Expert Opinion

Thermosensitive hydrogels for drug delivery

Zhenqing Li & Jianjun Guan†
†*The Ohio State University, Department of Materials Science and Engineering, Columbus, OH, USA*

Introduction: Controlled drug delivery has been widely applied in areas such as cancer therapy and tissue regeneration. Thermosensitive hydrogel-based drug delivery systems have increasingly attracted the attention of the drug delivery community, as the drugs can be readily encapsulated and released by the hydrogels.

Areas covered: Thermosensitive hydrogels that can serve as drug carriers are discussed in this paper. Strategies used to control hydrogel properties, in order to tailor drug release kinetics, are also reviewed. This paper also introduces applications of the thermosensitive hydrogel-based drug delivery systems in cancer therapy and tissue regeneration.

Expert opinion: When designing a drug delivery system using thermosensitive hydrogels, one needs to consider what type of thermosensitive hydrogel needs to be used, and how to manipulate its properties to meet the desired drug release kinetics. For material selection, both naturally derived and synthetic thermosensitive polymers can be used. Various methods can be used to tailor thermosensitive hydrogel properties in order to achieve the desired drug release profile.

Keywords: cancer therapy, drug delivery, thermosensitive hydrogel, tissue regeneration

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1. Introduction

A deeper understanding of disease mechanism and advances in molecule screening have led to an exponential growth of new drugs every year. Efficacy of drug therapy is largely dependent on the way it is administrated, as bioactive drugs have short half-lifes *in vivo*. To increase the duration of drug *in vivo* for enhanced therapeutic efficacy, one approach is to load the drugs in a proper delivery vehicle for continuous drug release. This allows continuous drug treatment of the target disease.

Stimuli-responsive material-based controlled drug delivery has increasingly attracted the attention of the drug delivery community. Drugs can be readily encapsulated and released by stimuli such as temperature [1-15], pH [16-21] and ionic strength [22-24]. Thermosensitive hydrogels are one type of stimuli-responsive material. They respond to environmental temperature change, resulting in a transformation of the sol-gel state. The sol-gel transition can trigger 'on/off' switching release of drugs; however, this is not a sustained release. Sustained release is desirable for most applications. It can be achieved by controlling thermosensitive hydrogel properties. This review discusses only thermosensitive hydrogel-based sustained drug delivery systems. Besides easy drug loading and high loading efficiency, administration of thermosensitive hydrogel-based drug delivery systems is also an advantage over the traditional drug administration approach. The sol-state thermosensitive hydrogels (at a temperature lower than the sol-gel transition temperature) can be injected together with drugs into the target tissue, which then quickly solidify at 37°C. Therefore, the thermosensitive hydrogel-based drug delivery systems may be

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Article highlights.

- Thermosensitive hydrogels have been used for temperature-mediated 'on/off' drug delivery and sustained drug delivery.
- Both naturally derived and synthetic polymers have been used as thermosensitive hydrogels.
- Various methods can be utilized to tailor thermosensitive hydrogel properties to achieve the desired drug release profile.
- Thermosensitive hydrogel-based drug delivery systems have been used in areas such as cancer therapy and tissue regeneration.

This box summarizes key points contained in the article.

administered by a minimally invasive surgery. Thermosensitive hydrogel-based drug delivery systems have been used for cancer therapy and tissue regeneration.

The thermosensitive hydrogels used for drug delivery application include naturally derived polymers, synthetic polymers, or a combination of both. In this review, thermosensitive hydrogels are introduced and discussed that can potentially be used for drug delivery, strategies to tailor hydrogel properties to fit the requirements of different applications and specific applications of these thermosensitive hydrogels.

2. Thermosensitive hydrogels

Naturally derived polymers such as collagen, chitosan, Matrigel and agarose can be used as or modified to be thermosensitive hydrogels. Their excellent biocompatibility makes them preferred candidates for drug carriers. However, they are less versatile for modification compared with their synthetic counterparts. By contrast, synthetic thermosensitive polymers such as poly(*N*-isopropylacrylamide) (PNIPAAm) and poly (ethylene glycol) (PEG)-based block polymers are easy to modify to possess various properties. Their properties can be readily tailored to control the drug release profile. To take advantage of the properties of both naturally derived and synthetic hydrogels, they can be combined together to serve as drug carriers.

2.1 Naturally derived polymer-based thermosensitive hydrogels

2.1.1 Chitosan-based thermosensitive hydrogels

Chitosan is a polysaccharide made from chitin, a main element in the exoskeleton of crustaceans and insects. Chitin is also the second most abundant naturally derived polymer [25]. Chitosan is obtained by deacetylation of *N*-acetyl-D-glucosamine of chitin to an extent > 60% [26]. Chitosan is soluble in acid solution (pH < 6). However, chitosan alone is not thermosensitive. Adding glycerophosphate (GP) in chitosan solution makes it thermosensitive. The function of GP is to form strong hydrogen bonding with chitosan at elevated temperature, leading to gel formation. The chitosan/GP system has been used to deliver bone morphogenetic protein (BMP) for cartilage regeneration. BMP was trapped in the hydrogel and injected subcutaneously using a rodent ectopic model. The *de novo* formation of cartilage in ectopic sites was observed after implantation (**Figure 1**) [27]. The chitosan/GP hydrogel has a long gelation time (~ 10 min). It is not ideal for applications where a faster gelation is needed. To improve its gelation property, one approach is to use chitosan chloride, a chitosan derivate that has better solubility than chitosan. The hydrogel obtained had a gelation time ~ 1 min and has been used to deliver insulin [19]. The released protein retained its integrity, which indicates that the chitosan chloride/GP hydrogel has potential to be used for diabetic therapy [19].

One limitation of chitosan/GP hydrogel is its fast release rate for both proteins and low-molecular-mass drugs [13,28]. Complete release mostly occurred within a couple of hours [27,29]. This significantly restrains its applications where long-term drug release is desired. To achieve a sustained release profile for the low-molecular-mass drug carboxyfluorescein, Ruel-Gariépy *et al.* mixed the drug with liposome followed by encapsulation in the chitosan/GP hydrogel [28]. It was found that the carboxyfluroscein was able to release in a sustained manner for 2 weeks. The release rate can be manipulated by liposome size and composition (with and without addition of cholesterol). Besides, addition of liposome did not affect the sol-gel transition temperature [28]. To achieve a sustained release profile for proteins, Gordon *et al.* used silicon nanoparticle (SNP) to encapsulate chicken ovalbumin and load it in the chitosan/GP hydrogel. The hydrogel demonstrated a relatively slow release profile; only 40% of protein released at day 14, compared with almost 100% release without SNP [13]. This slower release profile by adding SNP is possibly due to interaction of SNP and protein delaying the release.

The second concern about the thermosensitive chitosan/GP system is its potential toxicity. Molinaro *et al.* investigated the foreign body response of the chitosan/GP hydrogels with different ratios and demonstrated that all of them had a significant inflammatory response [30]. Administration of anti-inflammatory drugs such as icatibant, apafant and diphenhydramine did not significantly reduce inflammatory response.

2.1.2 Hyaluronic acid-based thermosensitive hydrogels

Hyaluronic acid (HA) is an enzymatically degradable glycoaminoglycan in the extracellular matrix (ECM) [31]. Besides its excellent biocompatibility and biodegradability, HA can readily form a gel with a high water content. Hyaluronic acid has been widely used as a delivery vehicle for drugs; however, HA is not temperature-sensitive. Temperature-sensitive components are used to modify HA to impart thermosensitivity.

One approach is to conjugate HA with thermosensitive PNIPAAm. The oligomer PNIPAAm-grafted HA showed a thermosensitive behavior similar to pure PNIPAAm. The thermal transition temperature of the modified HA was

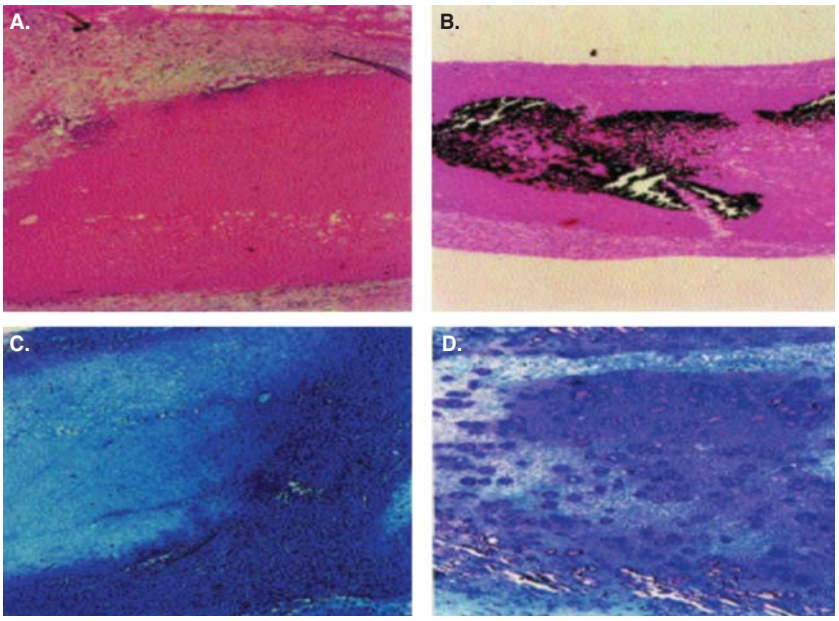

Figure 1. Chitosan/GP hydrogel delivery BMP and the cartilage formation after implantation in a rodent ectopic model. A. Von Kossa stain of CS/GP hydrogel only, only fibrosis was seen. **B.** Von Kossa stain of CS/GP with 10 μg BMP, showing a minerization. **C.** Toluidine blue stain shows CS/GP gels only; no cartilage formation was observed. **D.** Toluidine blue stain CS/GP gel with 30 μg BMP, showing chondrocytes and cartilage formation [27].

BMP: Bone morphological protein; CS: Chondroitin sulfate;
GP: Glycerophosphate.

independent of the HA molecular mass, grafting ratio of PNIPAAm and its chain length. The modified HA maintained the poor cell adhesive property of HA, compromising its application in tissue regeneration [32]. To improve the cell adhesive property, gelatin was incorporated. Zhang *et al.* found that the gelatin/HA/PNIPAAm hydrogel formed a better connection with the surrounding tissue in brain [15].

Hyaluronic acid-based thermosensitive hydrogels can also be generated by physical or chemical modification of HA with Pluronic. Pluronic is a family of thermosensitive copolymers with a structure of poly(ethylene oxide)-*b*-poly (propylene oxide)-*b*-poly(ethylene oxide) (PEO-PPO-PEO) (see Section 2.2.1). Mayol *et al.* blended HA with Pluronic and obtained a thermosensitive hydrogel. The hydrogel was capable of releasing acyclovir in a sustained manner [33]. Hsu *et al.* chemically modified HA with Pluronic via grafting. The hydrogel formed was utilized to deliver anticancer drugs such as cisplatin and carboplatin [34]. The release kinetics followed a typical Fickian diffusive mechanism. These studies demonstrated the feasibility of using HA/Pluronic hydrogel for drug delivery.

2.1.3 *Cellulose-based thermosensitive hydrogels*

Cellulose, a basic element in plant cell walls, is the most abundant naturally derived polymer in the world [25,35]. It is a linear polymer with β-(1,4)-D-glucose as the repeating unit. Cellulose has been widely used in wound healing and skin tissue engineering [35]. Cellulose itself is not thermosensitive. Chemical modification has been used to introduce hydrophobic groups into cellulose to make thermosensitive cellulose for drug delivery application.

The introduction of alkyl groups into the side chain imparts cellulose with thermosensitivity. The thermosensitive behavior of methylated cellulose (MC) was first found by Sarkar [36] in 1979 and studied further by Desbrieres *et al.* [37]. Incorporation of a longer alkyl group generally yields cellulose with a faster gelation rate [38]. Koffi *et al.* used alkylated cellulose for quinine hydrochloride encapsulation. It showed a durable release profile [39].

Besides chemical modification, blending is another approach for tailoring properties of the thermosensitive cellulose hydrogels. Naturally derived and synthetic polymers have been used. Chitosan and alginate are two natural polymers often used to blend with thermosensitive cellulose hydrogels. The chitosan/carboxymethyl cellulose (CMC) hydrogel showed an interesting dual sensitivity (pH and temperature) [40]. It is hypothesized that this hydrogel can be used for drug delivery under different pH and temperature conditions. The alginate/hydroxypropyl methyl cellulose (HPMC) hydrogel was developed for release of heparin. The sustained release lasted for up to 400 h, significantly longer than that in the pure HPMC hydrogel [41]. Various synthetic polymers have been blended with cellulose to adjust its drug release property. For example, poly(*N*-vinyl pyrrolidone) (PVP)

was blended with CMC for bovine serum albumin (BSA) release. The hydrogel formed responded to both pH and temperature. Its thermal transition temperatures ranged from 24 to 29°C at acidic condition (pH 1.2), but there was no thermal transition at base condition. The BSA release rate was found to increase gradually as the pH increased from acid to base. However, lowering the release temperature reduced the release rate [42].

2.1.4 *Other naturally derived polymers*

The temperature-responsive property also exists in other naturally derived polymers, such as collagen, gelatin, Matrigel and agarose. Collagen, gelatin and agarose have negative thermosensitivity, where they are in liquid-state at higher temperatures but form hydrogels at lower temperatures. By contrast, Matrigel shows a positive temperature thermosensitivity. Matrigel is a trade name used by Becton Dickinson and Company for a mixture of basement membrane components derived from chondrosarcoma. Its aqueous solution is in liquid form at 4°C and gradually forms solid gel at 37°C. Matrigel shows excellent cytocompatibility. Many cells, such as chondrocytes and endothelial cells, can turn into functional phenotype on the Matrigel [43]. It has therefore been widely used as a native-mimicking environment to test cell response to different drugs and growth factors *in vitro* [44]. Matrigel has also been used to deliver different drugs. For example, an anticancer drug gadolinium was loaded into Matrigel to suppress tumor progression [45,46]. Despite the advantages that Matrigel possesses, its potential carcinogenic effect is a concern for *in vivo* application because of its tumor origin.

2.2 Synthetic thermosensitive hydrogels

A wide variety of naturally derived polymer-based thermosensitive hydrogels is used for drug delivery; however, they are not as versatile as synthetic polymers. Most of these naturally derived polymers are composed of polypeptides or sugar rings that have limited capacity for further chemical modification. Given the diversity of drug delivery applications, naturally derived polymers may not be able to meet all the requirements of a specific application. Synthetic thermosensitive hydrogels, however, with flexibility in molecular design and chemical modification, can overcome this limitation and are more attractive for drug delivery.

2.2.1 *Pluronic hydrogels*

Pluronic, also named poloxamer, is a trade name of copolymers of PEO-PPO-PEO. As the length of each block is adjustable, a series of Pluronic copolymers are available. Pluronic copolymers are thermosensitive. The dominance of hydrophilic water–PEO interaction at low temperatures allows copolymer in a swollen coil state (sol), whereas the hydrophobic interaction governs at elevated temperatures to form an aggregated globule (gel) [47].

Pluronic has been used to deliver drugs, such as anticancer and antithrombotic drugs. One such drug is docetaxel. *In vitro*, docetaxel encapsulated in Pluronic F127 showed a higher cytotoxicity to mouse breast and ovarian cancer cell lines compared with free docetaxel, owing to continuously released docetaxel from F127 providing a sustained treatment effect. *In vivo*, the local drug concentration was maintained at an effective concentration even 11 days post intratumoral injection. These results demonstrate that Pluronic F127 is a promising vehicle for anticancer drug delivery (**Figure 2**) [48]. Liu *et al.* used Pluronic F127 as a delivery vehicle for antithrombotic polypeptide recombinant hirudin variant-2 (rHV2) [49]. The rHV2 showed a zero-order release profile. *In vivo* study demonstrated that encapsulation of rHV2 in Pluronic F127 improved rHV2 bioactivity and prolonged rHV2 retention time.

Pluronic copolymers are versatile for chemical modification because they have end-terminated hydroxyl groups. This approach can be used to manipulate their drug release property. Guo *et al.* conjugated linoleic acid to Pluronic F127 for tumor sensitization [50]. Paclitaxel (PTX) was loaded into the modified Pluronic F127 and injected into tumors. A strong cell cycle arrest and apoptosis were observed. The conjugated Pluronic demonstrated a greater effect than the unconjugated Pluronic, owing to the conjugated Pluronic showing a more sustained release behavior.

Hydrogels formed by Pluronic copolymers are not sufficiently stable at physiological conditions. The hydrogels have a fast dissolution rate. Long-term drug delivery from Pluronic is therefore a challenge [51-53]. To increase its stability, one approach is to chemically crosslink the hydrogel. Before crosslinking, the crosslinkable groups such as acrylate and thiol groups are introduced at both ends. The crosslinking has been found not only to increase significantly the stability of the hydrogels, but also to increase the drug retention time within the hydrogel [51]. Choi *et al.* [52] found that crosslinking even increased the drug (vascular endothelial growth factor) loading capacity [53].

Besides fast dissolution, other drawbacks for Pluronic hydrogels include low mechanical strength and non-degradability [51]. The low mechanical strength limits their application in circumstances where mechanical property is a requirement. In Pluronic hydrogels, the polyether chain cannot be degraded easily *in vitro* and *in vivo*. Pluronic hydrogels are therefore non-degradable. This limits their applications where degradable hydrogels are preferred.

2.2.2 *PEG-polyester thermosensitive hydrogels*

PEG-polyester hydrogels are biodegradable. They are prepared by linking biodegradable polyester chains at PEG ends. The polyesters include polylactide (PLA) [54-59], polyglycolide (PGA) [60], poly(lactide-*co*-glycolide) (PLGA) [60,61], polycaprolactone (PCL) [55,60,62-63] and poly(δ-valerolactone) [64].

Thermosensitive triblock copolymer PEG-PLA-PEG was first reported by Jeong *et al.* [65]. This work attracted extensive studies on PEG and polyester-based thermosensitive hydrogels. It was found that placing two polyester blocks at

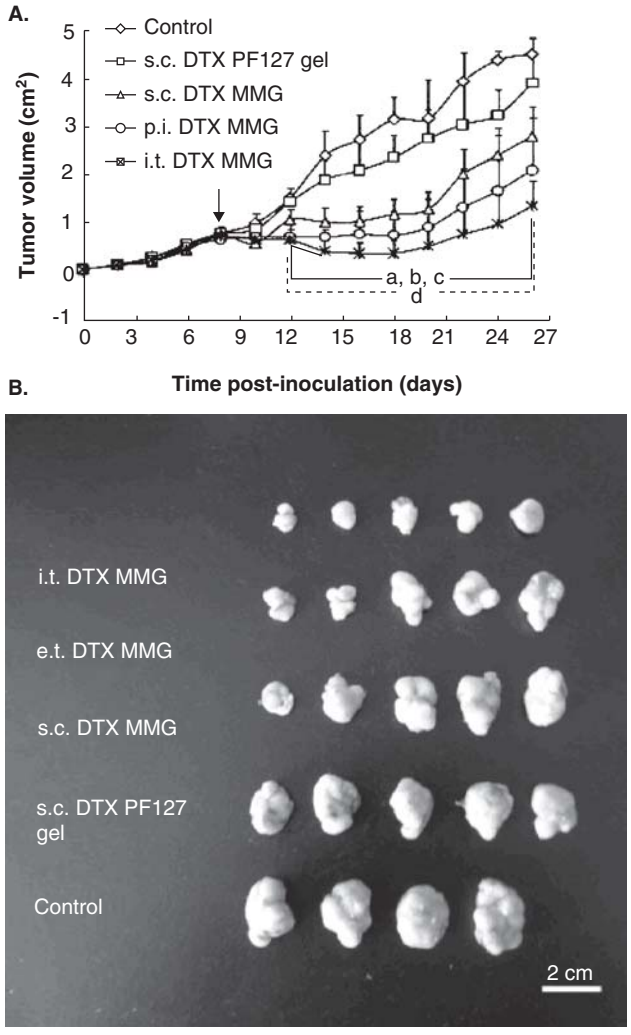

Figure 2. The effects of DTX drug loaded in different carriers. A. Tumor size versus post-injection time via different injection sites; PF127 gel is F127 gel only. **B.** Tumor taken out at day 18 post-injection [48].

DTX: Docetaxel; e.t.: Epitumoral; i.t.: Intratumoral; MMG: F127 with Tween 20 mixed micelle gel; p.t.: Peritumoral; s.c.: Subcutaneous.

PEG ends allowed hydrogels (polyester-PEG-polyester) to have a broader gelation window and higher mechanical strengths [54]. This type of hydrogel also showed excellent drug release profiles [59]. Besides homopolyesters, polyester copolymers can also be used to obtain thermosensitive PEG and polyester-based hydrogels. This includes poly(lactide-*co*-glycolide) and poly(caprolactone-*co*-glycolide) [60,66-67]. The diblock copolymers such as methoxy-terminated PEG-PCL (mPEG-PCL) and methoxy-terminated PEG-*b*-poly(caprolactone-*co*-lactide) (PCLLA) also possess thermosensitivity [55]. Jeong *et al.* synthesized PLGA-*g*-PEG copolymers and found that their thermal transition temperatures varied from 15 to 45°C by changing PEG ratio [56].

In addition to polyester-PEG-polyester and PEG-polyester structures, many other structures also show thermosensitive properties. For example, a PEG-PLA block copolymer with randomly inserted *p*-dioxanone (DX), PLA-PDX-PEG, is thermosensitive. It was used to deliver BMP. An *in vivo* study demonstrated that bone regeneration was linearly dependent on the BMP dosage and volume of the hydrogel [68]. Using a similar polymerization method, pH sensitivity can be introduced into the PEG-polyester hydrogel. For example, a pH-responsive sulfamethazine oligomer (SMO) was coupled into poly(caprolactone-*co*-lactide)-PEG-poly(caprolactone-*co*-lactide) (PCLA-PEG-PCLA) to form a copolymer SMO-PCLA-PEG-PCLA-SMO that displayed dual sensitivity (pH and thermal). The polymer solution remained in sol-state at pH 8.0 but gelled at physiological conditions (pH 7.4 and 37°C) (**Figure 3**). The degradation rate of the SMO-PCLA-PEG-PCLA-SMO hydrogel was relatively slow compared with the non-pH-sensitive counterpart, owing to the buffering effect of SMO groups [62].

A significant limitation of the PEG and polyester-based thermosensitive hydrogels is that the degradation products of PLA, PGA, PCL and their copolymers are acids, which may provoke severe inflammatory response *in vivo* [69].

2.2.3 *Thermosensitive hydrogels based on polyacrylamide derivatives*

Some *N*-substituted polyacrylamides are thermosensitive, such as PNIPAAm [3,9,14,15,17,18,20,23,32,70-94], poly(*N*,*N*-dimethylacrylamide) [84], poly(*N*-vinyl caprolactam) [81,95] and poly(*N*-(2-hydroxypropyl)methacrylamide lactate) [96]. For linear *N*-substituted polyacrylamides, when the temperature is below the lower critical solution temperature (LCST) water molecules hydrate the hydrophobic *N*-substituted groups to form a homogeneous solution. When the temperature is above LCST, hydrophobic interaction between the *N*-substituted groups increases and exceeds the water hydration energy, leading to aggregation of hydrophobic polymer chains and hydrogel formation. Crosslinked *N*-substituted polyacrylamides swell below the volume phase transition temperature (VPTT) and collapse above VPTT. Among different thermosensitive *N*-substituted polyacrylamides, the most widely used one is PNIPAAm. Its aqueous solution has a thermal transition temperature (or gelation temperature) ~ 32°C, which allows the polymer solution readily to form hydrogel at physiological temperature. In this section, recent progress regarding PNIPAAm-based thermosensitive hydrogels is discussed.

PNIPAAm has been widely used for drug delivery applications. However, pure PNIPAAm does not have a drug release behavior that satisfies various applications. A variety of chemical modification approaches have been used to modify the PNIPAAm hydrogel to tailor its drug release profile for different applications. A widely used approach is to copolymerize *N*-isopropylacrylamide (NIPAAm) with other monomers. Misra *et al.* [97] copolymerized NIPAAm with a monomer oligolactide-(2-hydroxymethyl methacrylate)

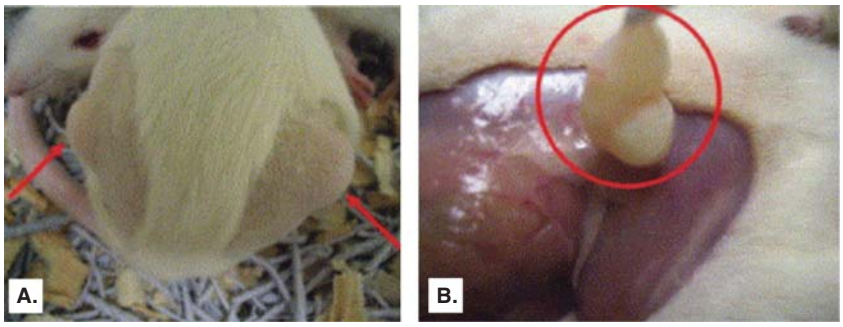

Figure 3. SMO-PCL-PLA-PEG-PCL-PLA-SMO block copolymer was solved first at pH 8 and (A) 200 μl gel solution was injected into the Sprague-Dawley rats. **B.** A solid gel was formed only 10 min post-injection [62].
PCL: Polycaprolactone; PLA: Polylactide; SMO: Sulfamethazine oligomer.

(oligoLA-HEMA). The copolymer formed was used for delivering insulin to the retina. The copolymer showed high encapsulation efficiency. Sustained release was observed throughout a 7-day period [97,98].

Physical modification is also used to tune the drug release profile of PNIPAAm hydrogel. It includes generation of porous PNIPAAm and blending PNIPAAm with other polymers. Zhang *et al.* fabricated a series of PNIPAAm porous hydrogels using poly(dimethyl siloxane) (PDMS) as a porogen [99]. The porous hydrogels had significantly higher protein loading efficiency compared with non-porous PNIPAAm. On blending PNIPAAm with PEG and PLGA, it formed thermosensitive polymersomes. The PNIPAAm polymersomes showed a sustained release profile for dextran [100].

One of the limitations of linear PNIPAAm-based hydrogels is their low stability in aqueous environment owing to fast dissolution, which causes fast drug release. Chemical crosslinking is a method to increase gel stability. Monomers with two double bonds are usually introduced to the polymer for chemical crosslinking [21,101-102]. For example, PNIPAAm was grafted with 2-hydroxyethyl methacrylate (HEMA) and crosslinked by *N,N*′-methylenebisacrylamide (MBAAm) [16]. The hydrogel obtained showed improved stability. In addition, a more sustained release profile for glaucoma therapy drugs was observed.

Forming an interpenetrating network (IPN) is another method to increase PNIPAAm hydrogel stability. A PNIPAAm IPN can be formed by immersing crosslinked PNIPAAm hydrogel in a NIPAAm/MBAAm solution, followed by polymerization of NIPAAm and MBAAm. The resulting hydrogel had a significantly higher stability than non-IPN PNIPAAm hydrogel. When BSA was encapsulated in the IPN hydrogel, a more sustained release profile was observed [103]. Besides NIPAAm and MBAAm, naturally derived and synthetic polymers can also be used to generate PNIPAAm IPNs. The silk fibroin/PNIPAAm IPN showed excellent stability [86].

A major issue for PNIPAAm-based hydrogels is their biodegradability. PNIPAAm is a non-degradable polymer with a gelation temperature ~ 32°C. It cannot be readily removed from the body at physiological conditions. This greatly limits its application. Many steps were taken to make biodegradable PNIPAAm hydrogels fulfil the requirement of biodegradability in some drug delivery applications, including copolymerization with degradable segments and manipulation of gelation temperature before and after degradation. Kim and co-workers synthesized a degradable PNIPAAm copolymer consisting of NIPAM, PLA and L-lysine. The degradability is derived from degradable PLA [87]. Zhao *et al.* incorporated biodegradable poly(L-glutamic acid) into poly(NIPAAm-*co*-HEMA) copolymer. The hydrogel formed was not only biodegradable but also possessed dual sensitivity (pH and thermal) [104]. The major limitation of these biodegradable PNIPAAm hydrogels is that the degradation products are mostly low-molecular-mass PNIPAAm segments, which are potentially toxic to cells. For example, low-molecular-mass PNIPAAm has effects on the reproductive system [105]. To address the issues of biodegradation and cytotoxic degradation products, Guan and co-workers developed biodegradable PNIPAAm copolymers that have different gelation temperatures before and after degradation [106-108]. Specifically, the copolymers have a hydrophobic and degradable side chain, which adjusts gelation temperatures of the copolymers before and after degradation. The copolymers have gelation temperatures < 37°C before degradation so that they form hydrogels at body temperature. After degradation of the side chain, the gelation temperatures increased to > 37°C, allowing the degradation products to dissolve in body fluids and be removed from the body. As the degradation occurred on the side chain without changing the backbone, the resulting degradation products retained a high molecular mass, eliminating the toxic issue associated with the low-molecular-mass PNIPAAm. The PNIPAAm copolymers were based on acrylic acid (AAc), acrylic *N*-succinicimide ester and 2-hydroxyethyl methacrylate polyester or 2-hydroxyethyl methacrylate polycarbonate (HEMA-PLA or HEMA-PTMC) (**Figure 4A, B**). Introducing hydrophobic, degradable segments (polylactide or poly(trimethylene carbonate)) initially decreased the gelation temperatures to room temperature. During the hydrolysis of polyester or polycarbonate, hydrophilicity of the copolymers gradually increased and the gelation temperatures were raised to > 37°C. The degraded

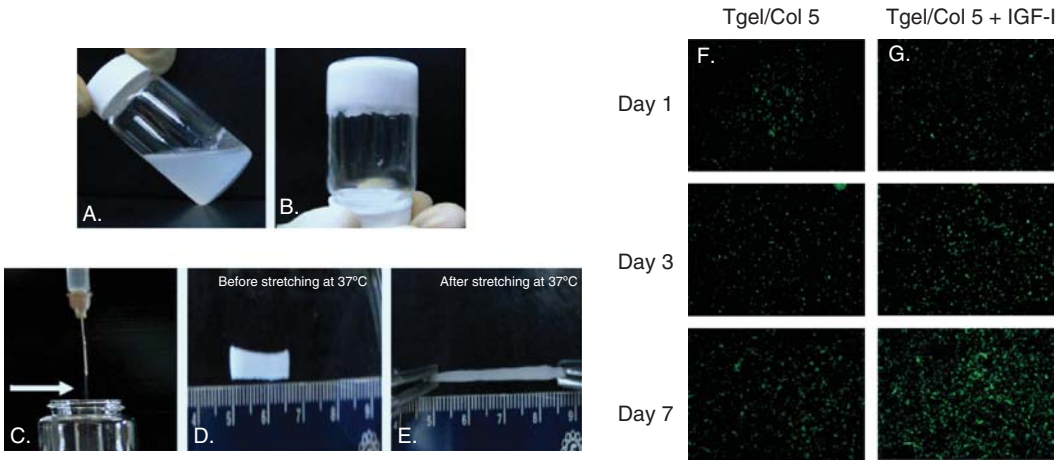

Figure 4. Poly(NIPAAm-*co*-AAc-*co*-AANHS-*co*-HEMA-PTMC) gel designed and synthesized in the authors' laboratory. A. Its liquid-state at 4°C. **B.** Gelation at 37°C. **C.** Injectability through a 26-gauge needle. **D, E.** Gel is flexible at 37°C. **F.** MSC proliferation in hydrogel with collagen. **G.** MSC proliferation in hydrogel conjugated with IGF-I [107].
AAc: Acrylic acid; AANHS: Acrylic *N*-succinicimide ester; HEMA-PTMC: 2-Hydroxymethyl methacrylate polycarbonate; MSC: Mesenchymal stem cell; NIPAAm: *N*-isopropylacrylamide.

products were non-toxic as examined by culturing cells supplemented with the degradation products [107,108].

2.2.4 *Poly(oligo(ethylene glycol) methacrylate)-based thermosensitive hydrogels*

Poly(oligo(ethylene glycol) methacrylate) (POEGMA)-based hydrogels are emerging thermosensitive hydrogels. They have excellent biocompatibility and low protein adsorption [109]. The latter may be ideal for some applications where nonspecific protein adsorption is an issue. However, it is not suitable for applications where protein adsorption is desired, for example, delivering both cell and drug.

POEGMA-based hydrogels have been used to encapsulate chemotherapy drugs [109]. Durable drug release can be achieved by using these hydrogels. POEGMA hydrogels can be modified to vary their thermal property for better control of drug release. For example, copolymerization of oligo(ethylene glycol) methacrylate (OEGMA) and 2-(2-methoxyethoxy)ethyl methacrylate (MEO2MA) yielded hydrogels with gelation temperatures ranging from 26 to 90°C, depending on the OEGMA content [110]. In addition, the thermal transition occurred in a narrow temperature range [111].

2.2.5 *Polyphosphazene-based thermosensitive hydrogels*

Polyphosphazenes are emerging candidates for thermosensitive drug delivery systems [112,113]. Polyphosphazenes are a series of polymers with alternating nitrogen and phosphorus atoms, connecting with alternating single and double bonds. Polyphosphazenes are versatile for modification and functionality. Their side groups can be modified with organic compounds to obtain poly(organo phosphazene)s with different functions [112]. For example, they were modified with hydrophobic L-isoleucine ethyl ester (IleOEt) and hydrophilic α-amino-ω-methoxy-poly(ethylene glycol) to have pH and thermal dual sensitivity [113]. Polyphosphazene-based hydrogels have good biocompatibility [112] and their degradation products (ammonia, phosphate and alcohol) are non-toxic. Their fast *in situ* gelation, good local drug retention, drug loading capacity and tumor suppression properties make them good candidates for anticancer drug delivery (**Figure 5**) [114].

3. Tuning thermosensitive hydrogel physical and chemical properties to tailor drug release kinetics

Different drug delivery applications have different requirements for the delivery matrix-thermosensitive hydrogel. Tuning hydrogel properties is necessary in most cases to meet the specific requirements. This section briefly introduces strategies used to manipulate thermosensitive hydrogel properties for various applications (**Figure 6**).

3.1 Modulating gelation temperature

Gelation temperature is a basic property of thermosensitive hydrogels. Drug release kinetics is largely dependent on the gelation temperature when the release temperature is settled. Besides, different tissues have different environmental temperatures. A thermosensitive drug delivery system suitable for skin wound healing may not provide satisfactory results for cancer therapy. Thus, proper adjustment of gelation temperature is needed.

The gelation temperature for a thermosensitive polymer is the temperature that induces sol-gel transition. It results from a change in the balance of hydrophilic and hydrophobic interactions among water molecules, polymer hydrophobic

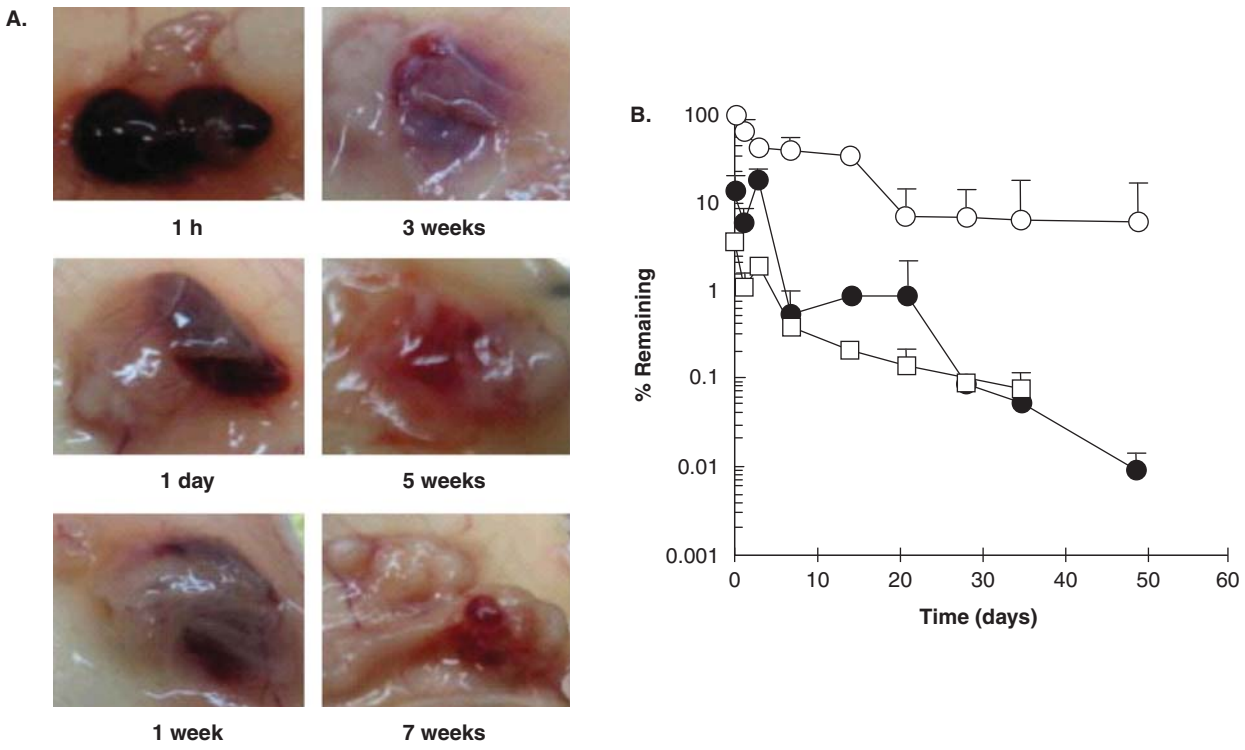

Figure 5. A. Local distribution of DOX-loaded phosphazene hydrogel by intratumor injection. **B.** The DOX level within (•) tumor tissue, (□) tumor site or (○) in polymer depot. The *y*-axis is percentage of initial dosage [113].
DOX: Doxorubicin.

groups and hydrophilic groups. Below this temperature, the polymer chains have a relatively strong hydrophilic interaction with water. Thus, water molecules disperse between polymer chains and hydrate them, and a homogeneous solution is formed. When the temperature is elevated, the hydrophobic interaction between hydrophobic domains of the polymer chains becomes predominant and the domains tend to aggregate together. The macroscopic hydrophobic phase starts to separate from the aqueous phase. The gelation temperature is approximately the temperature where the hydrophobic interaction starts to exceed the water hydration energy. In this regard, an increase in polymer hydrophobicity results in a lower gelation temperature, and an increase in hydrophilicity leads to a higher gelation temperature. In addition, ionic interaction can change the hydrophilic/hydrophobic interaction. Thus, for thermosensitive polyelectrolytes, changes in ion concentration and strength of ionic interaction alter gelation temperatures.

Thermosensitive naturally derived hydrogels have very limited capacity to tune gelation temperatures owing to fixed chemical structure. However, their gelation temperatures can be changed by chemical modification. Cellulose is an example. It is a polymer that does not have a sol-gel transition. A temperature-induced sol-gel transition can be observed after chemical modification with a hydrophobic methyl group or hydroxypropyl groups [4,37,38,40,115]. Increasing the hydrophobicity of alkyl groups yields hydrogels with decreased gelation temperatures [38]. To tailor gelation temperatures of hyaluronic acid-based thermosensitive hydrogels, Pluronic was conjugated into its backbone. Increasing the Pluronic content was found to decrease significantly the gelation temperature, from 29 to 19°C [116].

For synthetic polymers, gelation temperatures are manipulated by factors such as hydrophilic/hydrophobic interaction and polymer molecular mass. For polyester-PEG-polyester, PEG-polyester-PEG or PEG-polyester thermosensitive hydrogels, gelation temperatures can be easily modulated by changing the length of the hydrophobic polyester and hydrophilic PEG. Jiang *et al.* found that decreasing the length of poly(caprolactone-*co*-glycolide) block in poly(caprolactone-*co*-glycolide)-PEG-poly(caprolactone-*co*-glycolide) increased the gel-sol transition temperature [60]. However, a different trend was found for PEG-PLA-PEG triblock polymers, where increasing PLA segment length resulted in a broader gelation region with a higher gel-sol transition temperature [65,117]. Zhang *et al.* demonstrated that simply blending PEG with PLGA-PEG-PLGA block copolymer could modulate the gelation temperature [118]. To manipulate gelation temperatures of PNIPAAm hydrogels, Guan *et al.* developed a family of copolymers based on NIPAAm, hydrophilic AAc and hydrophobic macromer 2-hydroxyethyl methacrylate-*co*-poly(trimethylene carbonate) (HEMA-PTMC) [106]. The gelation temperatures were

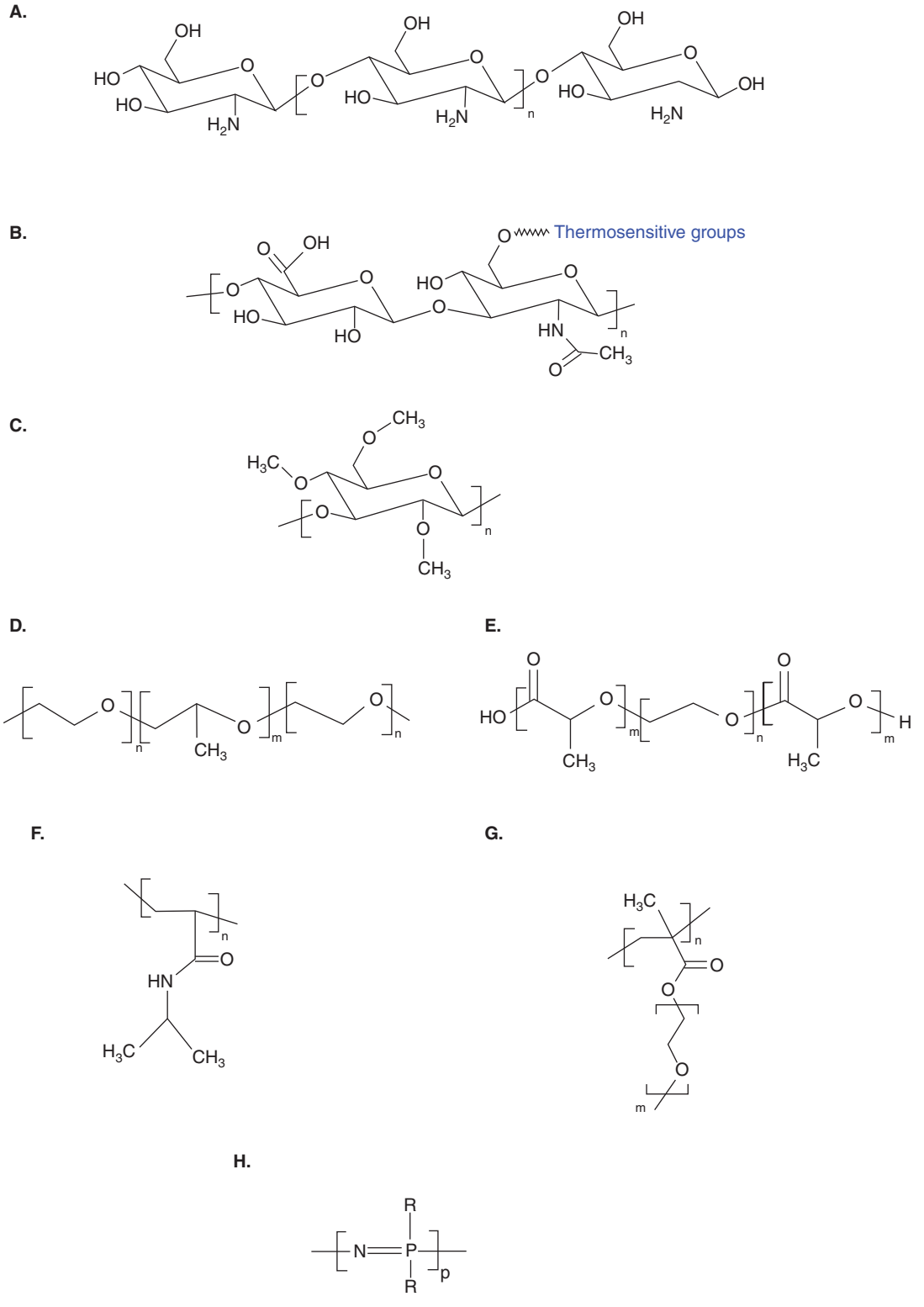

Figure 6. Chemical structures for thermosensitive hydrogels discussed in this review. A. Chitosan. **B.** Chemically modified HA. **C.** Methyl cellulose. **D.** Pluronic. **E.** PLA-PEG-PLA. **F.** Poly(*N*-isopropylacrylamide) PNIPAAm. **G.** Poly OEGMA. **H.** Polyphosphazene.

HA: Hyaluronic acid; PLA: Polylactide.

controlled by AAc and macromer contents. Increasing AAc or decreasing HEMA-PTMC content led to a decrease in gelation temperature.

3.2 Manipulating drug release rate

Different drug delivery applications need different drug retention times. Thus, regulating drug release kinetics is the key for a successful application. Drugs in polymers are often released by diffusion and/or polymer degradation. Polymer structure, molecular mass, degradation rate and affinity between drug and polymer determine release kinetics. Furthermore, thermosensitive behavior of the thermosensitive hydrogels can be utilized to control drug release [119-121]. In this section, strategies to regulate the drug release profile in thermosensitive hydrogels are discussed.

One of the benefits of using thermosensitive hydrogels is that drug release can be controlled by external temperature. When the temperature is below the thermal transition temperature of the hydrogel, it shows a slow release profile. Drug release is in the so-called 'off' state. Once the temperature is increased above the thermal transition temperature, hydrogel shrinkage leads to quick drug release. The release is now in the 'on' state. This property has been utilized for applications where an instant high dose of drug is needed. For example, Bikram *et al.* developed a drug release system based on poly(NIPAAm-*co*-acrylamide) hydrogel and silica-gold nanoparticles. Under irradiation of light with appropriate wavelength, the nanoparticles generate heat that increases the temperature of the hydrogel above its thermal transition temperature, causing a quick drug release [121]. Hydrogel molecular mass affects the 'on/off' release. For PNIPAAm-modified pullulan microspheres, when the PNIPAAm molecular mass was 1.5 kDa no significant 'on/off' release was observed. The significant 'on/off' release occurred when the PNIPAAm molecular mass was increased to 3.3 kDa [92].

One approach to increase drug retention time is to use chemical crosslinking to consolidate the vesicle surface. This is particularly useful for PEG-based thermosensitive hydrogels such as PLA-PEG-PLA and Pluronic. Crosslinked Pluronic hydrogel significantly reduced drug release rate and prolonged drug retention time compared with un-crosslinked Pluronic [52]. For crosslinked poly(NIPAAm-*co*-HEMA) hydrogel, the drug release rate can be readily tuned by crosslinking density. An increase in crosslinking density led to a decrease in release rate [16], owing to higher crosslinking density decreasing pore size in the hydrogel [101].

In some applications, controlled dissociation of a thermosensitive hydrogel is needed to break down the 'cage' to free the encapsulated drug. One approach is to incorporate a degradable segment in the hydrogel. Zhang *et al.* crosslinked a copolymer of PNIPAAm and poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) with disulfide and found that drug release was facilitated after adding reducing chemicals to the hydrogel to break down the disulfide bonds [71]. Jiang *et al.* crosslinked poly(2-aminoethyl methacrylamide) (PAEMA) and PNIPAAm by bis-2-azidyl-isobutyrylamide and cystamine. The obtained hydrogel showed fast degradation once triggered to break down the disulfide bonds [77].

The fact that the drug release profile is also dependent on the physical and/or chemical properties of the drug molecules should be addressed. Hydrophobic drugs diffuse slower in the hydrogel than hydrophilic drugs. Fundueanu *et al.* demonstrated that the hydrophobic drugs propranolol (PrB) and lidocaine free base (Lid B) were released slower than their hydrochloride bases, which are more hydrophilic [92]. For large hydrophobic drugs such as vitamin B_{12}, the release rate was much slower compared with PrB and Lid B. Thus, understanding the physical and chemical properties of the target drug molecules is important for tailoring drug delivery systems for different applications.

3.3 Incorporating multiple triggers

For some applications, controlling temperature is not enough to manipulate drug release. Extra triggers are needed to control more precisely the release. For example, the stomach is strongly acidic whereas the intestine is weak basic. Thus, when delivering drugs to the intestine by means of oral administration, proper protection of drugs under acidic environment needs to be considered. This requires more triggers besides the thermal trigger in the release system. One such trigger is pH. The pH and thermal-responsive hydrogels have been generated by many different strategies. One of them is to introduce pH-sensitive groups into the backbone of the thermosensitive hydrogel. Shim *et al.* modified the PCLA-PEG-PCLA triblock copolymer with a pH-sensitive SMO. The modified copolymer forms stable gels at pH 7.4 and 37°C, but dissociates quickly at pH 8.0 [62].

Another strategy is to copolymerize acid or base group-bearing vinyl monomers with thermosensitive polymers. For example, propylacrylic acid was polymerized with NIPAAm to form hydrogels sensitive to both pH and temperature [122]. The poly(NIPAAm-*co*-propylacrylic acid) copolymer gelled at acidic environment (pH 5) at 37°C, but dissolved at pH 7.4. Vascular endothelial growth factor (VEGF) was encapsulated into the hydrogel and pH-dependent release kinetics was observed. Metz and Theato crosslinked PNIPAAm hydrogel with basic liable 2,3,5,6-tetrafluoro-1,4-phenylene diacrylate (TFPDA). Addition of basic component isopropylamine led to the break-down of crosslinks [21].

4. Applications of thermosensitive hydrogel-based drug delivery systems

4.1 Cancer therapy

Controlled local delivery of chemotherapeutic drugs is considered to be a potential approach to treating cancers. It allows better targeting and sustained drug treatment compared with current therapeutic strategies. Thermosensitive hydrogels could serve as the drug carriers for this application.

Although there are no commercial products on the market so far, thermosensitive hydrogel-based cancer therapy is under active investigation.

Thermosensitive hydrogels, especially Pluronic copolymers, have been shown to be capable of dramatically changing the tumor cellular response to sensitizing the multi-drug-resistant effects. This is the major impedance for current cancer therapy research [102,123-128]. The interactions between Pluronic copolymers and tumor cells have been under investigation, and the mechanism is considered to be the incorporation of amphiphilic copolymer within the cell membrane [102,124]. To improve sensitization of cancer cells further, polyunsaturated fatty acid such as linoleic acid (LA) was conjugated to the Pluronic. Significant cytotoxicity and cell cycle arrest were observed for paclitaxel-loaded, linoleic acid-modified Pluronic based hydrogel [50].

Besides Pluronic hydrogels, other thermosensitive hydrogels are also used for anticancer drug delivery. Yu *et al.* synthesized a series of PLGA-PEG-PLGA triblock copolymers and used them to deliver PEGylated anticancer drug camptothecin [129]. Purushotham and Ramanujan grafted PNIPAAm chains onto magnetic nanoparticles and loaded with anticancer doxorubicin. The release of doxorubicin was triggered by the volume shrink transition induced indirectly via the heat generated from the vibration of nanoparticles under the alternating magnetic fields [78]. Regmi *et al.* showed the feasibility of using a PNIPAAm-iron oxide complex for controlled release of anticancer mitoxantrone by applying the same alternating magnetic field at the tumor site [3].

For cancer therapy, thermosensitive hydrogels are also used as vehicles to deliver angiogenesis-suppressing drugs to limit the nutrient/oxygen supply to the tumor cells so that the tumor growth can be controlled. Cho *et al.* loaded an angiogenic inhibitor 2-methoxyestradiol into a thermosensitive poly(organo phosphazene) [128]. The inhibitor was able to release continuously from the hydrogel. The released inhibitor showed a significant inhibition effect even at a relatively low initial loading concentration.

4.2 Tissue regeneration

Tissue regeneration attracts extensive attention in the biomedical field. To regenerate functional tissues, many bioactive components, including growth factors and drugs, are required at a proper time and in a proper way. Delivery vehicles are needed to protect the growth factors and drugs from denaturation on exposure to the native environment, and to control their release. Thermosensitive hydrogels are promising candidates for this application [130]. However, delivery of bioactive molecules may not be sufficient for tissue regeneration. Cells, including stem/progenitor cells, are often needed for efficient tissue regeneration. As a result, thermosensitive hydrogels are used to deliver both drugs and cells. Guan *et al.* have developed thermosensitive hydrogels that are capable of not only delivering growth factors but also encapsulating cells [106]. A prosurvival growth factor, insulin-like growth factor-I (IGF-I), was loaded into the hydrogel, and it was found that IGF-I released in a sustained manner for 2 weeks. The release kinetics can be controlled by incorporation of chondroitin sulfate (CS) in the hydrogel, where CS addition significantly delays IGF-I release. IGF-I-loaded hydrogel significantly augmented mesenchymal stem cell growth [108]. Besides, these hydrogels demonstrated attractive mechanical properties, they are highly stretchable and their stiffnesses are similar to the native heart tissue. These hydrogels can also be used to deliver superoxide dismutase (SOD), an enzyme that dismutates superoxide [131]. Superoxide is one of the reactive oxygen species (ROS) in the infarcted heart that induce cell death [132]. Delivering cells together with SOD is hypothesized to protect them from superoxide attack and improve their survival in the heart. These thermosensitive hydrogels represent a family of promising delivery vehicles for myocardial therapy.

Angiogenesis is another important issue for tissue regeneration. Timely angiogenesis is required for tissue development as it ensures the nutrient/oxygen supply for the engineered tissues. Delivering angiogenic growth factors is an approach to stimulate angiogenesis in tissues. Oh *et al.* used Pluronic F127 as VEGF carrier and injected it into the ischemic heart. It was found that local capillary density was significantly increased and the heart function was improved [133]. To facilitate angiogenesis in a hydrogel, endothelial cell migration within the hydrogel is critical. Introducing pores to the hydrogel may accelerate cell migration. Galperin *et al.* fabricated porous gel with pore size ~ 39 μm and found that cells migrated easily into the hydrogel [134].

5. Expert opinion

Thermosensitive hydrogels have been widely used in drug delivery applications. Each application has its specific requirements for hydrogel properties and drug release profile. Hydrogel properties such as thermal properties, chemical properties, injectability, biocompatibility and biodegradability determine drug/hydrogel interaction and control drug release kinetics. When designing a drug delivery system using thermosensitive hydrogels, one needs to consider what types of thermosensitive hydrogel to use and how to manipulate their properties to meet the desired drug release kinetics.

For material selection, many naturally derived and synthetic thermosensitive polymers can be used. Naturally derived polymers have excellent biocompatibility and biodegradability. However, their chemical structures afford them limited capability for further modification. Given the complex conditions of different drug delivery applications, naturally derived polymers may not be the ideal candidates. Synthetic thermosensitive polymers represent better candidates considering their versatility for property tailoring to meet the requirements of different applications.

Pluronic, PEG-polyester, PNIPAAm, POEGMA and polyphosphazene are commonly used synthetic thermosensitive hydrogels for drug delivery applications. Pluronic copolymers

(PEO-PPO-PEO) with different PPO and PEO lengths are commercially available. Their thermal behavior is largely dependent on the solution concentration and block length. Pluronic polymers are biocompatible with ability to sensitize tumor cells, thus have been widely used as anticancer drug carriers in cancer research. The disadvantage of Pluronic copolymers is that they are not biodegradable. In addition, the weak physical interactions in the hydrogel cause fast dissolution of the hydrogel in aqueous media, not allowing them to be used for long-term drug release. Chemical crosslinking of Pluronic copolymers improves their stability and imparts long-term drug release capability.

PEG and polyester-based thermosensitive hydrogels have been widely utilized to deliver drugs and proteins. The polyesters can be biodegradable PLA, PCL, PGA and their copolymers. Hydrogel properties are controlled by type and length of the polyester. They can also be modified further to impart other functions. However, the acidic degradation products from polyesters may induce inflammatory response *in vivo*.

Poly(*N*-substituted polyacrylamide) hydrogels are also major synthetic thermosensitive hydrogels for drug delivery applications. PNIPAAm is a typical polymer in this category. A major limitation of PNIPAAm is its non-degradability. Many approaches have been applied to introduce biodegradability into PNIPAAm hydrogel, such as crosslinking PNIPAAm with a biodegradable crosslinker and incorporating biodegradable segments in the PNIPAAm backbone. However, crosslinked PNIPAAm hydrogels have poor injectability, which may limit their application. The PNIPAAm hydrogels with biodegradable segments in the backbone generate low-molecular-mass PNIPAAm after degradation, which is cytotoxic [105]. To address these disadvantages, PNIPAAm hydrogels with a biodegradable polyester side chain were developed [107-109]. Degradation of the side chain increases the hydrogel gelation temperature to above body temperature, thus allowing the degraded polymer to dissolve in body fluids. Meanwhile, the degradation products are non-toxic because the polymer main chains are not degradable; they remain of high molecular mass when the side chain is degraded.

Following material selection, one needs to consider how to manipulate hydrogel properties to meet the desired drug release kinetics. Some applications require fast initial release, whereas others require sustained release. Various methods can be used to tailor thermosensitive hydrogel properties to achieve the desired drug release profile, for example: balancing hydrophobic/hydrophilic interactions can tune gelation temperature; crosslinking hydrogels yields a slow release profile; and rapid dissociation of hydrogel leads to a facilitated release profile. In some applications, sequential release of two or more drugs enhances therapeutic efficacy. Yuen *et al.* demonstrated that sequential release of angiogenic growth factors VEGF and PDGF stimulated vascularization and vessel maturation [135]. For thermosensitive hydrogels, simply controlling bulk properties may not be enough to achieve this. It may require extra stimulus sensitivity, such as pH sensitivity, to control drug release kinetics.

Thermosensitive hydrogels for drug delivery have been studied for more than three decades, and are still under investigation. New materials and modification strategies are continuously emerging. It is expected that this progress will result in more clinical applications of thermosensitive hydrogels.

Declaration of interest

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Affiliation

Zhenqing Li[1] & Jianjun Guan[†2] PhD
[†]Author for correspondence
[1]The Ohio State University,
Department of Materials Science and Engineering,
2041 College Road,
Columbus, OH 43210,
USA
[2]Assistant Professor,
The Ohio State University,
Department of Materials Science and Engineering,
2041 College Road,
Columbus, OH 43210,
USA
Tel: +1 614 292 9743;
E-mail: guan.21@osu.edu