Chapter 13
An Overview of the Recent Developments in Hydrogels

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Abstract Hydrogels are extremely hydrophilic polymers that are physically or chemically cross-linked. They exist in many types varying according to their mechanical and structural characteristics, method of synthesis, or the nature present on the molecules. The present chapter presents an overview of hydrogels, and their properties and applications in the field of drug delivery. In the first part, relevant parameters defining hydrogel properties and the strategies for fine-tuning them are discussed. In the second part, the application of hydrogels in drug delivery, different modes of drug delivery, as well as an in-depth overview of the applications of hydrogels in current scenario is presented. From an application point of view, hydrogels can be used as an excellent drug delivery matrices and tissue engineering scaffolds.

1 Introduction

Hydrogels are hydrophilic three-dimensional network polymers capable of expanding up to thousand times of its dry weight when immersed in aqueous solutions. The interactions within the hydrogel network involve covalent bonds, physical cross-links, hydrogen bonds, strong van der Waals interactions, and crystallite associations. A hydrogel system consists of a combination of two or more associations of the aforementioned interactions. These are biocompatible and are extensively used for in vivo studies. Sol–gel transforming properties shown by hydrogel make them useful in different microenvironments present in the body with varying parameters such as pH, temperature, and enzymatic activities at the diseased sites. Physiological temperature (37 °C) and pH (7.4) are the common conditions which induce a

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hydrogel to transform from the sol-state to the gel state. Hydrogels are often used for the delivery of hydrophilic drugs due to the hydrophilic polymer matrix. However, hydrophobic drugs are generally incompatible with hydrogels. This is due to limited loading quantity of hydrophobic drugs and their homogeneity in hydrogel matrices. Therefore, hydrogel modification for delivery of hydrophobic compounds is essential. This is a major challenge as hydrophobic drugs are being increasing used in the current pharmaceutical treatment systems. It is estimated that ~40% of the marketed drugs and 60% of the compounds that are in the research and development state present poor water solubility.

The hydrogels' swelling properties and resistance to dissolution are dependent on the hydrophilic groups and degree of cross-linking in the structure. The water absorption capacity of the hydrogel is attributed to the hydrophilic groups in the polymer, and the dissolution resistance is primarily due to cross-linking within the polymer network. Water plays a key role in providing the peculiar characteristics of hydrogels. Numerous materials, including natural and synthetic, adhere to the above description of hydrogels. However, novel ideas are being innovated by researchers in order to enhance hydrogel properties such as mechanical properties, biocompatibility, and superporous nature. Various new generations of hydrogels such as grafted hydrogels, hybrid hydrogels, and genetically engineered triblock copolymers with high stability and fast response time imitating hydrogels promise a smart future for these useful materials.

2 Classification of Hydrogels

Hydrogels may exist in different physical forms. The classification and types of hydrogels can be done based on its properties like its origin (natural and synthetic), compositions (homopolymeric, copolymeric, multipolymeric interpenetrating hydrogels, etc.), configuration (crystalline, semicrystalline, and amorphous), and the interaction among polymer network (permanent/chemical gel and reversible/physical gel); besides these, some other categories are also possible. Hydrogels derived from only one type of monomeric species are known as homopolymeric hydrogels; however, when the hydrogel is comprised of two or more different types of monomeric units it is known as a copolymeric hydrogel. In copolymeric hydrogels, the monomeric units can be arranged in various fashions like random, alternating, or in block, along the chain of polymer network. The interaction between the polymer networks in the hydrogel is another category of hydrogels. When the interaction between networks is covalent, a chemical or permanent gel is obtained. Molecular entanglements and/or other types of secondary forces like hydrogen bonding, and hydrophobic and ionic interaction give rise to a reversible or physical type of hydrogel.

2.1 Physical Hydrogels

Thermosensitive hydrogels are known to undergo a sol–gel phase transition in response to temperature changes from room to physiological temperature. This sensitivity is particularly useful, since the temperature control is easy. Thermosensitive hydrogels are generally triblock polymers constituting poly(ethylene glycol) (PEG) linked to hydrophobic polymer blocks. The triblock consists of A blocks and B blocks organized as ABA or BAB, where PEG (A block) is well established in hydrogel formulation due to its high water solubility, biocompatibility, and low immunogenicity. The B blocks increase the hydrophobicity of the hydrogel and thereby the drug loading capacity of hydrophobic drugs through micellization. Usually, thermosensitive hydrogels have a gelation transition temperature of 37 °C, which causes hindrances during syringe/needle administration. The patient's body at 37 °C induces rapid gelation of the hydrogel which blocks the needle. To overcome this barrier, researchers introduced pH-sensitive moieties to thermosensitive copolymers, so that a second condition must be fulfilled in order for gelation to begin.

2.2 Covalent Hydrogels

Another technique to confer hydrophobic domains in a conventional hydrogel network could be the cross-linking of hydrophobic chains/monomers with hydrophilic ones. A similar end result can be achieved with hydrophobic cross-linkers. Such hydrogels are referred to as amphiphilic hydrogels. Several strategies have been used to synthesize such hydrogels. Condensation between anhydrides and alcohols could lead to formation of such hydrogels by a simple synthetic process. For example, pyromellitic anhydride, a hydrophobic cross-linker with anhydride groups, can react with OH groups in other polymer chains. This strategy is advantageous over the others, due to the absence of initiators, coupling agents, or additives that could limit the biomedical applications of the hydrogels due to toxicity issues.

2.3 Nanoparticle-Containing Hydrogels

The nanoparticles can effectively introduce hydrophobic moieties in the hydrogel. Covalent linkage or absorption can be employed to introduce the nanoparticle into the hydrogel system. Nanoparticles can be covalently linked if they possess polymerizable groups on their surface that can be copolymerized with hydrophilic monomers. In addition, multifunctional particles can be used as cross-linkers for the hydrogel matrix. This approach could prevent loss of nanoparticles due to diffusion during the swelling process. Usually, the nanoparticles are incorporated before the cross-linking (physical or chemical) occurs; in this case, the particles are prepared in advance and

introduced into the reaction mixture. This technique enables easy incorporation of the nanoparticles, but they have the tendency to diffuse out of the matrix during swelling as they are not covalently attached to it.

2.4 Hydrogels Containing Cyclodextrins

Cyclodextrins (CDs) have been in great demand to produce hydrogels that form inclusion complexes with hydrophobic drugs. CDs are cyclic oligosaccharides formed from dextrose units bound by 1–4 carbon bonds. There are three classes: α (6 units), β (7 units), and γ-CD (8 units). Their structure is a truncated cone of hydrophilic outer surface enclosing a hydrophobic cavity. The hydrophobic cavity encourages the formation of inclusion complexes with hydrophobic molecules. The CDs are used in combination with chemical cross-linkers such as epichlorohydrin (EP), triazine, or diisocyanates. The CD molecules contain multiple OH which can readily react with the cross-linkers to yield hydrogels [1].

3 Hydrogel Network Properties

The bulk structure of hydrogels defines their suitability as biomedical materials and their performance in a particular application. The important parameters for characterizing the network structure of hydrogels include: (1) the molecular weight of the polymer chains between two neighboring cross-links (Mc), (2) the corresponding mesh size (ξ), and (3) the effective network density (ve). These parameters are interrelated and can be determined by applying the equilibrium-swelling theory and the rubber elasticity theory. Recently, an alternative method for characterization of cross-linked hydrogel networks was presented. High-resolution magic angle spinning (HR-MAS) NMR spectroscopy enables characterization and quantification of any unreacted cross-linkable moieties that occur in a chemically cross-linked, swollen hydrogel network. This methodology was first applied to quantify unreacted methacrylic amide residues in chemically cross-linked gelatin hydrogel. Since HR-MAS NMR spectroscopy is a fast, accurate, straightforward, and nondestructive technique, it may be applied more frequently in the future studies involving hydrogel network properties.

3.1 Temperature-Induced Hydrogel Formation

A large number of hydrogels tend to self-structure upon temperature variation. Temperature-sensitive materials are of two types: upper critical solution temperature (UCST) and lower critical solution temperature (LCST) materials. Both these

systems have great demand for biomedical applications that require the materials to gel or dissolve in situ depending on the exact UCST or LCST behaviors.

3.1.1 Upper Critical Solution Temperature

Reversible gelation through intermolecular hydrogen bonds of many biopolymers can be induced by the temperature. This thermoreversible process is characteristic behavior shown by gelatin (i.e., partially hydrolyzed collagen) and certain polysaccharides such as agarose, amylose, amylopectin, and carrageenan. The nucleation and growth of the helical aggregates are by the formation of double (for polysaccharides) or triple helices (for gelatin). Many synthetic polymers also form physical hydrogels via hydrogen bonding.

3.1.2 Lower Critical Solution Temperature

Another class of temperature-sensitive materials is the LCST systems, in which a homogeneous solution is obtained at low temperatures. On heating, aggregation of the hydrophobic moieties starts which induces phase separation and hydrogel formation. This endothermal gelation is driven by an entropy change, where the entropy increases during the hydrogel formation, even though there is an increase in order due to hydrophobic segments aggregating. This occurs due to the release of large quantity of water by the hydrophobic region of the polymer.

3.2 Cryo-Induced Hydrogel Formation

In addition to ambient temperature hydrogel formation, hydrogels can also be synthesized using cryogenic treatment. Cryogelation typically decreases both the critical monomer/polymer concentration and the reaction time required for gelation. Cryotropic gelation (aka cryogelation) is a specific type of gelation that takes place when gel-forming systems are cryogenically treated.

The primary requisite for cryogel formation is the bulk crystallization of the low-molecular-weight liquid present in the initial system. The crystallization of the pure solvent results in the total volume of the nonfrozen liquid microphase (NFLMP) being lower than the initial reaction volume. Consequently, the concentration of polymer/monomer in the NFLMP is significantly higher than the initial concentration. The polymer gel phase can be formed during one of the stages of cryogenic treatment: during freezing of the initial system, during storage of the samples in the frozen state, or during thawing of the frozen specimens. The aforementioned process results in the formation of a cryogel which is the porous scaffold of the hydrogel starting material.

4 Biopolymer-Based Hydrogel Systems

The polysaccharides and proteins frequently used for hydrogel preparation in regenerative medicine are as follows.

4.1 Polysaccharide Hydrogels

4.1.1 Chondroitin Sulfate

Chondroitin sulfate (CS) is a glycosaminoglycan composed of alternating units of N-acetyl-D-galactosamine and D-glucuronic acid. It possesses excellent biocharacteristics including the binding and modulation of certain growth factors. Because natural CS is readily water-soluble, chemical cross-linking of CS is required for in vitro or in vivo hydrogel application.

A variety of methods was described for cross-linking CS. A biocompatible hydrogel film was prepared using the adipic dihydrazide derivative of chondroitin sulfate (CS-ADH), in which a pendant hydrazide functionality generated a gel using a small molecule or a macromolecular cross-linker. The most frequently applied cross-linking reagents include a combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS). The cross-linking reaction has often been performed in the presence of collagen or other amine-containing reagents (e.g., 1,12-diaminododecane). However, cross-linking using EDC often resulted in (partial) matrix collapse in aqueous media.

CS-based hydrogels have previously found widespread application in the field of tissue engineering. Hydrogels composed of gelatin and CS were applied as controlled release systems for antibacterial proteins. Incorporation of CS in cross-linked gelatin gels significantly increased the protein loading capacity of the gels and extended the release time. Alternatively, gelatin-CS-hyaluronantric copolymer scaffolds were selected to mimic natural cartilage. It was observed that the presence of CS promoted the secretion of proteoglycan and type II collagen. Bilayer gelatin-CS-hyaluronan biomatrices have also been studied for wound treatment. The results showed that in addition to a permanent coverage with histologically normal and adequately differentiated epithelial tissue, a well-defined dermal–epidermal junction and a collagen network in the dermis were present. As a result, the skin substitute had a positive effect on the promotion of the wound healing process and could be used to assist the regeneration of full-thickness skin defects. Another application of the tri-copolymer scaffold included the regeneration of the human nucleus pulposus. Furthermore, both microcarriers and membranes, composed of CS and gelatin, were prepared in view of different therapeutic strategies.

4.1.2 Hyaluronic Acid

Hyaluronic acid (i.e., hyaluronan, HA) is a non-sulfated glycosaminoglycan, composed of alternating units of D-glucuronic acid and D-N-acetylglucosamine, linked together via alternating β-1,4 and β-1,3 glycosidic bonds. HA is one of the major components of the extracellular matrix of skin, cartilage, and the vitreous humor. The first hyaluronan-based biomedical product (Healon) was developed in the 1970s and is FDA approved for the use in eye surgery (e.g., corneal transplantation). At present, the most often used commercially available HA-based product is HYAFF (i.e., benzyl ester of HA). The product exists with varying esterification degrees, and various research groups have already reported on their differences in mechanical properties and biological response. HA has also been combined with alginate and poly-L-lysine to develop scaffolds for a variety of tissue engineering applications including nerve regeneration. More recently, composite scaffolds were also prepared starting from complementary chemical functionalities.

4.1.3 Chitosan

Chitosan is the partial deacetylated derivative of chitin, which is obtained from the shells of crabs and shrimp. This biocompatible, cationic polymer dissolves in water up to a pH of 6.2. An increased basicity results in a gel-like precipitation of the hydrated polymer by neutralization of the amine groups. The pH responsiveness can be extended to a pH-dependent, thermoresponsive system (i.e., LCST-characterized system) by adding polyol salts including β-glycerophosphate (GP). These formulations dissolve at neutral pH and ambient temperature. Upon heating to body temperature, gelation occurs. It was observed that both the stability at room temperature and the gelation time increase with decreasing deacetylation degree. The solubility at ambient temperature and pH 7 is induced by the hydration of the chitosan chain, promoted by the GP. Upon heating to body temperature, the bound water is partially released inducing chain interactions and subsequent gelation [2].

5 Methods for Preparation of Hydrogel

Cross-linking of polymer chain is the main principle behind hydrogel preparation. This can be done by either using inherent ability of the polymer to cross-link, external cross-linking agent, chemical modification, temperature variations or exposure to high-energy radiation. The hydrogel preparation can be broadly classified into two categories, i.e., physical and chemical cross-linking techniques. Chemical techniques involve the formation of new covalent bonds between polymer chains in the hydrogel, while physical interactions exist between polymer chains in physically cross-linked hydrogel. Both physical and chemical techniques have their own benefit and drawbacks.

5.1 Physical Cross-Linking Methods

Physical cross-linking involves various physical interactions among polymer chains like ionic interaction, hydrophobic interaction, stereocomplex formation, hydrogen bonding, and protein–polysaccharide interaction resulting in hydrogel formation. Physical cross-linking techniques are being evolved as an important tool due to the absence of external cross-linker and its associated side effects. Physical cross-linking provides reversible hydrogel, and they are subject to structural imperfections or in homogeneities due to the presence of free chain ends.

5.2 Ionic Cross-Linking or Ionic Interaction

Ionic polysaccharides like sodium alginate can be cross-linked by the addition of counter ions (like calcium ions). The hydrogel can be cross-linked under mild conditions, at physiological pH and temperature. However, the gelation rate is hard to control and non-uniformity in the structure is an additional issue. The gelation rate increases at low concentrations of alginate and increases with increasing concentration of counter ions and temperature. Slow gelation was found to yield mechanically robust gels with uniform structure.

5.3 Hydrophobic Interaction

Polymers with hydrophobic domains are known to cross-link in aqueous atmosphere via reverse thermal gelation or "sol–gel" chemistry. Hydrophobic interaction occurs in amphiphilic polymer solution at elevated temperature. Though such polymers are soluble at low temperatures, when the temperature increases, aggregation of the hydrophobic domains takes place, in order to minimize the contact with water molecule. This process maximizes the solvent entropy in the solution. The larger hydrophobic segment contributes more toward solvent entropy, driving more hydrophobic interaction and lowering the gelation temperature.

5.4 Thermoreversible Gelation

Polysaccharides like carrageenan or gelatin undergo physical cross-linking upon cooling forming a hydrogel. The gel formation is due to helix formation, helix association, and formation of junction zones. Carrageenans exist as random coils above their transition temperature, which upon cooling turns to rigid helical rods. Stable

gels form in aggregates in the presence of ions (Na^+, K^+, etc.) due to repulsion of sulfonic group (SO^{3-}).

5.5 Complex Coacervation

The mixing of poly-cationic and poly-anionic polymer results in a complex coacervate gel. This technique is driven by the principle of oppositely charged polymers aggregating together to form complexes that are highly dependent on pH and concentration of the solution. The mechanical properties of the hydrogel change from fragile (at pH close to pKa of chitosan, amine groups) to stretchable and strong (at pH close to pKa of hyaluronic acid, carboxylic groups). Similarly, proteins below their isoelectric point are positively charged and they tend to associate with anionic polysaccharides to form coacervate complex hydrogels.

5.6 Hydrogen Bonding

Hydrogen-bonded hydrogel can be produced by lowering the pH of the solution containing carboxyl functionalized polymer. For the synthesis of carboxymethylcellulose (CMC)-based hydrogel, the CMC is first dispersing in 0.1 M HCl solution. In acidic solution, sodium ions were replaced by hydrogen promoting hydrogen bonding and thereby decreasing the solubility of CMC, resulting in an elastic hydrogel. Polyacrylic and polymethacrylic acid forms a hydrogel with polyethylene glycol at low pH, due to the H-bonding interaction between the acidic group (−COOH) of acrylate and the hydroxyl groups (−OH) of PEG.

5.7 Freeze–Thaw

The freeze–thaw technique is one of the most promising techniques for hydrogel synthesis, especially for polysaccharide-based gels due to their biocompatibility and nontoxicity. Freeze–thaw usually involves freezing of polymer solution to a relatively low temperature (−20 to −80 °C) followed by thawing at room temperature. The hydrogel properties can be controlled by monitoring the pH, freezing duration, temperature, rate of thawing, and number of thawing cycles.

5.8 Chemical Cross-Linking Methods

Though physically cross-linked hydrogels have the advantage of developing without any cross-linking agents or chemical modification, they are limited by their poor mechanical performance. This in turn affects various other properties directly. However, chemically cross-linked hydrogels are mechanically robust, resist dilution of hydrogel matrix, and prevent diffusion of hydrogel. Chemical cross-linking involves chemical modification of polymer chains or use of additional cross-linking agent to bind polymer chains. Different chemical cross-linking techniques have been reported in the literature, and two important chemical techniques are discussed below.

5.8.1 Grafting

The grafting technique involves the polymerization or addition of a monomer on the backbone of a preformed polymer, like polysaccharides. The activation of polymer chains is carried out by the action of chemical reagents or by treatment with high-energy radiation. Thus, the grafting of functional monomer on activated polymer chains results in branching, and this is followed by cross-linking. The chemical modification of edible polymers via grafting constitutes an important method to improve their properties and expand the range of its application. Starch grafted with hydrophilic monomers like acrylic acid, acrylamide, and acrylonitrile has been used as a super-absorbent hydrogel. Such hydrophilic monomer-grafted polysaccharide exhibits higher water absorption capacity. The grafting technique can be chemical or radiation grafting, depending on the source of activation. Chemical grafting uses chemical initiators (like potassium persulfate, benzoyl peroxide, etc.) for the activation of polymer chains, while radiation grafting involves the use of high-energy radiation (like γ-radiation) as a source of initiators.

5.8.2 Cross-Linking

The use of a chemical cross-linker, such as glutaraldehyde, epichlorohydrin, glyoxal, PEG, in situ generated cross-linker, etc., in hydrogel formation has being practiced with both synthetic and natural polymers. This type of cross-linking involves the insertion of a new molecule with reactive functionality between the polymeric chains. However, this cross-linker (like glutaraldehyde) increases the toxicity of hydrogel which limits their application potential. In order to counter such problems, polysaccharide-derived novel biocompatible cross-linkers that are generated in situ were applied as a superior alternative for chemical cross-linker. Such biocompatible hydrogels find wider applications in biomedical, agriculture, and food-related applications. Periodate oxidation of polysaccharide to generate dialdehyde groups was reported as a safe and efficient biocompatible cross-linker. The degree of cross-linking can be controlled by monitoring the extent of oxidation.

6 Edible Polymer-Based Hydrogels

Hydrogel preparation is carried out using both synthetic and natural polymers. However, some synthetic hydrogels may be non-biodegradable, may elicit inflammatory responses, and may have toxic side effects. Although synthetic polymers have precisely controlled chemical structures which are suitable for hydrogel designing at the molecular level, natural polymers have also shown favorable properties for forming hydrogels. Thus, natural polymers can act as an alternative sources to traditional synthetic polymers with increased perks of good biodegradability and biocompatibility properties as well as minimal waste and pollution. Many natural hydrogel-forming polymers have been found to be edible; however, the mechanical properties of these edible polymers have been a subject of concern. Although it can be improved by using suitable bio-cross-linker or plasticizer, the toxicity of the cross-linkers remains to be tackled. The properties of the hydrogels are greatly influenced by the nature of the polymers. Linear polysaccharide associated with proteins has a stiff and rigid nature and is found in membrane, sheets, and coatings, while flexible and globular polysaccharides form film-type hydrogels. To date, numerous types of edible natural polymer-based hydrogels have been synthesized and utilized for different applications such as coating, drug delivery and packaging. The subsequent section concisely describes different types of edible polymer-based hydrogels [3].

7 Applications of Hydrogel

7.1 Drug Delivery

The fascinating physical properties of hydrogels, especially their porosity, offer tremendous edge in drug delivery applications. A local concentration of active pharmaceutical ingredient can be retained over a long period of time through release mechanism that can be controlled by diffusion, swelling, chemical or on environmental stimuli. Hydrogels that deliver drugs via diffusion control make use of reservoir or matrix devices that release drugs by diffusion through a hydrogel mesh or pores filled with water. The reservoir delivery system is composed of a hydrogel membrane coated on a drug-containing core. The cargo can be in the form of capsules, spheres, or slabs with high drug concentration in center of the system that ensures a constant drug release rate. While the reservoir delivery system produces time-independent and constant drug release, the matrix system works via the macromolecular pores or mesh. In this type of time-dependent drug release, the initial release rate is proportional to the square root of time, rather than being constant.

The hydrogels showing swelling-controlled drug release make use of drugs dispersed in a glassy polymer which starts swelling upon associating with bio-fluid. The expansion of the polymer during the swelling process facilitates drug diffusion and polymer chain relaxation. This process termed Case II transport supports

time-independent, constant drug release kinetics. In addition, the gradient between the dispersed drug in the hydrogel and its surrounding environment facilitates the active diffusion of the drug from a region of higher concentration (hydrogel matrix) to a lower one, and this phenomenon is referred to as anomalous transport since the processes of diffusion and swelling that facilitate drug release are combined. Ocular drug delivery carriers make use of covalently cross-linked hydrogels. These soft, biodegradable hydrogels that have high swelling capacity remain in situ in the lacrimal.

Poly(ethylene glycol) hydrogels are commonly used for producing ophthalmic drug delivery systems. Drug release on exposure to environmental stimuli would be ideal for a delivery system as the release is controlled. The non-specific side effects associated with nontarget sites can also be prevented. Therefore, stimuli-responsive drug delivery vehicles that respond to changes in pH, temperature, ionic strength, or glucose concentration are being preferred for treatment of diseases such as cancer and diabetes, which are characterized by physiologically different microenvironments that are specific to various disease stages. The polymer composition of such hydrogels is manipulated in order to induce responsiveness to the environment [4].

Hydrogels enhance therapeutic outcome of drug delivery, and therefore they have found enormous clinical application. Hydrogels have greatly enhanced the temporal and spatial delivery of macromolecular drugs, small molecules, and cells. Hydrogel-mediated drug delivery has its share of challenges and requires constant improvements for being best suited for specific drug delivery purposes.

7.1.1 Ocular Delivery

Hydrogels containing hydrophobic moieties have been used for the delivery of hydrophobic drugs. However, ocular delivery of hydrophobic drugs using hydrogels has not been extensively explored. The two routes for ocular administration are implantable systems or drug-loaded contact lenses. For example, a PEG/silica hydrogel matrix has the potential to deliver hydrophilic and hydrophobic drugs. This system was to be injected directly into the eye for the sustained delivery of dexamethasone. In the study, multiarm poly(ethylene glycol) (PEG)/silica hydrogels were synthesized using the sol–gel method by hydrolysis and condensation of poly(4-arm PEG silicate). Similarly, thermosensitive injectable hydrogel using poly(trimethylene carbonate) and Pluronic F127 for mitomycin C delivery has also reported. The hydrogel system released all the drug within 25 days.

7.1.2 Transdermal Delivery

The transdermal route could be a good alternative to oral drug delivery. It can be self-administered painlessly. Moreover, transdermally administered drugs can avoid the harsh conditions of the GI tract. However, the transdermal route of administration is limited by the fact that only a few drugs have the physicochemical requirements

to permeate passively through the skin. pH-sensitive hydrogels capable of loading hydrophobic drugs are used to treat different skin conditions. A pH imbalance leads to skin inflammation and acne. Under normal conditions, the surface of the skin has pH ranging between 5 and 6. Changes in the skin pH can compromise the barrier function of the stratum corneum. A novel hydrogel system consisting of hyaluronic acid and cellulose was reported as the hydrophobic molecule, to deliver an antimicrobial drug (isoliquiritigenin) to inhibit acne growth. This hydrogel system showed pH sensitivity and released maximum drugs at around pH 7. The colony formation of acne presents the peak of activity at this pH. The drug was able to permeate the skin barrier via the follicular pathway as the hydrogel aided in swelling of the skin.

Injectable hydrogels are greatly sort out in drug delivery and tissue engineering. Though hydrogel applications for brain disorders are restricted to preclinical investigations, hydrogels are being projected as effective tools in the treatment of neurodegenerative diseases and cerebrovascular disorders in forthcoming years. The minimally invasive implantation and unique mechanical properties relatable to soft tissues required for the brain and spinal cord can be achieved using hydrogels. They have been known to facilitate cell transplantation survival and stabilize the short half-life of drugs. Furthermore, polymer-based hydrogels can be used for local delivery of pharmacological moieties directly to the host tissue, thereby reducing systemic side effects.

7.2 Hydrogel-Based Targeted Drug Delivery

7.2.1 Supramolecular Hydrogels

The supramolecular hydrogel system is composed of two or more molecular entities held together by non-covalent intermolecular interactions. The non-covalent cross-linking helps resolve the issues of limited drug loading potential and drug incorporation in implantables. This non-covalent cross-linking provides physical stability as well as simultaneous drug loading and gelation in an aqueous environment without the need for a covalent cross-linking. Recently, supramolecular hydrogels prepared using self-assembled inclusion complexes of cyclodextrins and biodegradable block copolymers have exhibited sustained and controlled release of macromolecular drugs.

8 DNA Hydrogels

Hybrid bio-nanomaterials could be developed using DNA as the building block. Predictable two- or three-dimensional structures are formed from DNA molecules. Highly structured networks are formed by hybridizing complementary DNA

molecules, and the resultant hydrogel structures expand upon encounter with an aqueous environment. These materials tend to append to other type of nucleic acid molecules (such as siRNA and miRNA) and are also capable of loading DNA binding drugs. Such hydrogels possess high solubility, biocompatibility, versatility, and responsiveness. They can also be fluorescently tagged for tracking in in vitro biological experiments. There has been great improvement in hydrogel modifications in order to enhance shape (e.g., external stimuli such as temperature). This stress responsivity behavior is an example of the construction of supramolecular hydrogel with tunable mechanical properties and multi-shape-memory effects. These hydrogels make use of physically cross-linked agar and a supramolecular network that is cross-linked by suitable chemical bonds that fix shapes temporarily and produce a multi-shape-memory effect. The supramolecular hydrogels are biocompatible and biodegradable and rely on non-covalent interactions to promote self-assembly of small molecules in water. The structures thus formed have supramolecular architectures and encapsulate water.

A programmed temporary shape can turn into the memorized original shape when placed in an appropriate environment or exposed to a trigger. Such shape-memory hybrid hydrogels could also be synthesized using DNA cross-linkers. These hydrogels not only undergo phase transitions in the trigger of the stimulus, but also possess memory code to recover to the original matrix shape.

9 Bio-Inspired Hydrogels

A newer variety of drug delivery hydrogels used for biomedical applications are the bio-inspired hydrogels. These 3D materials replicate biological microenvironment pertaining to the disease condition and support studies on how the targeted drug delivery process could be optimized, how the therapy behaved in vivo, how the disease progressed, and so on. These are particularly useful in cancer therapy as the disease is particularly complex and associated with intricate cellular and physiological changes that require monitoring. Engineering such microenvironments would thus be a very useful approach to promote research and study the disease condition and therapeutic process better. The stiffness of the 3D model used for studying liver cancer is a critical attribute to regulate molecular diffusivity and malignancy. The elastic moduli of the collagen gels were increased by stiffening interconnected collagen fibers with varied amounts of poly(ethylene glycol) di(succinic acid N-hydroxysuccinimidyl ester). The softer gels produced malignant cancer spheroids, while the stiffer ones showed suppressed malignancy. The model provided better understanding and regulation of the emergent behaviors of cancer cells.

10 Translation to the Clinic

With enormous potential for therapeutic applications, several hydrogel formulations have crossed the barriers of in vitro/preclinical studies into the market. Some of them are still in the clinical study phases. Hydrogels have evolved over time to one of the best and the most versatile drug delivery platforms [4].

11 Conclusions

Hydrogels offer a versatile platform for the therapy of several diseases including cancer and diabetes. The water-loving nature of hydrogels and the ability to shrink and swell depending according to environmental cues or the presence of water are appealing for drug delivery applications. They have a high degree of porosity, and the polymers building blocks could be cross-linked to varying degrees by adjusting their densities. The ability to modify the physical structure in several ways and the hydrogel applications can be extended beyond targeted drug delivery. They can be used for hygiene products, wound dressings, contact lenses, and tissue engineering. The recent developments of hydrogels for targeted drug delivery include modification with targeting ligands and diverse polymer types. Ophthalmic drug delivery is receiving significant attention in therapy from hydrogels. From comfortable contact lenses to biodegradable drug delivery, the applications in eye care have been enormous. They are 90% water and provide sustained drug release over a period of days or months. They are capable of delivering small molecules or large proteins and are fully absorbed in delivery, and they may remain visible during monitoring. The application of pH-responsive hydrogels for cancer therapy and glucose-responsive hydrogels for diabetes are noteworthy developments. The use of modified stem cell membranes for targeted delivery is a very recent and attractive strategy for drug delivery. These membranes coated on hydrogels (nanogels) loaded with drugs are highly specific to the disease site in cancer and are highly biocompatible. Though the hydrogel-based drug delivery was originally influenced by the hydrophobicity of the drugs, several improvements have been made recently including development of cyclodextrins modified to accommodate the hydrophobic drug. Adhesive and conductive patches developed using hydrogels have been useful in cardiac repair and vascularization. Remotely controlled motility of hydrogel (mimicking motion of a magbot) and the DNA hydrogels are novel ideas to facilitate targeted drug delivery. There are several hydrogel formulations in clinical use, and there is always scope for improvement and modification of hydrogels to enhance their applications. With subtle modifications to the existing ones, the hydrogels could become superlative drug delivery vehicles. Such hydrogel systems could outperform several conventional delivery forms and provide promising therapy of several illnesses.

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