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Smart Hydrogels: Therapeutic Advancements in Hydrogel Technology for Smart Drug Delivery Applications

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Abstract
Hydrogels are a fusion of solid and liquid phases which closely mimic biological tissue. As such they have enormous potential for drug delivery systems as they are biocompatible and may be tailored to specific applications. The aim of this chapter is to look at the current research into hydrogels, technology development, and treatment, which has led to innovations in the field. The main focus of this chapter will be on smart hydrogels, which have enormous potential in various applications. Environmental variables, such as pH and temperatures, are found in the body, and either pH-sensitive and/or temperature-sensitive hydrogels can be used for site-specific controlled drug delivery. There is an increasing focus in the biomedical industry on combination products, which incorporate drug delivery aspects, medical device and biologic aspects together. As such, we wish to draw attention to the future of hydrogels and demonstrate how smart hydrogel technology may be utilized.

Keywords: Smart hydrogels, drug delivery, polymers, stimuli-responsive, tissue engineering

1.1 Introduction

Hydrogels are widely used in biomaterial applications, mainly due to their low interfacial tension, useful swelling properties and high lubricity. In addition to their promising biocompatibility characteristics, certain hydrogels are desirable in the biomedical field due to their sensitivity to the physiological or biological environment where they are used. There are many current applications for hydrogels, and this includes 8,000 different kinds of medical devices and 40,000 different pharmaceutical preparations [1]. In recent years, research has focused on environmentally responsive hydrogels, which exhibit swelling changes due to an external stimulus [1]. Although hydrogels already

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contribute greatly to the improvement of health, the need exists for improved polymer systems and improved methods for their characterization [2]. Gels are a hybrid of liquid and solid characteristics and show complex physical and mechanical behavior. The human body is composed of various gels, ranging from the vitreous humor to muscles. Industrial applications of gels are numerous, with typical examples including heat sinks and contact lenses. Ferry defines a gel as a substantially diluted system which exhibits no steady state flow [3], whereas Kramer defines a gel as a soft, solid or liquid-like material of two or more components, one of which is a liquid present in a substantial quantity [4]. Masao Doi defines a polymer gel as a three-dimensional network of polymer chains joined together at a number of connection sites [5]. The connections may be due to covalent chemical bonds or physical interactions such as hydrogen bonds or electrostatic forces. Doi states that the process of gelation is complicated, and depending on the rate of crosslinking, non-uniform gels can be formed [5]. This non-uniformity has an effect on the physical properties of the gel. Figure 1.1 shows a representation of a polymer gel.

An important issue in discussing gels is the concept of a network. In classifying networks, Flory proposed four types of networks, namely [6]:

1. Well-ordered lamellar structures, including mesophases, e.g., soap gels;
2. Covalent polymer networks, e.g., polymeric thermosets;
3. Networks formed through physical aggregation, e.g., thermoreversible gels;
4. Particulate, disordered structures, e.g., protein gels.

A hydrogel is a specific type of gel which may be described as a three-dimensional, hydrophilic, polymeric network capable of imbibing large amounts of water or biological fluids to form a soft and elastic material that maintains its three-dimensional structure or network [7,8]. Hydrogels based on both natural and synthetic polymers are of interest for encapsulation of cells and are especially attractive as matrices for repairing and regenerating a wide variety of tissues and organs [7,8,9]. Furthermore, hydrogels

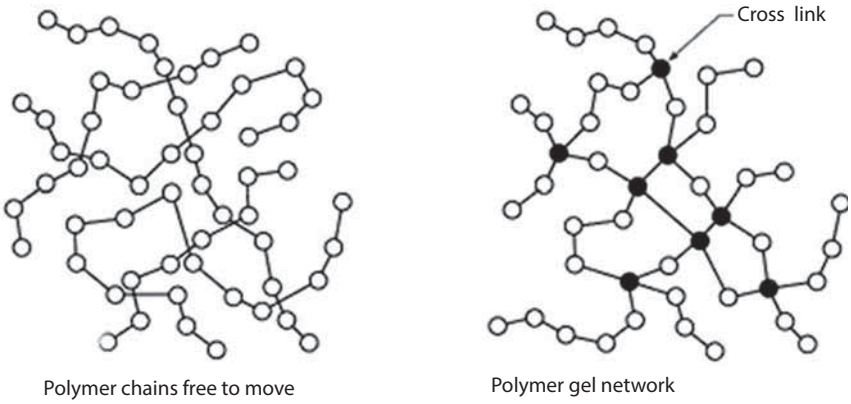

Figure 1.1 Schematic of a polymeric gel network.

have important applications in the areas of controlled drug delivery, as coatings in gastrointestinal pharmaceutical applications and as dissolution and binding agents in tablets [10,11]. Hydrogels may be composed of homopolymers, copolymers or blends of different polymers, and are insoluble due to the presence of chemical crosslinks or physical crosslinks [8,12]. Certain hydrogels react to differences in the environment with properties such as volume or viscosity changing in response to pH, temperature or mechanical stress [13]. Furthermore, hydrogels can control drug release by changing the gel structure. In addition, hydrogels can also incorporate some co-monomers into the network that makes them sensitive to various stimuli, such that the hydrogels can change its properties as a response to the environment, including pH, temperature, electrical fields, light, pressure, etc. These hydrogels are referred to as stimuli-sensitive hydrogels or smart hydrogels. The most investigated of these systems are hydrogels sensitive to pH and temperature [16], since they have made remarkable progress in drug delivery applications as they can deliver a drug to a specific target location and control its release in response to specific environmental conditions. Smart hydrogels that can respond at specific stimulus are classified into three categories: physical, chemical or biological [17]. Some important factors that a smart polymer should have are: biodegradability, controlled release profile, high drug loading capacity, low immunogenicity, and an excellent stability profile [18]. Stimuli-responsive materials increase the versatility of invasive medical devices and make targeted delivery of drugs possible [14,15]. Hydrogels have many different physical forms and some typical examples and suggested applications are listed in Table 1.1 [7]. Some of the benefits of hydrogel are that it is biocompatible; can be injected *in vivo* (in a whole, living organism) as a liquid that then gels at body temperature; can protect cells; has good transport properties such as nutrients to cells or cell products from cells; allows a timed release of medicines or nutrients; is easy to modify and can be biodegradable or bioabsorbable. However, its general limitations include its high cost; low mechanical strength; can be hard to handle; difficult to load with drugs/nutrients; may be difficult to sterilize; and is non-adherent.

Table 1.1 Various physical forms of hydrogels.

HYDROGEL FORMS
(a) solid molded forms (e.g., soft contact lenses)
(b) pressed powder matrices (e.g., pills or capsules for oral ingestion)
(c) micro particles (e.g., as bioadhesive carriers or wound treatments)
(d) coatings (e.g., on implants or catheters; on pills or capsules; or coatings on the inside capillary wall in capillary electrophoresis)
(e) membranes or sheets (e.g., as a reservoir in a transdermal drug delivery patch; or for 2D electrophoresis gels)
(f) encapsulated solids (e.g., in osmotic pumps)
(g) liquids (e.g., that form gels on heating or cooling)

1.2 Types and Properties of Smart Polymer Hydrogels

Several types of smart hydrogels exist, including those which react to temperature, pH, light, electricity, glucose or are multi-responsive materials. In this section, an overview will be given of the different types of smart hydrogels together with their specific properties and some recent state-of-the-art.

1.2.1 Temperature-Responsive Hydrogels

Temperature-responsive smart hydrogels undergo a change in their structural properties in response to temperature changes in the environment. Many polymers present a phase transition in response to temperature changes. A common characteristic of these temperature-responsive smart hydrogels is the presence of hydrophobic groups such as methy, ethy and propyl groups. Temperature-responsive hydrogels have some additional parameters, in essence either or both a lower critical solution temperature (LCST) and upper critical solution temperature (UCST) [QUU]. Additional types of temperature-sensitive hydrogels are based on the intermolecular association as in the case of Pluronics or Poloxamers [19]. Since their LCST is around the temperature of the body they are widely used for development of controlled drug delivery systems.

Hydrogels made of LCST contract as the temperature increases above the LCST. This type of swelling behavior is known as inverse (or negative) temperature dependence. In addition, upon onset of the LCST, hydrogels polymeric monophasic system becomes hydrophobic and insoluble, leading to phase separation, although below the LCST the polymers are soluble. An example is poly(N-isopropylacrylamide) (PNIPAAm), which presents a LCST at 32°C in water solution. A phase separation occurs above the LCST due to predomination of hydrophobic interactions. Below the LCST the enthalpy term is responsible for the polymer dissolution. When raising the temperature above the LCST, the entropy dominates and leads to precipitation of the hydrogel. Generally, LCST systems are relevant to specific controlled drug release and protein [20]. The LCST of hydrogels can be changed by incorporating hydrophobic or hydrophilic segments of the polymer. For instance, when PNIPAAm is copolymerized it shows an on/off drug release at low and high temperatures, respectively, enabling pulsatile drug release [21].

Hydrogels made of UCST contract upon cooling below the UCST. Hydrogels networks consisting of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) have positive temperature dependence of swelling [22]. The swelling of those hydrogels was reversible. This resulted in reversible changes in the release of a model drug.

One of the most commonly used thermoresponsive materials is one prepared from poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PluronicsR, TetronicsR, poloxamer) [23]. Depending on the Pluronic, the polymer solution is a free-flowing liquid at ambient temperature and a gel at body temperature. The response to temperature can thus be achieved by incorporating or grafting temperature-responsive moieties or by using some temperature-sensitive crosslinking agents

Ishida *et al.* [24] synthesized temperature-responsive PNIPAAm hydrogels with movable crosslinking points via the radical copolymerization with cyclic poly(ethylene glycol) (PEG). The resulting hydrogel exhibited fast volume shrinking due to the increased mobility of the polymer chains.

The major advantage of temperature-sensitive hydrogels is the avoidance of toxic organic solvents, reduced systemic side effects, site-specific drug delivery, and sustained release properties. However, there are limitations associated with these systems, including high-burst drug release, low mechanical strength of the gel leading to potential dose dumping, lack of biocompatibility of the polymeric system and gradual lowering of pH of the system due to acidic degradation [25,26].

Recent developments on temperature-sensitive hydrogels have been studied by our group [27]. Temperature responsiveness made by poly(N-isopro-pylacrylamide)–poly(vinylpyrrolidinone) with random copolymers was produced by free radical polymerization, using 1-hydroxy cyclohexyl phenyl ketone as an ultraviolet-light-sensitive initiator, and poly(ethylene glycol) dimethacrylate as the crosslinking agent (where appropriate). The hydrogels were synthesized to have lower critical solution temperatures (LCST). In summary, the hydrogels showed that changes in test temperature had an obvious effect on the rate of drug release from the copolymers. In all cases, the active agents were released at a slower rate at temperatures above the LCST. As the hydrophobic interactions become more dominant above the LCST, this significantly slows the rate of water sorption and thus the drug release time. Furthermore, as the drug release pattern is nearly identical for both the physically and chemically crosslinked copolymers, use of the chemical crosslinking agent is not essential for these drug delivery systems. This is advantageous, as crosslinkers used in the synthesis of the hydrogels are not known to be biocompatible.

1.2.2 pH-Sensitive Hydrogels

All pH-sensitive polymers consist of a pendant acidic or basic group that either accept or release protons in response to changes in environmental pH [28]. The structural properties of these hydrogel types are altered by a high and a low predetermined pH. Polymers that contain a large number of ionizable groups are known as polyelectrolytes. Polyelectrolytes are classified into two types: weak polyacids and weak polybases. Figure 1.2 shows examples of structures of anionic and cationic polyelectrolytes and their pH-dependent ionization. At neutral and high pH, weak polyacids release

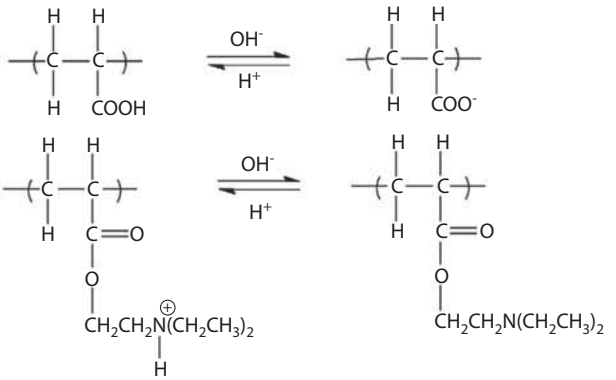

Figure 1.2 pH-dependent ionization of polyelectrolytes: poly(acrylic acid) (top) and poly(N,N′-diethylaminoethyl methacrylate) (bottom).

protons and accept protons at low pH [29]. Most pH-sensitive hydrogels are based on poly(acrylic acid) (PAA), (Carbopol®, carbomer) or derivatives thereof, including poly(methacrylic acid) (PMAA). When the pH of the environment changes, an ionization occurs on the pendant acidic group at specific pH, known as pKa, and the generated electrostatic repulsive force leads to an increase in the hydrodynamic volume of the polymeric hydrogel (i.e., swelling). This transition between expansion and contraction is influenced by any condition that modifies electrostatic repulsion such as pH and ionic strength. In addition, such transition can be explained by the changes in the osmotic pressure; at the swelling equilibrium, the osmotic pressure is balanced by the elastic pressure generated by the stretching of the polymer network. The pH range that has a reversible phase transition can be modulated by selecting the ionizable groups with a pKa matching the desired pH range. Consequently, the proper selection of polyacid should be considered for the desired application. Furthermore, incorporation of hydrophobic groups into the polymer chains can control their nature, amount and distribution. This is due to the hydrophobic modification of the polymeric structure and would translate to greater values of electrostatic repulsion to separate the increasing force of hydrophobic polymer–polymer interactions [30]. Polyacidic polymers will be unswollen at low pH, since the acidic groups will be protonated and unionized. When increasing the pH, a negatively charged polymer will swell. The opposite behavior is found in polybasic polymers, since the ionization of the basic groups will increase when decreasing the pH.

Yoshikawa *et al.* [31] synthesized a triblock copolymer, pH-responsive smart hydrogels consisting of pH-sensitive poly(2-(diisopropylamino)ethyl methacrylate) (PDPA) and biocompatible poly(2-(methacryloyloxy)-ethyl phosphorylcholine) (PMPC). These hydrogels allowed fine-tuning of the mechanical environment experienced by mouse myoblast cells. The hydrogel elasticity could be regulated via precise pH adjustment without adversely affecting cell viability. The myoblast cells exhibited pronounced stress fiber formation and flattening upon increasing the hydrogel elasticity. Interestingly, this concept can be utilized to monitor how cells adapt their morphology with respect to changes in their mechanical environment.

The limitation in using synthetic pH-sensitive polymers is their non-biodegradability. Therefore, in hydrogels, most of the pH-sensitive polymers have to be removed from the body after use. Up to a certain point the non-biodegrability is not a problem, such as in oral drug delivery. However, when it comes to implant drug delivery agents or implantable biosensors this could be a serious problem. Consequently, attention has been focused on overcoming this problem [32,33]. Synthetic polypeptides have been used in the synthesis of biodegradable hydrogels because of their regular arrangement and less versatile amino acid residues than those derived from natural proteins. Some synthetic polypeptide hydrogels include poly(hydroxyl-L-glutamate) and poly(aspartic acid) [33]. The overall extent of pH-responsive swelling could be engineered by modification of the polypeptide by changing its hydrophobicity and degree of ionization.

Our group developed a novel pH-sensitive hydrogel composite for the delivery of aspirin to wounds. The research showed that the incorporation of APIs, in this case aspirin, can have a significant effect on the overall mechanical properties of freeze/thaw PVA/PAA hydrogels. The effect of incorporating aspirin within the hydrogel led to a decrease in the mechanical properties of the overall structure. The decrease in the

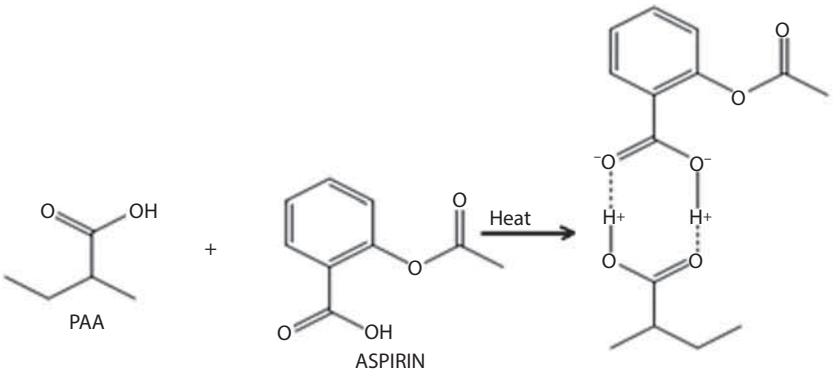

Figure 1.3 Diagram of reaction between PAA and aspirin.

strength of the gels can possibly be explained by the formation of carboxylic acid dimers between the PAA and aspirin. These dimers form readily at elevated temperatures and are essentially hydrogen bonding between the PAA and the aspirin. A diagram of this reaction can be seen in Figure1.3. To compensate for this loss in mechanical strength, a novel hydrogel-film composite was produced. The film acted as a reinforcing film within the hydrogel. Furthermore, aspirin had a plasticizing effect, effectively lowering the Tg of the PVA within the gels by more than 25°C. Additionally, by the analysis of solvent uptake studies carried out, it was observed that less swelling occurred in media of pH 4 than in pH 9. This is due to the pH-sensitive nature of the hydrogel caused by the addition of PAA and aspirin, which contain reactive groups [34].

1.2.3 Glucose-Responsive Polymers

Glucose response polymers have the ability to mimic normal endogenous insulin secretion, which minimizes diabetic complications and can release the bioactive compound in a controlled manner. These types of hydrogels are sensitive to sugar and can show variability in response to the presence of glucose. Additionally, these hydrogels are used in insulin-delivery and glucose-sensing applications. However, glucose-sensitive hydrogels have a limitation, which is their short response time. The sensitivity to glucose occurs by the response of the polymer toward the byproducts that result from the enzymatic oxidation of glucose. For example, in the case of poly(acrylic acid) conjugated with the GOx system, as the blood glucose level is increased, glucose is converted into gluconic acid, causing the reduction of pH and protonation of PAA carboxylate, facilitating the release of insulin. This pattern is increasingly successful due to its release design, mimicking that of the endogenous release of insulin.

Another system is based on chemically modifying its structure by introducing a functional group and then attaching to a carrier which can only be interrupted by the glucose itself in competitive concanavalin A, where insulin is displaced in response to glucose stimuli, thus working as a self-regulating insulin delivery system. Concanavalin A has also been frequently used in modulated insulin delivery. Concanavalin A is a glucose-binding protein obtained from the jack bean plant, *Canavalia ensiformis* [35]. In this

type of system, the molecules of insulin are attached to a carrier through specific interactions which can be interrupted by glucose itself.

1.2.4 Electro-Signal Sensitive Hydrogels

Hydrogels can also be sensitive to electric field, often made of pH-sensitive and electro-sensitive hydrogels that are able to convert chemical energy to mechanical energy [36]. Electro-signal sensitive hydrogels can contract or expand when exposed to an electric field. This process is non-uniform, producing a bending of the hydrogel when it is not in contact with the electrode [36,37]. The direct contact perpendicular to the electrode produces a contraction. If only water or an aqueous phase is in contact with the electrode, the hydrogel will be different [38].

Contractions of hydrogels have been applied for controlled drug delivery. Hydrogel bending has been studied to produce, e.g., valves, artificial muscles, and molecular machines systems. The precision of the applied electrical field depends on the controllable voltage source. The majority of the electro-sensitive hydrogels can manage with no electrolytes. However, developments in regard to working under physiological conditions are still in progress.

Hydrogels can be natural, such as hyaluronic acid and agarose, or synthetic, mostly based on (meth)acrylate. Conducting polymers are generally electrical responsive, but electro-responsive hydrogels are biocompatible and can be used for drug delivery. For example, Kumar *et al.* [39] developed a sulfonated-polystyrene that shows swelling, shrinking and bending when exposed to an external field.

A novel sulfonated poly(vinyl alcohol) (S-PVA) electro-responsive smart hydrogel was designed by Yang *et al.* [40] with sulfonation of a semicarbonized poly(vinyl alcohol) with concentrated sulphuric acid. The hydrogel exhibited an electro-sensitive behavior when a direct current (DC) was applied. The voltage and the ionic strength were used to correct bending, that is a reversible behavior. This can be applied to artificial muscles, actuators and electrodriven chemomechanics.

A 3D semi-interpenetrating network was developed using an electro-sensitive anionic PAA and incorporating biodegradable fibrin [41]. The PAA was synthesized with free-radical polymerization followed by crosslinking with ammonium persulfate, tetramethylethylenediamine and N,N-methylenebisacrylamide. The electrical-sensitive hydrogel, when subjected to an electrical field, showed a high alignment and cell penetration with the tissue. This resulted in potential applications such as synthetic vascular tissue and systems to stimulate cell migration.

1.2.5 Light-Sensitive Hydrogels

Light-sensitive hydrogels change physical and chemical properties by exposition to light. They can be categorized by the wavelength of the light that activates the phase transition, by visible and UV light-sensitive hydrogels, which are composed of polymeric network with light reactive groups. Infrared light can also be employed by some visible light-sensitive hydrogels, which have high accuracy and instant response [29]. Light-sensitive hydrogel is biodegradable, water soluble and biocompatible. This type of hydrogel can be applied in biomechanics and engineering and is used in opthalmic

drug delivery devices and optical switches. It can be used for triggering drug delivery systems, so the encapsulated drug can be released or activated once exposed externally to the body with a light source [18].

Visible light-sensitive hydrogels are easily available, safe, easy to use and inexpensive. They were developed, according to Suzuki and Tanaka [42], using trisodium salt of copper chlorophyllin, a light-sensitive chromosphere, with poly(N-isopropylacrylamide) hydrogels. By exposing chromophore to appropriate visible light wavelength, the absorption increases the local temperature of the hydrogel and the heat diffuses locally, and depends on the duration of the exposition and the chromophore concentration. Poly(N-isopropylacrylamide) expands with the increase of temperature. By combining this hydrogel with other functional groups it is possible to add other sensitivities, such as pH-sensitivity. Suzuki *et al.* [43] used a pH-sensitive hydrogel to expand and deactivate the hydrogel, which was contracted by visible light.

The first demonstration of applying multiphoton effect that promotes a structural change of a photoresponsive hybrid up-conversion nanoparticle hydrogel system was developed by Zhu *et al.* [44]. A 980 nm near infrared light source was used to release biomacromolecules of the gel-sol transition in the aqueous solution of the hydrogel.

UV-Sensitive hydrogels, according to Mamada *et al.* [45], were developed by using bis(4-dimethylamino)phenylmethyl leucocyanide, a leuco derivative molecule. This type of molecule when exposed to UV-light releases two ions of triphenylmethane leuco derivatives, and triphenylmethyl cations. This type of hydrogel expands while it is exposed to UV-light, contracting once the light is interrupted. This behavior is proportional to the increase of the temperature promoted by the absorption of the light and by the osmotic pressure due to the cyanide ions. The UV irradiation promotes an irregular volume phase transition, and the interruption induces a continuous volume phase transition.

A thermal-sensitive diarylated Pluronic F-127 solution was developed by Lee *et al.* [46] to accelerate the photopolymerization. The solution was irradiated by a UV-light source before injection *in situ*. This procedure reduces the damage on the tissue around the injection, dismissing the UV-light crosslinking after treatment. This system requires a high initial burst release, toxicity of unreacted monomers, need for long induction periods and rapid release rate due to the low penetration of the light. It requires a high concentration of photosensitive initiators.

In a study by Zhang *et al.* [47], PNIPAM and graphene oxide were combined to achieve a nanocomposite hydrogel. When this hydrogel was exposed to laser it presented a controlled volume phase transition, which is reversible once the laser is interrupted. The results revealed high photothermal sensitivity. It has prospective application in microdevices.

In Yan *et al.* [48], poly(N-isopropylacrylamide) hydrogels without any chromophores were irradiated by a CO2 laser infrared. Bending behavior and volume phase transition were achieved during the irradiation of the laser. The bending is proportional to the power of the laser, and its normalization after exposition had an exponential behavior.

Roy *et al.* [49] developed photosensitive hydrogels based on photodegradable ortho-nitrobenzyl macromer chains by redox polymerization. Photorheology was used to quantify the rate of degradation with 370 nm irradiated light source and power density of 10 mW/cm^2. The degradation constant increased with the decreasing of

aryl ethers on the ortho-nitrobenzyl group or with the modification of the functionalities of the primary and secondary benzylic sites. The hydrogel can also be applied to encapsulate and release human mesenchymal stem cells without decreasing cell viability.

The disadvantages of applying light-sensitive hydrogels are the slow response due to the thermal reaction with the light exposure, and dark toxicity. The response can also be inconsistent due to the contraction and expansion behavior of the chromophores.

1.2.6 Multi-Responsive Smart Hydrogels

Multi-responsive hydrogels are polymeric structures sensitive to two or more external stimuli. This dual stimuli-responsiveness has high efficacy and better targeting in complex hydrogel systems; likewise, in other functions such as those reported in references [44–47]. The multi-responsive hydrogel sensitive to temperature and pH is achieved by combination of ionizable and hydrophobic functional groups [54]. Dual sensitivity has been achieved by the development of new monomers.

Nguyen *et al.* [55] reported poly(amidoamine)-poly(ethylene glycol)-poly(amidoamine) (PAA-P PAA), a novel triblock copolymer sensitive to pH and temperature via Michael tion polymerization by conjugating PA PEG. A solution of 12.5 wt% was injected *in vivo* and modified into a gel upon contact with the ra This hydrogel lacks cytotoxicity and high degradability.

Other pH- and temperature-sensitive cores were presented by Leung *et al.* [56]. A smart core-shell microgel was synthesized with no surfactants by graft copolymerization based on poly(ethyleneimine), PNIAAm to the temperature-sensitive cores, and MBAAM. The pH-sensitive shells were developed on cationic water-soluble polymers. This hydrogel showed a consistent core-shell structure. Mocanu *et al.* [57] developed a multi-sensitive hydrogel with pH-sensitive properties that interacts with biomolecules, such as proteins and antioxidants, that can be used in drug release systems. The hydrogel developed was produced with Jeffamine M-600 and M-2005 crosslinked with carboxymethylpullulan. Kurata and Dobashi [58] developed an intelligent drug delivery system based on L-glutamic acid and L-aspartic acid. In a study by Rodríguez-Cabello *et al.* [59], elastic-like hydrogels were synthesized which have potential application in genetics engineering research. This type of hydrogel presented a pH and temperature sensitivity, and can be applied in biomedical devices research. Materials developed by fermentation were also studied, which is considered sustainable and environmentally friendly.

Alonso *et al.* [60] presented pH- and temperature-sensitive vehicles for peptide delivery formed by a combination of NIPAAm, butylmethacrylate and acrylic acid. The ionic strength is proportional to the loading efficiency, which can be determined by hydrophobic interactions. Suzuki *et al.* [43] presented a pH- and temperature-sensitive polymer soluble in water, constituted by poly(acryloyl-*N*-propylpiperazine) (PAcrNPP). At 37°C the water showed lower critical solution temperature (LCST). Another way to develop multi-responsive hydrogels is also done by combining thermosensitive polymers with polyelectrolytes [35].

1.3 Applications of Smart Polymer Hydrogels

The versatility and potential of smart hydrogel systems make them one of the most exciting interfaces of chemistry and biology systems for various biomedical applications. This section of the chapter focuses on the various applications of smart polymer hydrogels in the field of tissue engineering, drug delivery, gene delivery and protein delivery.

Hydrogels that produce responses to external physiological stimulus are now being extensively researched in the therapeutic areas. Lower critical solution temperature behaving polymers, and those with ionizable groups that can result in reversible phase transitions, can now be utilized in the production of targeted drug delivery systems. One system developed by Yan *et al.* [61] resulted in the formation of PEI–pluronic encapsulated nanoparticles exhibiting temperature sensitivity. Using PEG disulphide linkages to attach vascular endothelial growth factor siRNA to the PEI–pluronic encapsulated nanoparticles produced a nano-matrix capable of siRNA controlled delivery to the cytosol, which can then target and silence the objective mRNA.

A doxorubicin hydrogel delivery system was developed by Dadsetan *et al.* [62] utilizing sodium methacrylate, having a minutely negative charge to modify Sodium methacrylateoligo(poly(ethylene glycol) fumarate) to produce a product with sensitivity to environmental pH and ionic strength. Experimental results indicated that controlled release was achieved due to ionic exchange between the charge potential of the drug and the hydrogel matrix.

An anticancer drug delivery system was developed by Shenoy *et al.* [63] utilizing a mix of Pluronic F108 and Poly(β-amino ester) PBAE in combination with the drug paclitaxel to produce nanosized matrix particles to target tumor cells. Experimental results indicated that the treatment showed enhanced effectiveness to that of the untreated drug due to its pH sensitivity and tumor intercellular disintegration.

Combination hydrogel delivery systems have also been produced for protein delivery of calcitonin, which have both an anionic and pH mode of action that results in a temperature-based protein release from the gel matrix.

1.4 Conclusion

Smart sensitive hydrogels have potential in different fields of research. This chapter summarizes the current literature and shows the applications and future perspectives on smart hydrogels. Instead of a static or passive action as seen with previous generations of biomaterials, these smart materials respond to the surrounding environment. Temperature, pH, electrical, light glucose and multi-sensitive hydrogels have a wide range of research, from basic molecular to biomedical applications. For all medical applications stimuli-responsiveness is highly needed, to detect specific molecules triggering signals or release active compounds. Controlled biocompatibility and biodegradability in hydrogels is an important aspect to be considered.

The majority of hydrogels are in many ways sensitive to variations of temperature and pH. These hydrogels can be used as drug delivery due to the physiological conditions

of the human body, like low pH of approximately 7.4 and temperature between 36°C and 38°C. Therefore they provide a connection between therapeutic applications and drug delivery.

Light-sensitive hydrogels can contract or expand by the exposition to irradiation, UV or visible light, and infrared laser emissions used. The hydrogel can be exposed before or after injection on the target area, without the need of extra equipment. The absorption of light promotes heat locally, allowing contraction and expansion. With other functional groups, pH sensitivity can be added to the hydrogel. This kind of hydrogel has several cons such as toxicity, slow response, low absorption of light, etc.

Electro-sensitive hydrogels can be used in drug delivery as well, and also in bioseparations. This type of hydrogel shows contraction, expansion and bending in the presence of an electrical field, directly on the hydrogel or on the surroundings, water or aqueous solution.

Multi-sensitive hydrogels are a combination of temperature and pH sensitivity that provide high efficacy and better targeting in complex systems. This type of hydrogel is achieved by a combination of ionizable and hydrophobic functional groups. In addition, multi-stimuli-responsive materials provide technologies that combine these properties, augmenting both the specificity and efficacy of cell targeting, cell responsiveness and drug delivery. By appropriate copolymerization, crosslinking and ligand attachment, the properties of smart materials can be tailored to meet the needs of specific applications.

These novel strategies for producing smart materials are so far providing exciting new tools for drug delivery, neuronal and other cell manipulation and tissue engineering for regenerative medicine.

As smart materials are entering the commercial market for cell culture, there is little doubt that these will be utilized in the near future for tissue development.

For future prospective use, fast hydrogels is one field that needs improvement to synthesize faster, smaller and thinner hydrogels. It is possible to say that the field still has some practical points that need to be addressed.

For many stimuli-sensitive hydrogels, the variations occur on a reasonably slow time-scale; therefore fast-acting polymer systems are required. In addition, the toxicity and the fact that most of these hydrogels are non-biodegradable make them unsuitable as implants. Idealistically, smart materials must be nontoxic, not invoke a host inflammatory response and have a fast response time. Additionally, much of the work published is purely experimental and of little immediate clinical benefit. To address this, materials must continue to be optimized to specific and exacting requirements before their successful application for clinical therapies. Since such conditions are very challenging, the future of smart hydrogels is very promising. Additionally, it is important to concentrate efforts on the environmental conditions of the human body, since this is the situation in which these smart hydrogels will be used. Thermoresponsive polymers are well characterized and have proven themselves in a wide range of applications.

Results of cell sheets for tissue engineering have focused on the rat model or used carcinoma cell lines; for regenerative medicine and for translation to clinical applications there must be studies using more appropriate cell types. These include human embryonic stem cells, induced pluripotent stem cells, MSCs or primary cell lines. The future of smart biomaterials as therapeutic agents should prove very exciting!

References

1. N.A. Peppas, Y. Huang, M. Torres-Lugo, J.H. Ward, and J. Zhang, Physicochemical foundations and structural design of hydrogels in medicine and biology, *Annu. Rev. Biomed. Eng.*, 2 (1), 9-29, 2000.
2. R. Langer, and N.A. Peppas, Advances in biomaterials, drug delivery, and bionanotechnology, *AIChE Journal*, 49 (12), 2990-3006, 2003.
3. J.D. Ferry, *Viscoelastic Properties of Polymers*, John Wiley & Sons, 1980.
4. K. Almdal, J. Dyre, S. Hvidt, and O. Kramer, Towards a phenomenological definition of the term 'gel,' *Poly. Gels Networks*, 1 (1), 5-12, 1993.
5. M. Doi, *Introduction to Polymer Physics*, Oxford Science Publications, 1995.
6. P.J. Flory, *Principles in Polymer Chemistry*, Ithaca and London: Cornell University Press, 1953.
7. A.S. Hoffman, Hydrogels for biomedical applications, *Adv. Drug Deliv. Rev.*, 64, 18-23, 2012.
8. N.A. Peppas, P. Bures, W. Leobandung, and H. Ichikawa, Hydrogels in pharmaceutical formulations, *Eur. J. Pharm. Biopharm.*, 50 (1), 27-46, 2000.
9. B. Jong, and A. Gutowska, Lessons from nature: Stimuli-responsive polymers and their biomedical applications, *Trends Biotechnol.*, 20 (7), 305-311, 2002.
10. M.D. Kurkuri, and T.M. Aminabhavi, Poly(vinyl alcohol) and poly(acrylic acid) sequential interpenetrating network pH-sensitive microspheres for the delivery of diclofenac sodium to the intestine, *J. Control. Release*, 96 (1), 9-20, 2004.
11. T.G. Park, Temperature modulated protein release from pH/temperature sensitive hydrogels, *Biomaterials*, 20 (6), 517-521, 1999.
12. J.F. Yaung, and T.K Kwei, pH-sensitive hydrogels based on polyvinylpyrrolidone-polyacrylic acid (PVP-PAA) semi-interpenetrating networks (semi-ipn): Swelling and controlled release, *J. Appl. Polym. Sci.*, 69 (5), 921-930, 1998.
13. A. Kishida, and Y. Ikada, "Hydrogels for biomedical and pharmaceutical applications," in: S. Dumitriu, ed., *Polym. Biomater.*, 2nd ed., pp. 133-145, 2002.
14. R.J. LaPorte, *Hydrophilic Polymer Coatings for Medical Devices: Structure/Properties, Development, Manufacture and Applications*, CRC Press, 1997.
15. J.P. Cohen, (ed.), *Physical Properties of Polymeric Gels*, John Wiley & Sons, 1996.
16. J. Kopecek, Hydrogels: From soft contact lenses and implants to self-assembled nanomaterials, *J. Polym. Sci. Part A: Polym. Chem.*, 47 (22), 5929-5946, 2009.
17. N.A. Peppas, J.Z. Hilt, A. Khademhosseini, and R. Langer, Hydrogels in biology and medicine: From molecular principles to bionanotechnology, *Adv. Mater.*, 18 (11), 1345-1360, 2006.
18. Honey Priya James, Rijo John, Anju Alex, and K.R. Anoop, Smart polymers for the controlled delivery of drugs – A concise overview, *Acta Pharm. Sin. B*, 4 (2), 2211-3835, 2014.
19. W. Brown, K. Schillen, and S. Hvidt, Triblock copolymers in aqueous solution studied by static and dynamic light scattering and oscillatory shear measurements: Influence of relative block sizes, *J. Phys. Chem.*, 96 (14), 6038-6044, 1992.
20. W. Hassouneh, S.R. Macewan, and A. Chilkoti, Fusions of elastin-like polypeptides to pharmaceutical proteins, *Methods Enzymol.*, 502, 215-237, 2012.
21. N.S. Satarkar, D. Biswal, and J.Z. Hilt, Hydrogel nanocomposites: A review of applications as remote controlled biomaterials, *Soft Matter*, 6 (11), 2364-2371, 2010.
22. M.A. Ward, and T.K. Georgiou, Thermoresponsive polymers for biomedical applications, *Polymers*, 3 (3), 1215-1242, 2011.
23. M. Fernandez-Tarrio, F. Yañez, K. Immesoete, C. Alvarez-Lorenzo, and A. Concheiro, Pluronic and tetronic copolymers with polyglycolyzed oils as self-emulsifying drug delivery systems, *AAPS PharmSciTech*, 9 (2), 471-479, 2008.

24. K. Ishida, T. Uno, T. Itoh, and M. Kubo, Synthesis and property of temperature-responsive hydrogel with movable cross-linking points, *Macromolecules*, 45 (15), 6136-6142, 2012.
25. E. Ruel-Gariépy, and J.C. Leroux, In situ-forming hydrogels – Review of temperature-sensitive systems, *Eur. J. Pharm. Biopharm.*, 58 (2), 409-426, 2004.
26. D. Schmaljohann, Thermo- and pH-responsive polymers in drug delivery, *Adv. Drug Delivery Rev.*, 58 (15), 1655-1670, 2006.
27. M.J. Mc Gann, C.L. Higginbotham, L.M. Geever, and M.J.D. Nugent, The synthesis of novel pH-sensitive poly(vinyl alcohol) composite hydrogels using a freeze/thaw process for biomedical applications, *Int. J. Pharm.*, 372 (1), 154-161, 2009.
28. C.A. Schoener, H.N. Hutson, and N.A. Peppas, pH-responsive hydrogels with dispersed hydrophobic nanoparticles for the delivery of hydrophobic therapeutic agents, *Polym. Int.*, 61 (6), 874-879, 2012.
29. A.P. Goodwin, J.L. Mynar, Y.Z. Ma, G.R. Fleming, and J.M.J. Fréchet, Synthetic micelle sensitive to IR light via a two-photon process, *J. Am. Chem. Soc.*, 127 (28), 9952-9953, 2005.
30. C. Čestmír, and R. Bansil, Swelling equilibria of ionized poly(methacrylic acid) gels in the absence of salt, *Polymer*, 30 (4), 677-680, 1989.
31. H.Y. Yoshikawa, F.F. Rossetti, S. Kaufmann, T. Kaindl, J. Madsen, U. Engel, A.L. Lewis, S.P. Armes, and M. Tanaka, Quantitative evaluation of mechanosensing of cells on dynamically tunable hydrogels, *J. Am. Chem. Soc.*, 133 (5), 1367-1374, 2011.
32. H.C. Chiu, G.H. Hsiue, Y.P. Lee, and L.W. Huang, Synthesis and characterization of pH-sensitive dextran hydrogels as a potential colon-specific drug delivery system, *J. Biomater. Sci. Polym. Ed.*, 10 (5), 591-608, 1999.
33. P. Markland, Y. Zhang, G.L. Amidon, and V.C. Yang, A pH- and ionic strength-responsive polypeptide hydrogel: Synthesis, characterization, and preliminary protein release studies, *J. Biomed. Mater. Res.*, 47, 595-602, 1999.
34. M.J. Mc Gann, C.L. Higginbotham, L.M. Geever, and M.J.D. Nugent, The synthesis of novel pH-sensitive poly(vinyl alcohol) composite hydrogels using a freeze/thaw process for biomedical applications, *Int. J. Pharm.*, 372 (1), 154-161, 2009.
35. S.K. Samal, M. Dash, P. Dubruel, and S. Van Vlierberghe, "Smart polymers and their applications," in: M.R. Aguilar, and J.S. Román, eds., *Smart Polymer Hydrogels: Properties, Synthesis and Applications*, Woodhead Publishing Limited, pp. 237-270, 2014.
36. J. Bünsow, and D. Johannsmann, Electrochemically produced responsive hydrogel films: Influence of added salt on thickness and morphology, *J. Colloid Interface Sci.*, 326 (1), 61-65, 2008.
37. R.V. Kulkarni, and B. Sa, Electroresponsive polyacrylamide-grafted-xanthan hydrogels for drug delivery, *J. Bioact. Compat. Polym.*, 24 (4), 368-384, 2009.
38. R. Messing, and A.M. Schmidt, Perspectives for the mechanical manipulation of hybrid hydrogels, *Polym. Chem.*, 2 (1), 18-32, 2011.
39. A. Kumar, A. Srivastava, I.Y. Galaev, and B. Mattiasson, Smart polymers: Physical forms and bioengineering applications, *Prog. Polym. Sci.*, 32 (10), 1205-1237, 2007.
40. S. Yang, G. Liu, X. Wang, and J. Song, Electroresponsive behavior of a sulfonated poly(vinyl alcohol) hydrogel and its application to electrodriven artificial fish, *J. Appl. Polym. Sci.*, 117 (4), 2346-2353, 2010.
41. N. Rahimi, D.G. Molin, T.J. Cleij, M.A. van Zandvoort, and M.J. Post, Electrosensitive polyacrylic acid/fibrin hydrogel facilitates cell seeding and alignment, *Biomacromolecules*, 13 (5), 1448-1457, 2012.
42. A. Suzuki, and T. Tanaka, Phase-transition in polymer gels induced by visible light, *Nature*, 346 (6282), 345-347, 1990.
43. A. Suzuki, T. Ishii, and Y. Maruyama, Optical switching in polymer gels, *J. Appl. Phys.*, 80 (1), 131-136, 1996.

44. C.-H., Y. Lu, J. Peng, J.-F. Chen, and S.-H. Yu, Photothermally sensitive poly(N-isopropylacrylamide)/graphene oxide nanocomposite hydrogels as remote light-controlled liquid microvalves, *Adv. Funct. Mater.*, 22 (19), 4017-4022, 2012.
45. A. Mamada, T. Tanaka, D. Kungwachakun, and M. Irie, Photoinduced phase transition of gels, *Macromolecules*, 23 (5), 1517-1519, 1990.
46. S.H. Lee, S.H. Choi, S.H. Kim, and T.G. Park, Thermally sensitive cationic polymer nanocapsules for specific cytosolic delivery and efficient gene silencing of siRNA: Swelling induced physical disruption of endosome by cold shock, *J. Control. Release*, 125 (1), 25-32, 2008.
47. X. Zhang, Y. Li, Z. Hu, and C.L. Littler, Bending of N-isopropylacrylamide gel under the influence of infrared light, *J. Chem. Phys.*, 102 (1), 551-555, 1995.
48. B. Yan, J.-C. Boyer, D. Habault, N.R. Branda, and Y. Zhao, Near infrared light triggered release of biomacromolecules from hydrogels loaded with upconversion nanoparticles, *J. Am. Chem. Soc.*, 134 (40), 16558-16561, 2012.
49. D. Roy, J.N. Cambre, and B.S. Sumerlin, Future perspectives and recent advances in stimuli-responsive materials, *Prog. Polym. Sci.*, 35 (1), 278-301, 2010.
50. R.P. Dumitriu, G.R. Mitchell, and C. Vasile, Multi-responsive hydrogels based on N-isopropylacrylamide and sodium alginate, *Polym. Int.*, 60 (2), 222-233, 2011.
51. M. Guenther, D. Kuckling, C. Corten, G. Gerlach, J. Sorber, G. Suchaneck, and K.F. Arndt, Chemical sensors based on multiresponsive block copolymer hydrogels, *Sensor. Actuator, B*, 126 (1), 97-106, 2007.
52. L. Wang, M. Liu, C. Gao, L. Ma, and D. Cui, A pH-, thermo-, and glucose-, triple-responsive hydrogels: Synthesis and controlled drug delivery, *React. Funct. Polym.*, 70 (3), 159-167, 2010.
53. Y. Zhang, L. Tao, S. Li, and Y. Wei, Synthesis of multiresponsive and dynamic chitosan-based hydrogels for controlled release of bioactive molecules, *Biomacromolecules*, 12 (8), 2894-2901, 2011.
54. C. Ramkissoon-Ganorkar, M. Baudys, S. Wan Kim, Effect of ionic strength on the loading efficiency of the model polypeptide/protein drugs in pH-/temperature-sensitive polymers, *J. Biomater. Sci., Polym. Ed.*, 11 (1), 45-54, 2000.
55. M.K. Nguyen, D.K. Park, and D.S. Lee, Injectable poly(amidoamine)-oly(ethylene glycol)-poly(amidoamine) triblock copolymer hydrogel with dual sensitivities: pH and temperature, *Biomacromolecules*, 10 (4), 728-731, 2009.
56. M.F. Leung, J. Zhu, P. Li, F.W. Harris, Novel synthesis and properties of smart core-shell microgels, *Macromol. Symp.*, 226 (1), 177-185, 2005.
57. G. Mocanu, Z. Souguir, L. Picton, and D. Le Cerf, Multi-responsive carboxymethyl polysaccharide crosslinked hydrogels containing Jeffamine sidechains, *Carbohydr. Polym.*, 89 (2), 578-585, 2012.
58. K. Kurata, and A. Dobashi, Novel temperature and pH-responsive linear polymers and crosslinked hydrogels comprised of acidic L-α-amino acid derivatives, *J. Macromol. Sci., Part A: Pure Appl.Chem.*, 41 (2), 143-164, 2004.
59. J.C. Rodríguez-Cabello, J. Reguera, A. Girotti, M. Alonso, and A.M. Testera, Developing functionality in elastin-like polymers by increasing their molecular complexity: Power of the genetic engineering approach, *Prog. Polym. Sci.*, 30 (11), 1119-1145, 2005.
60. M. Alonso, V. Reboto, L. Guiscardo, A.S. Martin, and J.C. Rodríguez-Cabello, Spiropyran derivative of an elastin-like bioelastic polymer: Photoresponsive molecular machine to convert sunlight into mechanical work, *Macromolecules*, 33 (26), 9480-9482, 2000.
61. B. Yan, J.C. Boyer, D. Habault, N.R. Branda, and Y. Zhao, Near infrared light triggered release of biomacromolecules from hydrogels loaded with upconversion nanoparticles, *J. Am. Chem. Soc.*, 134 (40), 16558-16561, 2012.

62. M. Dadsetan, Z. Liu, M. Pumberger, C.V. Giraldo, T. Ruesink, L. Lu, and M.J. Yaszemski, A stimuli-responsive hydrogel for doxorubicin delivery, *Biomaterials*, 31 (31), 8051-8062, 2010.
63. D. Shenoy, S. Little, R. Langer, and M. Amiji, Poly(ethylene oxide)-modified poly(β-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs, 1: In vitro evaluations, *Mol. Pharmaceutics*, 2 (5), 357-366, 2005.