Advances in Research and Applications of Smart Hydrogels Part I: Preparation Methods and Classification

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Abstract- **Smart hydrogels have the ability to respond to various kinds of stimulus such as physical stimuli including temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields, and chemical or biochemical stimuli including pH, ions, glucose, enzyme, antigen and DNA. Smart hydrogels are an interesting class of materials that can be prepared by variety methods. The molecular design of polymer architectures of smart hydrogels is particularly important to show the potentially powerful combination of thermodynamic and kinetic regulation of smart hydrogels. The objective of this series is to present the latest research results together with basic concepts from the viewpoints of their preparation methods and classification (Part I) and characterizations and applications (Part II). Future trends in this area of research are presented and issues regarding technology development and new applications are highlighted.**

Keywords: **smart hydrogels, stimuli, stimuli-responsive hydrogels, biomaterial, drug delivery**

I. INTRODUCTION

As a class of material, hydrogels are unique, they consist of a self-supporting, water-swollen three-dimensional (3D) viscoelastic network which permits the diffusion and attachment of molecules and cells [1]. Due to the hydrophilic structure of hydrogels, they are the polymeric materials with the ability to absorb large amounts of water or biological fluids and to swell without dissolving and to maintain their dimensional stability by either physical or chemical crosslinking. In the hydrogels structures, physical networks have transient junctions while chemical networks have permanent junctions.

Hydrogels may have different physical forms, including solid molded forms, pressed powder matrices, microparticles, coatings, membranes or sheets, encapsulated solids, and liquids. Natural hydrogels such as collagen, gelatin and polysaccharides have many advantageous features, including low toxicity, good biocompatibility, environmentally-friendliness and renewability [2]. Synthetic hydrogels are traditionally prepared using chemical polymerization methods. As expected, natural hydrogels were gradually replaced by synthetic types due to their higher water absorption capacity, long service life, and wide varieties of raw chemical resources [3]. Hydrogels are very sensitive to environmental stimulus, which is manifested by a sharp phase transition [4]. Key factors such as hydrophilic/hydrophobic balance in the molecular composition have been modified in order to produce hydrogels with desired features. Successful examples of different applications of hydrogels in everyday products are water reservoir in agriculture [5], contact lenses, wound dressings, superabsorbents [6], drug delivery systems [7,8], and tissue engineering [9]. Meanwhile, commercial hydrogel products are still limited because of their high production costs and their potentials, which have not been fully explored yet. Many hydrogel-based drug delivery devices and scaffolds have been designed, studied and in some cases even patented, however, not many have reached the market, especially in the fields of tissue engineering and drug delivery [10]. With the capacity of hydrogels to embed pharmaceutical agents in their hydrophilic crosslinked network, they form promising materials for controlled drug release and tissue engineering. Despite all their beneficial properties, there are still several challenges to overcome for clinical translation [11].

The application of new physicochemical strategies to simultaneously control not only the gelation process, but also the interactions between the gel and native tissues would further expand the utility of hydrogels for both in drug delivery and tissue engineering-based applications [12].

The properties of some types of hydrogels change in response to environmental stimuli. Their ability to swell and deswell according to conditions makes them interesting for use as new intelligent materials [13]. Polymers that

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can change some of their properties upon the application of external stimuli are called 'smart' polymers [14]. The stimuli-responsive hydrogels are also called 'smart hydrogels'. The physical stimuli include temperature, electricfields, solvent composition, light, pressure, sound and magnetic fields, whereas the chemical or biochemical stimuli include pH, ions and specific molecular recognition events. Smart hydrogels have been used in various applications [15-19].

The objective of this series is to focus on the latest research results together with basic concepts related to the most advanced researches and applications of smart hydrogels. The preparation methods, classifications and characterization of smart hydrogels are discussed. Then, all the main fields of applications of smart hydrogels, such as tissue engineering, injectable drug delivery systems, actuators and sensors are highlighted. The future trends in biotechnology and biomedicine applications of smart hydrogels are discussed in the end of the series. The scientific issues and proposed solutions regarding various results, prototypes and achievements obtained in the best academic and industrial laboratories worldwide are presented in a rigorous scientific way. At the same time, practical solutions and their realization, believed to be of the interest to industrial partners, are presented and explained.

II. THE PREPARATION METHODS OF SMART HYDROGELS

There are several methods for production of hydrogels. A large quantity of materials, such as polyethylene oxide (PEO), polyvinyl pyrollidone (PVP), polylactic acid (PLA), polyacrylic acid (PAA), polymethacrylate (PMA), polyethylene glycol (PEG), or natural biopolymers, such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been used in different studies to produce corresponding hydrogels [20].

Hydrogels can be classified based on their preparation methods in four groups: 1) homo-polymers, 2) co-polymers, 3) semi-interpenetrating networks and 4) interpenetrating networks. The first group consists of cross-linked networks of one type of hydrophilic monomer unit but the second group is produced by a cross linking of two monomer units. Interpenetrating polymeric hydrogels are produced by preparing a first network that is then swollen in a monomer [21].

Some of the preparation methods of hydrogels in each group are explained in the following. For homo-polymers hydrogel, there are some types of methods which are known as click chemistry, freezing and thawing, radiation technique and so on.

In the click chemistry, some azide and alkyne functional groups from different molecules are clicked together in the presence of a catalyst. This method is used for production of PEG hydrogel [22]. The second method which is freezing and thawing has been reported for production of PVA hydrogel. It has been also declared that the hydrogels which are produced by this method are mechanically stronger than the hydrogels obtained by UV radiation as the cross-linking agent. PVP (polyvinyl pyrrolidone) hydrogels are produced by this method using UV radiation as the cross-linking agent [23].

In the co-polymer group of hydrogels, at least one of the monomers is hydrophilic in nature. One of the methods for production of poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PECE) co-polymeric hydrogel involves a ring opening copolymerization of the monomers. This method results in production of a new hydrogel which can be used in drug delivery of both hydrophobic and hydrophilic materials [24].

The same method of freezing and thawing can be also used for co-polymer hydrogels as well as homo-polymer hydrogels. Free-radical copolymerization of monomers in the presence of a cross-linking agent is also reported to be used in different studies. Thomas *et al.* used the free-radical copolymerization method for production of an anti-microbial agent which was transparent and embedded by silver nanoparticles [25].

In the third group of hydrogels, a linear monomer penetrates another cross-linking agent without any other chemical bonds. In one study, crosslinked copolymer of poly(2-hydroxyethyl methacrylate) (pHEMA) was synthesized in the presence of ammonium persulfate and N, N-methylene bisacrylamide as initiator and crosslinking agent, respectively. This hydrogel also showed acceptable antibacterial properties [26].

Semi-interpenetrating hydrogels composed of alginate and amine-terminated poly(N-isopropylacrylamide) (PNIPAAm) were prepared by crosslinking with calcium chloride. It was proved by FTIR that the formation of a polyelectrolyte complex was provided from the reaction between the carboxyl groups in alginate and amino groups in modified PNIPAAm. This hydrogel was sensitive to temperature, pH and ionic strength of swelling medium [27].

In inter-penetrating network hydrogels at least one of the polymers is synthesized or cross-linked in the immediate presence of the other. In one study, polyethylene glycol diacrylate (PEGDA) hydrogels modified with β-chitosan were produced with UV radiation cross-linking method. This hydrogel proved to absorb 77-83% of water [28].

The use of UV irradiation for cross-linking is also reported for production of biocompatible hydrogels which are promising materials for 3D scaffolds for vascular tissue engineering and regeneration [29].

The preparation of hydrogels can also be classified as physical crosslinking, chemical crosslinking, grafting polymerization, and radiation crosslinking methods, which have been reported in different studies. There are also some modifications that can help scientist to produce multi-functional hydrogels. Physical and chemical cross-linking methods are described in the following sections.

A. Physical Crosslinking

Since there is no need to use any cross-linking agent in the physical cross-linking method, there has been an increased interest in physical or reversible gels due to their relative ease of production. One of the disadvantages of using these agents is the need for their removal before application. They also can affect the integrity of substances to be entrapped within cells, proteins, etc.

B. Heating/Cooling a Polymer Solution

The formation of physically cross-linked gels can take place when hot solutions of gelatin or carrageenan are being chilled. The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. It turns to rigid helical rods when the solution is being cooled. It is deducted that the aggregation of helices is due to the screening of repulsion of sulphonic group (SO^{-3}). In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerization [30]. Some of the hydrogels that are produced by this method are polyethylene oxide, polypropylene oxide and polyethylene glycolpolylactic acid hydrogel [31].

C. Ionic Interaction

Ionic polymers can be cross-linked by the addition of di- or tri-valent counter ions. This method is carried out by the principle of gelling a polyelectrolyte solution (e.g. Na^{+} alginate-) with a multivalent ion of opposite charges. Chitosan-polylysine, chitosan-glycerol phosphate salt and chitosan-dextran are some examples of these hydrogels [32].

D. Complex Coacervation

Complex coacervate gels can be formed by mixing of a polyanion with a polycation. Polymers with opposite charges stick together and form soluble and insoluble complexes which depends on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan [33].

E. H-Bonding

A hydrogen bond is formed through the association of electron deficient hydrogen atom and a functional group of high electron density. Hydrogels with hydrogen bonds can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. An example of such hydrogel is the formation of hydrogen bonds between PA and PNVP which leads to production of a hydrogel with excellent mechanical properties [34].

F. Freeze-Thawing

Physical crosslinking of a polymer to form its hydrogel can also be achieved by using freeze-thaw cycles. The method was explained before for production of homo- and co-polymers hydrogels. The mechanism of this method is the formation of microcrystals in the structure which can happen due to freeze thawing. Examples of this type of gelation are freeze-thawed gels of polyvinyl alcohol and xanthan [35].

G. Chemical Crosslinking

Chemical crosslinking involves linking of monomers on the backbone of the polymers chains through the reaction of their functional groups (such as OH, COOH, and NH_2) with crosslinkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). There are a number of methods which are reported in literature to obtain chemically crosslinked permanent hydrogels [36].

H. Chemical Crosslinkers

Crosslinkers such as glutaraldehyde, epichlorohydrin, etc have been widely used to impart sufficient mechanical strength to the polymers and provide hydrogels with excellent water absorbency. One of the examples of this method is the hydrogel prepared by crosslinking of corn starch and polyvinyl alcohol using glutaraldehyde as a crosslinker [37].

I. Grafting

The polymerization of a monomer on the backbone of a preformed polymer is called grafting. The backbone of a polymer is activated by the action of chemical reagents, or high-energy radiation treatment. One of the important factors which can lead to more crosslinking is the growth of functional groups of the monomers on the chains [38]. Grafting can also be divided to two groups: chemical

grafting and radiation grafting [39].

III. CLASSIFICATIONS OF SMART HYDROGELS

Smart hydrogels can be classified based on the type of stimuli that hydrogels are responsive to them. The hydrogels responing to physical stimuli including temperature, light, pressure, magnetic and electric fields, chemical stimuli such as pH, ionic factors and chemical agents, and biomolecule stimuli such as glucose, antigen, enzyme and ligand are some smart hydrogels which are described below [40,41].

A. Physical Stimuli-Responsive Hydrogels

A.1. Temperature-Responsive Hydrogels

Critical solution temperature is the measure for classification of this type of smart hydrogels to positive and negative temperature hydrogels (Fig. 1) [42].

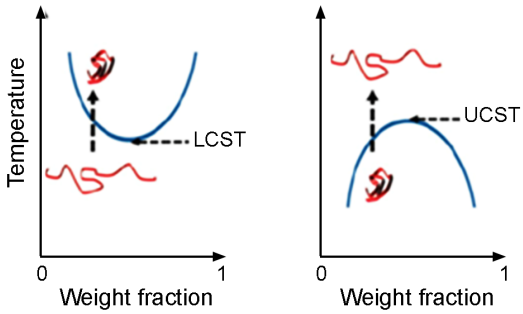

Fig. 1. Schematic showing phase transition associated with LCST and UCST [48].

UCST

Positive temperature hydrogels are known by UCST (upper critical solution temperature), the hydrogels shrink and release solvents from matrix below this temperature due to the formation of a complex structure by the hydrogen bonds and upper than UCST, swelling takes place in hydrogel network because of the structure dissociation and breaking the hydrogen bonds. There are lot of UCST polymers such as poly(acrylamide-co-butyl methacrylate) and poly(acrylic acid-co-acrylamide-co-butyl methacrylate) [43].

LCST

Negative temperature hydrogels have LCST (lower critical solution temperature), which means that the hydrogels will shrink at temperature above the LCST and will swell at temperature below this critical temperature. LCST as the most important parameter for negative temperature-responsive hydrogels can be changed under different process conditions, such as mixing by ionic copolymers or by changing the solvent composition. For example with more hydrophobic constituent, LCST of polymers shifts to lower temperatures [44]. Water or fluid molecules interact with hydrophilic parts of polymers via hydrogen interaction. With increasing the temperature above LCST, the hydrophobic interaction with the hydrophobic parts and the hydrogen bonds will become stronger and weaker, respectively. So, the absorbed water/fluid will go out through shrinking process. Poly(N-isopropyl acryl amide) is the best example of a negative thermosensitive polymer [45,46].

Thermo-reversible hydrogels unlike the two mentioned thermo-sensitive hydrogels are not covalently cross-linking systems and gel will undergo a sol-to-gel transition instead of shrinking-swelling transition. Poly(ethylene oxide)-poly(phenylene oxide)-poly(ethylene oxide) or PEO-PPO-PEO is an example for this class of thermo-responsive hydrogels [47].

A.2. Photo-Responsive Hydrogels

Photo-responsive hydrogels usually consist of a polymeric 3D network and a functional part such as photochromic chromophore. Optical signals captured by chromophores convert to a chemical signal via photoreactions such as cleavage, isomeration and dimerization. 4-Methacryloyloxy azobenzene polymer and azobenzene-trimethylammonium bromide surfactant are examples for photoreactive groups that react through trans-to-cis reaction, 4-(4-(1-chloroethyl)-2-methoxy-5-nitrophenoxy) butanate ester is activated by photo cleavage, cinnamylidene acetate ester is a photo dimerized functional group, copper chlorophyllin and gold nano rods are the samples for photothermal effect in a significant irradiations [48]. Photo-responsive hydrogels can be used in biotechnology applications, such as photo-controlled enzymatic bioprocessing and separation/recovery systems in bioMEMs [49].

A.3. Pressure-Responsive Hydrogels

This type of hydrogel is actually thermo- or pH-responsive in which the response to temperature or pH stimuli and changing the pressure or ionic strength of a solution are simultaneously, and therefore, are useful for fabrication of pressure-sensitive drug delivery systems [50].

A.4. Magnetic Fields-Sensitive Hydrogels

The magnetic-sensitive gels, or "ferrogels" are chemically crosslinked polymer networks that have a colloidal dispersion of magnetic nanoparticles. In ferrogel, magnetic nanoparticles are attached to the polymeric network by different adhesive forces, resulting in a direct coupling between magnetic and elastic properties.

Incorporation of these nanoparticles into macroscopic gels provides the magneto-responsive gels. In ferrogels, these nanoparticles are the primary carriers of magnetic moment. In a static magnetic field, the magnetic dipoles become aligned in the direction of the applied field. A volume contraction of the gel can be observed at sufficient field strength due to enhanced inter-particle interactions. Magnetic shape-memory nano-composites using thermo-responsive gels with ferrite particles have been developed for biomedical applications.

Hence, the choice of materials and the processing techniques is dependent on the application and required functionality. For example, magnetic nanoparticles have played an important role in diagnosis and treatment of cancer, targeted drug delivery systems and magnetically assisted bioseparation [52,53,54].

B. Chemical Stimuli-Responsive Hydrogels

B.1. pH-Responsive Hydrogels

Polymeric hydrogels with ionizable weak acidic or basic moieties on the polymer backbone that are able to accept or donate protons via environmental pH change are in this group of smart hydrogels. Ionic hydrogels are classified in to anionic hydrogels with pendent groups such as carboxylic or sulfonic acid and cationic hydrogels with functional groups such as amine groups. Anionic hydrogels are deprotonated when the surrounding pH is above pKa and cationic ones are ionized below the pKa and in both of them swelling happens during electrostatic repulsions. Poly(diethylaminoethyl) methacrylate (PDEAEMA) and chitosan are examples of synthetic and natural pH-responsive hydrogels [55,56,57].

Two general applications can be obtained from changing ability of pH-responsive hydrogels. A valve can be fabricated through the swelling and contracting of this type of hydrogels. Another approach for using these hydrogels is as a pH detector or sensor [58].

pH-responsive hydrogels have great potential uses in cell encapsulation, drug delivery and tissue engineering [59]. Surface coating fabricated from this group of smart hydrogels are useful in the development of microfluidic devices, anti-fog and self-cleaning surfaces and sensors [60]. For example, pH-sensitive hydrogels have been prepared from the interpenetration polymer networks (IPN) of carboxymethyl chitosan (CMCTS) and alginate in order to use in oral insulin delivery [61].

B.2. Ionic-Strength-Sensitive Hydrogels

The ionic phase in hydrogel consists of the ionic monomer on polymeric chains and the mobile ions in the surrounding fluid. The presence of the ionic monomers in the hydrogel plays a key role in the responsive effects of the hydrogel to external stimuli. Ionic strength of the solution is a measure of ion concentration in the solution. This type of hydrogels are named as the ionic-strength-sensitive hydrogels.

External conditions such as ionic strength can induce drastic changes on the state of the swollen network. Polyelectrolyte gels may undergo a volume change as a result of coupling between ionization degree and elasticity of hydrogel network [62].

Usually this group of smart hydrogels are synthesized by either a weak or strong soluble monomer such as acrylic acid (AA) or [(methacrylamido) propyl]-trimethylammonium chloride (MAPTAC). These soluble groups on the polymer backbone of hydrogel would dissociate and create different charges on the polymeric chains when the hydrogel is immersed into a solution. The mobile ions in the solution diffuse into the hydrogel and bind to the counterions in the hydrogel until to reach the equilibrium state. The unbound fixed charges in the hydrogel attract the counterions diffusing into the hydrogel and continuously repel the other ions out of the hydrogel to maintain the electrical-neutrality inside the hydrogel, which leads to the distributive difference of mobile ions across the interface between the hydrogel and the solution. The osmotic pressure is thus produced by the concentration gap, and it drives the swelling/deswelling of the hydrogel. The electrostatic force between unbound fixed charges also makes a contribution to expand the hydrogel. When the system is in the kinetics and reaches to equilibrium state, the solid network is stretched or compressed and the internal stress occurs. The kinetic swelling/shrinking mechanism shows that the dissociation and binding ability of the hydrogel to a large extent determine the swelling/shrinking capability of the ionic-strength-sensitive hydrogel and depend on several factors including the intrinsic dissociation and binding constant of the monomers in the hydrogel, the polymer structure of the hydrogel, the ionic species, and the ionic strength of the solution [63].

C. Biomolecule -Responsive Hydrogels

Stimuli-responsive hydrogels that respond to biomolecules or biomolecule-responsive hydrogels, are required to develop self-regulating systems by mimicking natural feedback signals.

C.1. Glucose-Responsive Hydrogels

Glucose-sensitive hydrogels can deliver amounts of insulin in response to changing glucose levels in body. This system could led to better control of blood glucose amounts in

diabetic patients. Gluconic acid is formed via the reaction of glucose with glucose oxidase, therefore the pH of blood will increase. In this type of smart hydrogels, the trapped insulin in hydrogel network releases due to change in pH and gel swelling or shrinking.

There are important parameters controlling the behavior of glucose-responsive hydrogel system.

The equilibrium and dynamic degrees of swelling are important parameters for calculating network mesh size and molecular weight between crosslinks under different experimental conditions. The permeability characteristics of the gels are also important when considering the system for insulin release [64].

Fully-implantable glucose sensors, embedded in the body, are ideal for continuous glucose monitoring (CGM) [65]. The highly-sensitive, biostable, long-lasting and injectable fluorescent hydrogel microbeadshave been developed for in vivo CGM. When the glucose concentration increases, the fluorescence intensity of the hydrogel microbeads increases. The fluorescent microbeads are simply injected under the dermis using a needle, minimizing pain and damage to tissues.

C.2. Enzyme-Responsive Hydrogels

Enzymes play a key role in several physiological processes and their level in body has been associated with many pathological disorders. Enzyme-responsive polymer hydrogels can also be prepared from natural materials and because of metabolically processing and the pristine biologically relevant functionalities offer advantages over synthetic polymers [66].

For example, proteases are enzymes that catalyze the hydrolysis of peptide bonds in body. Over expression of protease level underlies many diseases, such as inflammatory, neurodegenerative, cancer, cardiovascular, bacterial, viral, and parasitic diseases. Protease-responsive polymer hydrogels were prepared by chain-growth photo-initiated polymerization of peptide-containing poly(ethylene glycol) (PEG) diacrylate macromers [67].

Glycosidases catalyze the hydrolysis of glycosidic bonds in polysaccharides, hence this class of enzyme-responsive hydrogels are typically based on biodegradable carbohydrate polymers. By varying the concentration of the glucomannan composition, the rate of therapeutic release such as physically encapsulated-drug (docetaxel anticancer drugs) in hydrogel can be modulated [68].

C.3. Antigen-Responsive Hydrogels

Antigen-responsive hydrogels are prepared to diagnose a specific antigen and induce the volume changes of the smart hydrogels. The antigen-antibody binding forms upon recognition of an antibody with specific antigen through several noncovalent bonds, such as electrostatic, hydrophobic, hydrogen and van der Waals interactions. Antigen-responsive drug release systems were constructed using antigen–antibody semi-IPN hydrogels as smart devices for self-regulated drug delivery that the drug permeates through hydrogel system in the presence of a target antigen. This smart hydrogel system controls drug release in response to changes in the concentration of the target antigen [69].

C.4. DNA-Responsive Hydrogels

DNA-responsive hydrogels shrink or swell in response to DNA aptamers as the crosslinks that selectively recognize a variety of target molecules. For example, in one type of this smart hydrogel, the hydrogels formed by hybridization of the DNA aptamer and two kinds of single-stranded DNAs conjugated with polyacrylamide are dissolved by the addition of adenosine, which is the target molecule to competitively bind the DNA aptamer [70].

Biomolecule-responsive hydrogels conjugated with DNA have many advantages in sensing systems and the selective release of therapeutic agents in response to the target molecule demonstrating physiological changes [71].

IV. CONCLUSIONS

Smart hydrogels are an interesting class of materials that can be used in diverse applications. They have the ability to respond to various kinds of physical, chemical or biochemical stimuli. In this series, the latest research results together with basic concepts from the viewpoints of the smart hydrogels preparation methods, characterizations and applications were presented. In this part, the preparation methods and classifications of smart hydrogels were discussed.

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