensitive Hydrogels

Glucose-responsive hydrogels, which exhibit a response to glucose concentration, are widely applicable in the management of insulin-dependent diabetes [15,16]. Bio-responsive self-regulatory hydrogels for the controlled release of insulin are fabricated through the use of different sensors such as glucose oxidase, an enzyme producing gluconic acid that alters the pH of the environment, and causes swelling of the hydrogel leading to the controlled release of insulin (Figure 3) [16], concanavalin A [17], phenylboronic acid [18] and glucose binding protein [19]. A polymer chain used for intelligent insulin delivery is shown in Table 1.

Other Stimuli-Sensitive Hydrogels

Temperature-, pH-, and glucose-sensitive hydrogels have been widely used in the pharmaceutical area. However, due to their limited application, other smart hydrogels based on electric field, pressure, sound, and light have reduced popularity in the field of drug delivery [5,15]. Electro-sensitive hydrogels are usually synthesized from polyelectrolytes; when electric current is applied to the system, electrolytes move towards the cathode or anode, which causes swelling or deswelling of the hydrogel. Light-sensitive hydrogels are mainly classified as UV-responsive

and are made up of leuco-derivative molecules that ionize on exposure to radiation causing swelling of the hydrogel. In contrast, visible light-sensitive hydrogels are made using light-sensitive chromophores that increase the temperature of the hydrogel in the presence of light causing hydration of the gel [20,21].

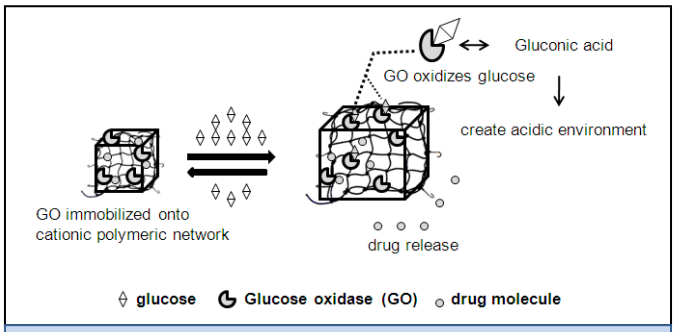

Figure 3: Self regulatory glucose-sensitive hydrogel with an automatic shut-off mechanism.

METHODS OF SYNTHESIS OF HYDROGELS

As mentioned earlier, two main methods for the development of hydrogels are chemical cross-linking and physical cross-linking. In this review, novel cross-linking methods widely used to create hydrogels will be briefly discussed.

Chemical Cross-Linking Methods

Cross-linking by radical polymerization: Radical polymerization is one of the commonly used methods to synthesize hydrogels. Monomers are cross-linked by using a multifunctional co-monomer known as a cross-linker. The technique mainly involves the introduction of cross-linkers between the polymeric chains to produce cross-linked chains (Figure 4b). A variety of hydrogels can be designed by this procedure, for example, different stimuli-sensitive hydrogels using hydrophilic or a combination of hydrophilic and hydrophobic polymers [4].

Jeong et al. [22] studied the optimal condition for the fabrication of hydrogels synthesized by free-radical polymerization using Sorbitan Methacrylate (SMA) as a monomer, ethylene glycol dimethacrylate as a cross-linking agent and α, α'-azo-bis (isobutyro-nitrile) as an initiator [22]. One type of hydrogel that has both pH- and temperature-responsive characteristics is prepared with monomers like (2-dimethyl amino) ethyl methacrylate (DMAEMA), *N*-Isopropylacrylamide (NIPAAm) and 2-Hydroxyethyl Methacrylate (HEMA) by free radical polymerization using ethylene glycol di-2-bromoisobutyrate as initiator [23]. Similarly, Wu et al. [24] prepared pH-sensitive semi-IPN structural hydrogels that are composed of poly (vinyl alcohol) and star poly [2-(dimethylamino) ethyl methacrylate] with different designed molecular weights, i.e., 25,000, 50,000, and 100,000 using epichorohydrin as cross-linking agent [24].

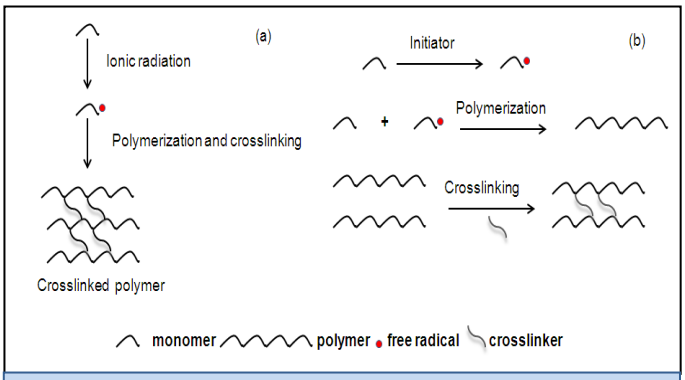

Figure 4: Reaction mechanism for (a) radiation polymerization, (b) radical polymerization.

Cross-linking by chemical reaction of functional groups: The hydrogels are formed by the covalent bonds between different functional groups like a reaction between carboxylic acid and substituted amines, aldehyde, and hydrazide. Cross-linking of water-soluble polymers can also occur by additional reactions, where the hydrogels are formed using higher functional cross-linking agents such as 1,6-hexamethylenediisocyanate and divinylsulfone. Another frequently applied synthesis of hydrogels involves formation of polyamides and polyesters due to the reaction between NH2 with –COOH and –OH, respectively. N,N-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC) is an efficient reagent to establish chemical cross-linking of water-soluble polymers with amide bonds in the preparation of gelatin hydrogels [4,25].

Cross-linking by high-energy irradiation: This method has significant advantages, such as highly accelerated reaction rates, an absence of any toxic chemical agents as either initiators or cross-linkers, excellent morphological characteristics, and a higher yield making it an efficient method of synthesis. In addition, simultaneous synthesis and sterilization of hydrogels are unique advantages of radiation processing. In general, the radiation intensity, radiation time and monomer concentration are directly proportional to the cross-link density of hydrogel [26]. Gamma radiation, electron beams, and

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microwave radiation are commonly used for the polymerization of the system. These ionic radiations produce free radicals that initiate polymerization and cross-linking (Figure 4a). Gamma radiation was used to cross-link biodegradable hydrogels that consist of bacterial cellulose and acrylic acid, and exhibit pH-dependent swelling behavior. It plays a significant role in site-specific drug delivery [8,27,28]. Similarly, temperature-responsive hydrogels of PNIPAAm were prepared by microwave irradiation using Mars-5 microwave accelerator [28]. Meena et al. [29] synthesized hydrogels of k-Carrageenan (kC) and Acrylamide (AAm) by microwave irradiation using a domestic microwave oven at neutral pH in the presence of the initiator (potassium persulfate), and they observed that this hydrogel exhibits excellent absorbent behavior [29].

Cross-linking using enzymes: An emerging and interesting approach for hydrogel synthesis is based on enzyme-induced cross-linking. Enzymes from various sources, such as transglutaminase, which plays an important role in blood clotting, and tyrosinase, an oxidative enzyme that converts phenol or tyrosine residue into reactive quinones, are widely used in the synthesis of gelatin gels. Chena et al. [30] synthesized gels of gelatin and chitosan by using these two enzymes, and compared the strength of both gels [30]. Similarly, Jeffrey et al. [31] formulated hydrogels of two macromolecules (polyethylene glycol and polypeptide) using the action of enzyme transglutaminase. They observed that gelation of the gel depends upon macromolecule concentration and experimental condition [31]. Jin et al. [32] prepared dextran-tyramine hydrogels using an enzymatic cross-linking method and evaluated this method for different parameters [32].

Physical Cross-Linking Methods

In permanent hydrogel synthesis, cross-linkers are generally used for polymerization, but they are mostly toxic in nature and can be harmful. This can be overcome by proper purification and verification. To avoid the use of cross-linking agents, various physical cross-linking methods have been investigated.

Cross-linking by ionic interactions: Ionic cross-linking can be achieved either by using multivalent counter ions or by positively charged polymer chains (Figure 5). These interactions are usually pH-dependent. For example, hydrogels formed by cross-linking chitosan with glycerol-phosphate disodium salt show evidence of a temperature-dependent sol-gel phenomenon [33]. Natural polymer sodium alginate cross-linked with di- or trivalent ions have been used to produce hydrogels or alginate beads that have been extensively used in drug encapsulation and controlled-release delivery system [34]. Similarly, Xin et al. [35] synthesized a series of branched cationic β-cyclodextrin polymers, and formed a complex with an anionic drug. They incorporated this complex to alginate hydrogels that were synthesized using the ionic gelation method [35].

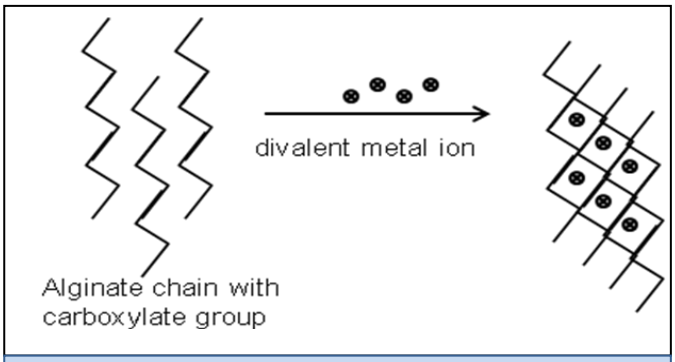

Figure 5: Reaction mechanism of ionic interactions.

Cross-linking by crystallization: Apart from the ionic or hydrophobic interactions in physical cross-linking, crystallites may work as physical cross-linkers in block copolymers, and even in homopolymers. Steneke et al. [36] synthesized dextran hydrogels and microparticles using a novel method of crystallization [36]. Similarly, Jong et al. [37] prepared hydrogels of lactic acid oligomers of opposite chirality by stereocomplex (racemic crystallites) formation [37].

Cross-linking by hydrogen bonds: Hydrogen bonds could also provide physical interactions between –o- and OH group-containing polymers leading to the formation of a hydrogel (Figure 6). A spontaneous formation of a hydrogel was observed by mixing two water-soluble phospholipids polymers, such as poly (2-methacryloyloxyethyl phosphorylcholine-co-methacrylic acid) (PMA) and poly (2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (PMB), in an aqueous medium at ambient temperature. Similarly, spectroscopic and FT-IR analyses revealed that carboxyl groups in Methacrylic Acid (MA) formed dimers when two

polymer solutions were mixed, due to the formation of hydrogen bonds by protonation of carboxylic acid groups, which leads to gelation of the polymeric solution [38]. The inter-polymer complexation occurs between poly (acrylic acid), poly (methacrylic acid) and poly (ethylene glycol) that forms a viscous network because of the hydrogen bonding between the -o- of PEG and –COOH of acrylic acid and methacrylic acid. Additionally, the intermolecular hydrophobic interactions are also responsible for the complexation process [39].

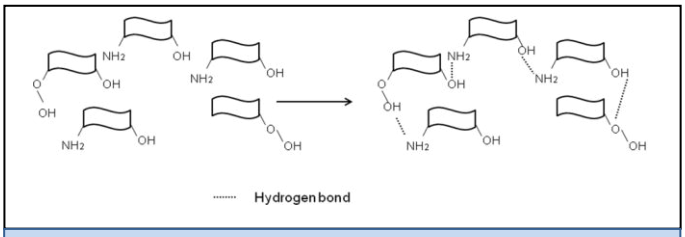

Figure 6: Reaction mechanism cross-linking by hydrogen bonds.

Cross-linking by protein interactions: Another novel method for producing hydrogels involves cross-linking by protein linkages, either by using genetically engineered proteins or by cross-linking antigen–antibody interactions. Halstenberg et al. [40] synthesized protein-graft-poly (ethylene glycol) hydrogels by using a protein interaction method. They prepared an artificial protein using a recombinant DNA technique, and grafted it on a backbone of PEG using protein interaction [40]. Similarly, an antigen-sensitive hydrogel was prepared by Miyata et al. [41] in which an antibody acted as an additional cross-linker in the grafting of an antigen (rabbit IgG) onto the backbone of chemically cross-linked polyacrylamide [41].

HYDROGEL INTERPENETRATING POLYMERIC NETWORK (IPN) AND FUNCTION

An IPN is formed when at least one network is polymerized in the presence of another. It can be done by immersing a pre-polymerized hydrogel in the monomeric solution of another polymer along with an initiator, with or without a cross-linker. In the presence of a cross-linker, full IPNs are produced, while in the absence of a cross-linker, semi-IPNs are produced. These IPNs are considered to have better physical and mechanical properties, controlled swelling, drug loading, and release, in comparison to conventional hydrogels due to the dense hydrogel matrix [42].

IPN phases that have different swelling and degradation properties in response to environmental stimuli can be used to control the release property and release kinetics of drugs. The pore size and surface chemistry can vary according to the hydrogel drug and tissue interaction [43]. IPN composition can also control burst release by restricting the equilibrium swelling of both, or any one of the components of the hydrogel network. In contrast, the semi-IPN network provides rapid release and environment response because of the absence of the restricting polymeric network. Thus, drug loading, release kinetics, and environmental sensitivities can be adjusted by changing the nature of the polymeric network, density of the network, pore sizes and surface chemistries by choosing a semi- or fully-IPN hydrogel.

CHARACTERIZATION OF HYDROGELS

Hydrogels are usually characterized by their surface morphology, swelling index and mechanical properties. Various techniques have been investigated to investigate the cross-linking interactions between the polymers.

Scanning Electron Microscopy (SEM)

SEM photomicrographs of the polymers are taken in order to monitor surface topology and texture of biomaterial. SEM can produce magnified images of a sample (10 to 500,000×) by using electron beams. This is widely used to study characteristic network structure and factors affecting the surface integrity of prepared hydrogels. For example, Zhanq and Peppas (2002) investigated the effect of environmental factors on surface morphology of thermo- and pH-sensitive hydrogels of PNIPAAm and poly (methacrylic acid). They analyzed wet gels and dry gels by using cryogenic SEM and conventional SEM, respectively [44].

X-ray Diffraction

X-ray diffraction is another technique used to describe the retention or deformation of the crystalline structure of polymers during the processing pressurization. Crystalline or amorphous structures have played an important role in the release profile of drug. Szepes et al. [45] characterized and investigated the morphological effects of Isostatic Ultrahigh Pressure (IUHP) on starch-based gels (potato and maize starch). X ray pattern of both maize and potato starch revealed that the crystalline structure of maize starch was sensitive to IUHP, but potato starch remained stable. The release pattern of drugs from

potato starch gel was faster than the reference, but maize starch gel showed evidence of sustained release due to a change in crystalline structure [45].

Magnetic Resonance Imaging (MRI)

MRI is a powerful non-invasive imaging technique that provides internal pictures of formulation and materials without any destruction by using a magnetic field and radio frequency pulses at micro and macroscopic level. In the case of hydrogels, this technique is used to study the polymer network integrity, nature of the bond formed and the dynamics of water. Kowalczuk and Tritt Goc, [46] investigated the effect of microwave irradiation on the physical characteristics of Hydroxypropyl Methylcellulose (HPMC) hydrogels by using MRI [46]. In contrast, Ganapathya et al. [47] used Proton Magnetic Resonance (PMR) imaging to measure volume-phase-transition of thermo-reversible gels that consist of polymer poly (N isopropylacrylamide) [47].

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy has been used to identify chemical compounds, and to determine the purity of compound, polymer interaction and morphological changes in the hydrogel network. FTIR is a molecular absorption and transmission technique that produces IR spectra that is unique to particular compound(s). Superabsorbent hydrogels, fabricated by grafting of AA/-acrylamido-2-methyl-1 propanesulfonic acid (AMPS) to the backbone of CMC and montmorillonite, have been evaluated for their morphological property by FTIR. The results revealed that porous hydrogel structures contained carboxylate, carboxamide, and sulfate at their side chain [48]. Chiu et al. [49] investigated the effect of ionic strength and surrounding pH on ionization of acrylic acid fraction present in dextran hydrogels using FTIR-ATR spectroscopy [49].

Swelling Behavior

When hydrogels are submerged in water, aqueous medium, or specific pH medium, they swell many times their original weight due to penetration of water molecules into the polymeric networks that results in expansion of the hydrogel. The swelling is calculated by dividing the difference of the weight of the wet and dry hydrogel with the weight of the dry hydrogel. Yu and Xiao [50], prepared gelatin-based hydrogels by using a small molecule, dialdehyde konjac glucomannan (DAK), as a cross-linker and estimated its swelling ratio. They found that the cylindrical form of the gel is significantly different in the swollen state (4.0 cm) compared to the dry state (1.5 cm) diameter [50]. Similarly, Zhao et al. [51] examined the swelling and deswelling kinetics of thermo-sensitive gels in aqueous media, below and above the LCST. These poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogels were synthesized through normal water-bath heating and microwave irradiation. It was observed that microwave-irradiated hydrogels had lower swelling/deswelling activation energy in comparison to the conventional method [51]. The percentage swelling of a hydrogel is also affected by the pH of the external environment. The swelling of pH-sensitive hydrogels composed of psyllium and polyacrylamide have been studied by Singh et al. [51] using the gravimetric method [52].

Rheological Method

In a small amount of studies, the viscosity of hydrogels is measured by a Cone/Plate viscometer at constant temperature (generally 4°C). However, frequently flat-plate measuring geometry is used [53]. The rheological studies give information regarding the nature of the water–polymer interaction. Jianga et al. [54] studied the phase transition behavior of water within hydrogels of chitosan/polyacrylate. They observed changes in the structure of these gels by comparing rheological measurements taken by oscillatory shear rheology at, above, and below freezing point [54].

HYDROGELS FOR ADVANCED BIOMEDICAL APPLICATIONS

High water retention capacity, biocompatibility and biodegradability makes hydrogels promising formulations for controlled and targeted drug delivery, wound care devices, injectable implants, tissue engineering, and biosensors. Smart or intelligent hydrogel systems have attracted substantial attention as efficient carriers for protective and site-specific delivery of enzymes, peptides, and proteins. Currently, they are widely used in transdermal, ophthalmic, nasal, parenteral, rectal, and vaginal drug delivery systems [55]. Transdermal systems are gaining popularity because of their capability to control delivery of drugs for a long duration, terminate the therapy at any time, and increase bioavailability by bypassing hepatic metabolism. They are widely used for wound healing due to their hydrophilic nature, easy removal (water-washable) and desirable release [55,56]. These include adhesive and thermo-sensitive microgels of poly(acrylic acid-cosodium

acrylate), poly(acrylic acid-co-2-ethylhexyl acrylate), and poly(N-isopropyl acrylamide), which have been incorporated in a Carboxymethyl Cellulose (CMC) matrix for the transdermal delivery of caffeine [56]. Fang et al. [57] examined the stereoselectivity of skin for both the R- and S-forms of selegiline by using a hydrogel-based transdermal system containing SoluporÒ polyethylene membranes (as the rate controlling membrane) [57].

The hydrophilic nature and bioadhesive property of hydrogels makes them suitable for treating local infection of oral cavities such as oral cavity cancers, fungal, bacterial, and viral infection. The sublingual and buccal route for bioadhesive hydrogels is an excellent way to prolong the delivery of a drug with high first-pass metabolism. A number of formulations such as hydrogel-based ointment or gels, tablets and patches have been prepared for the local treatment of mouth diseases. In the case of fungal infection, chitosan-based hydrogels have been frequently used because, in addition to its mucoadhesive and sustained release properties, chitosan itself acts as an antifungal agent. It restricts the adhesion of *Candida albicans* to human buccal cells [58]. Microencapsulated beads of alginate with water-soluble chitosan were created by Lin et al. [59]. They found that these beads have desirable properties for delivering proteins and peptides to different regions of the intestinal tract [59]. Environment-sensitive or smart-hydrogels, especially containing polysaccharides that are degraded by polysaccharidase enzymes present in the colon, are mostly used for colon-targeted delivery of a drug [52].

In the case of the ocular route, topical delivery is preferred over systemic delivery due to many physiological constraints. Conventional drug delivery systems are not promising because more than 95% of the drug is lost by effective removal mechanisms (blinking, tear drainage, and low corneal permeability). Thus, in order to overcome frequent dosing, low absorption, and short retention time, *in situ* hydrogels are excellent options for long-term ocular delivery of a drug. *In situ* hydrogels of PEG were evaluated for swelling, drug loading, percentage release, and subsequent pupillary constriction. A strong correlation between pilocarpine and pupillary response make it suitable for ocular delivery of drug [60]. Similarly, *in situ* PEG hydrogels of doxycycline were investigated for wound healing efficacy in rabbit corneas. The histology and immunofluorescence studies revealed that wound-healing efficacy of *in situ* gel was higher than that of a doxycycline solution [61]. Biocompatibility is a primary requirement for implantable material. High water retention, their soft and elastic nature, their capability to cause less in vivo irritation, and their desirable release behavior makes hydrogels suitable for subcutaneous delivery [62]. These delivery systems are frequently used for targeting delicate drug delivery (peptides and proteins). These injectable PluronicÒ hydrogels possess all required characteristics such as bioadhesion, thermo-sensitivity, and injectable properties for controlled delivery of a gene and protein [63]. Huynh et al. [64] created a pentablock polymer by using poly (β-amino ester) (PAE) [64]. This polymer was used to synthesize the novel pH/temperature-sensitive injectable hydrogel for controlled protein/drug delivery [65]. Injectable hydrogels are capable of targeting a drug to any part of the body. The majority of these formulations are used in the treatment of cancer. For instance, injectable chitosan hydrogels have been synthesized for localized cancer therapy using paclitaxel as a model drug [66].

Tissue engineering deals with the development of biological substitutes, and it involves expertise from various fields such as, material science, medical and biological science. The hydrophilic nature of a non-dissolving three-dimensional network of polymers, along with its permeability and biocompatibility, makes it an attractive formulation for cell encapsulation and tissue engineering. The physical characteristics of the cross-linked structure of hydrophilic hydrogels are usually similar to soft tissue, and they are highly permeable for nutrients, tissue metabolites, and oxygen, which are frequently used in tissue regeneration or replacement [40,67,68]. Recently, hydrogels were also used as effective culture media for cell growth, as reported by Dang et al. [69]. They found that a Chitosan-α, β-Glycerophosphate (CS-α, β-GP) thermo-sensitive hydrogel with low gelation temperature is feasible to use in a 3D culture system for Penaeus chinensis lymphoid cells. Hydrogels were also used for the coating catheters, as it provides a smoother surface in comparison to 100% silicon [70]. It has also been reported that epicardial application of an amiodarone-releasing hydrogel would produce therapeutic myocardial drug concentrations, while systemic levels would remain low during sinus rhythm

maintenance [71]. Similarly, chitosan/STS hydrogels came in flux, which has great potential as embolizing and sclerosing agents for endovascular repair [72]. On the other hand, hydrogels have also been used as sensing platforms in DNA hybridization assays [73].

CONCLUSIONS AND FUTURE PERSPECTIVE

In the past few decades, many novel hydrogel systems have emerged as potential and multipurpose materials with enormous possibilities in the field of targeted and sustained/controlled release drug delivery systems. With proper network design, more new biodegradable and biocompatible polymers would be successfully produced for applications in the biomedical field. A variety of interesting cross-linking methods for hydrogel preparation are presently known, but there is certainly a need for further advancement. Development of smart hydrogels, which respond to external stimuli, is the toughest challenge in the present era. These drug delivery devices, due to their unique characteristics, are widely gaining attention as intelligent drug carriers. These hydrogels have been used in the formation of nano-biotechnology products and have amazing applications in the field of tissue engineering and dosage form development. The development of injectable hydrogels with *in situ* polymerization, without cytotoxicity, and with the ability of controlled and targeted drug delivery would be of significant importance in the field of biomedical application. Additionally, development of hydrogels with on-off drug delivery could be beneficial for the long-term delivery of analgesics and insulin. There is a need for improvement in hydrogels, not only in the area of synthetic drugs, but also in the delivery of biomolecules such as antigens, antibodies, and hormones. The tremendous application of hydrogels will grow in the future with growing efforts committed to targeted or controlled drug delivery systems. Finally, it can be foreseen that the hydrogel systems will be further developed and used in many applications in the biomedical and pharmaceutical areas in the near future.

CONFLICT OF INTEREST

Authors of the manuscript do not have a direct financial relation with the commercial identity mentioned in this paper.

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