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REVIEW

Polymer-based thermoresponsive hydrogels for controlled drug delivery

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ABSTRACT

Introduction: Controlled drug delivery through hydrogels is generally limited by the poor barrier that polymeric network can create to diffusion mechanism. Stimuli responsive polymers can help in this way guaranteeing that delivery can be sustained and finely controlled using an external stimulus.

Area covered: This review provides an overview of recent studies about the use of temperature as an external stimulus able to work as an efficient new route of drug's administration. Thermoresponsive hydrogels are discussed and compared in terms of physical properties and mechanism of drug release considering their classification in intrinsical (formed by thermosensitive polymers) and non-intrinsical (polymers with thermosensitive moieties) hydrogels.

Expert opinion: Thermoresponsive hydrogels can be developed by using different polymers added or not with micro/nanoparticles of organic or inorganic origin. In both cases, the final system represents an innovative way for the local and sustained drug delivery in a specific site of the body. In particular, it is possible to obtain an on-demand release of drug by applying a local increase of temperature to the system.

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Drug delivery; thermoresponsive; hydrogels; macromolecules; polymers

1. Introduction

Hydrogels are three-dimensional structure of polymeric networks able to swell in the presence of a water solution [1–5]. Thanks to their ability of containing a large quantity of water and physiological fluids, they are highly biocompatible and able to mimic the biological tissue [6–8]. This represents one of the reasons that make them highly promising for medical and pharmaceutical applications [9–11]. Hydrogels can be developed by using different techniques such as chemical or ionic crosslinking [12,13], photopolymerization [14], or external stimuli such as temperature, pH, and ionic strength [15]. In the last case, a particular class of polymers is used and they are called 'sensitive polymers' due to the ability of changing their physicochemical characteristics and phase state in response to an external stimulus [16]. Stimuli-responsive polymers are known for their responsivity to environmental stimuli, including temperature [17], ultraviolet/visible (UV/vis) light [18,19], mechanical trigger [20,21], electric field [22], magnetic field [23,24], and chemical [25,26] and biological stimuli [27,28]. The addition of stimuli-responsive groups into a hydrogel system has attracted particular interest in the diverse applications in actuators, sensors, scaffolds, and drug delivery. Among them, thermoresponsive polymers showed great promises in drug delivery field. They exhibit a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) that represent the boundaries of solubility in an aqueous phase [29,30]. Taking into consideration all these properties, the final formed hydrogel will be the result of physical- or chemical-type binding between polymer chains. Compared to physical hydrogels, easier to use thanks to their sol-to-gel transition once being injected in the body, the covalently linked hydrogels can be formed in situ after a chemical or photo-induced crosslinking, otherwise before the implantation [31]. Hydrogels made of physical interactions between polymer chains have a sol-gel or vice versa transition at the critical solution temperature, whereas those made of chemical cross-linked interactions exhibit a volume transition [32]. Stimuli-responsive hydrogels are polymeric structure able to change their volume after the application of a particular stimulus such as temperature and pH [1]. This review will focus the attention on thermoresponsive hydrogels and their potential application for controlled drug release (Figure 1).

2. Thermoresponsive behavior in polymers and hydrogels

Thermoresponsive polymers present the particular property of exhibiting a phase transition at a certain critical temperature. The critical temperature is known as LCST in case of a sol-gel transition or as UCST in case of gel-sol transition phase. For polymers which exhibit a LCST, above this temperature it is verified as the so-called 'hydrophobic effect' [33,34]. The sol-gel transition at LCST is thermodynamically favored by an increment of entropy. Indeed, when the polymer is in its hydrophilic state, the polymer-water molecule hydrogens bonds lead to a structure which limits the movements of water molecule and in this configuration the enthalpy results higher than the entropy. When the temperature is above the LCST, the desolvation of the hydrogel leads to an increase in water mobility which in turn leads to an increase in the

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Article highlights

- Controlled drug delivery through polymeric hydrogels is generally limited by the poor barrier to diffusion mechanism.
- Stimuli responsive polymers can guarantee sustained and controlled delivery using external stimuli promoting on-off on demand release.
- Temperature can work as efficient external stimulus able to induce structural conformation within polymeric networks and tunable release rates.
- Thermal responsivity can be intrinsically formed so by thermosensitive polymers or non-intrinsically where polymers are added with thermosensitive moieties.
- Despite the very promising results, some issues, like manufacturing, should be solved before reaching clinics.

entropy of the system. Thus, when $\Delta G < 0$, the gel form is thermodynamically favored [33,35,36]. Thermoresponsive hydrogels are of particular interest in the field of drug release because of their ability to modify their structure in response of temperature. Their property allows them to pass from the sol to the gel phase once injected in the body and then release the drug in a controlled way. The property of being injected is very important for mini-invasive biomedical application. Moreover, one of the principal advantages of injectable hydrogel is to have a high concentration of drug in the desired site avoiding the systemic circulation of the drug [37]. Indeed, hydrogels act as a drug reservoir and achieve a long-term sustained release. The sustained and local drug release avoid the long circulation of the drug in the bloodstream and the frequent times of administration [38,39]. Hydrogels can include natural polymers such as chitosan, collagen, hyaluronic acid, and methyl cellulose that have the advantage of being biodegradable, more biocompatible, and similar to the extracellular matrix (ECM) with the possibility to stimulate specific cellular response compared to the synthetic ones [40]. On the other hand, the advantage of synthetic polymers is to be modified in order to change rheological properties, molar mass, or degradation of the hydrogel in order to be more suitable for a specific application [41]. The principal synthetic polymers that exhibit a LCST are poly (N-isopropylacrylamide) (PNIPAM) with a LCST of 32°C, poly (N,N-diethylacrylamide) (PDEAAm) with a LCST between 25°C and 32°C, poly(N-vinylcaprolactam) (PVCL) with a LCST between 25°C and 35°C [42,43], poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) with a LCST around 50°C [44], and poly(ethylene glycol) (PEG) with a LCST around 85°C [31,45]. Some natural polymers such as agarose, methyl cellulose, and collagen have a temperature-dependent gelation, which reveals them suitable for gelation after injection inside the body [46]. The other natural polymers that have no intrinsically temperature-dependent gelation can be functionalized in order to obtain this property. For example, the research group of Kim *et al*. [47] functionalized the chitosan with β-glyceroposphate in order to have an injectable hydrogel with a gelation temperature around 37°C and able to release ellagic acid into glioblastoma cells for the treatment of brain cancer. As for natural polymer, also the synthetic polymers can have an intrinsically temperature-dependent behavior; otherwise, they can be used with other compounds to develop a thermoresponsive hydrogel. The following paragraphs summarize examples of these two categories and their applications.

3. Thermoresponsive hydrogels made with thermoresponsive polymers

3.1. Synthetic polymers

Among synthetic polymers, PNIPAM is surely the most studied one for developing thermoresponsive biomedical systems. Beside the well-known thermoresponsive properties, it is also biocompatible and biodegradable polymer [48]. Its molecular structure presents hydrophilic amine groups and hydrophobic propyl groups. Below its lower critical solution temperature (LCST) of about 32°C, the polymer assumes hydrophilic property thanks to the presence of hydrogen bonds between water and amine groups. Above the LCST, the dehydratation of amine groups favors the interaction between the hydrophobic groups, leading to the collapse of the polymer and its

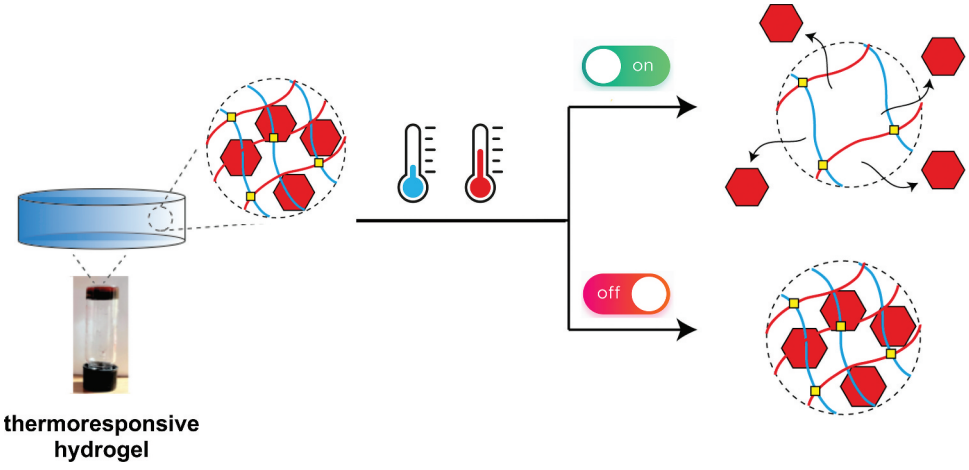

Figure 1. Schematic representation of thermoresponsive hydrogels that can answer to an external stimuli with local increase of temperature, change of polymeric network conformation, and consequent release of drug molecules (red hexagons).

aggregation [39]. Its coil-to-globule phase transition is exploited in drug release systems because it is responsible of a first phase of polymer compression and fast release of drug, followed by a controlled release [49]. When co-polymerized with other polymers, PNIPAM is able to change its LCST as well as biochemical and mechanical properties [50]. For example, the physical properties of hydrogels based on PNIPAm can be modulated by using hydrophilic polymeric crosslinkers, such as PEG chains. Depending on the concentration and molecular weight of PEG, it is possible to tune the LCST and swelling/deswelling behavior for the specific application. In particular, the use of low molecular weight crosslinker leads to a highly rigid hydrogel with more limited swelling capacity with respect to high molecular weight crosslinker, as well as the presence of higher concentration of crosslinker leads to different conformation of polymer chains during swelling/deswelling phase [51]. Recently, a lot of studies were conducted to use PNIPAm and its copolymers inside hydrogels for biomedical applications. Saibo Chen *et al*. developed an in situ gelling system based on PNIPAm and PLEL (PLA-PEG-PLA terminated with diacrylate), a biodegradable crosslinker in order to have a thermoresponsive and degradable hydrogel suitable for the release of hydrophilic drugs [52]. A thermoresponsive hydrogel containing PNIPAm and PEG-DA (poly(ethylene glycol) diacrylte) as crosslinker was used for ocular drug delivery of proteins (bevacizumab and ranibizumab) [53]. The hydrogel has the property of being able to be injected intravitreal and release drugs to the posterior segment [54]. Thanks to its thermoresponsive property, NIPAAm-based hydrogels can be used to provide a controlled release of drug dependent on temperature [55]. The work of Park *et al*. [56] is based on the use of NIPAAm together with acrylic acid (AAc) to form molecularly imprinted hydrogels able to release the drug in a temperature-dependent way. The hydrogel is able to modify its volume, thanks to the so-called volume phase transition temperature (VPTT) below which it is hydrophilic, so it absorbs and swells, and above which it is hydrophobic, so it shrinks. If the temperature is higher than VPTT (about 37°C), the compression of the hydrogel favors the diffusion of the drug molecules from the cavity. The release of doxorubicin (DXR) from the hydrogel was studied at 25°C, 37°C, and 42°C until 20 h. The results showed that at 42°C the release profile is the highest due to the compression of the hydrogel which favors the diffusion of the drug. At 37°C, the release profile is the lowest because hydrogel network is less shrunken and the drug is trapped inside, whereas at 25°C the release profile is in the middle because at this temperature the hydrogel is completely swollen and the drug is smaller than the cavity, and thus easily diffuse outside. As previously reported, the transition temperature of PNIPAm increases with the copolymerization of hydrophilic monomers. In addition, if the hydrophilic monomer presents some charged groups such as -COOH or -NH_2, the final copolymer is also pH responsive [57,58]. In the presence of a particular pH, the electrostatic interactions of charged groups can influence the thermosensitivity of the copolymer [59]. For example, if it is copolymerized with methacrylic acid (MA), poly(NIPAAm-co-MA) one placed in a surrounding environment at pH = 7.4 shows a higher LCST because of the presence of ionized groups of MA which increase the hydrophilicity content [60], but if there are positively charged amino groups of the hydrophobic drug, the copolymer regains its thermosensibility and the LCST decreases (Figure 2). Instead,

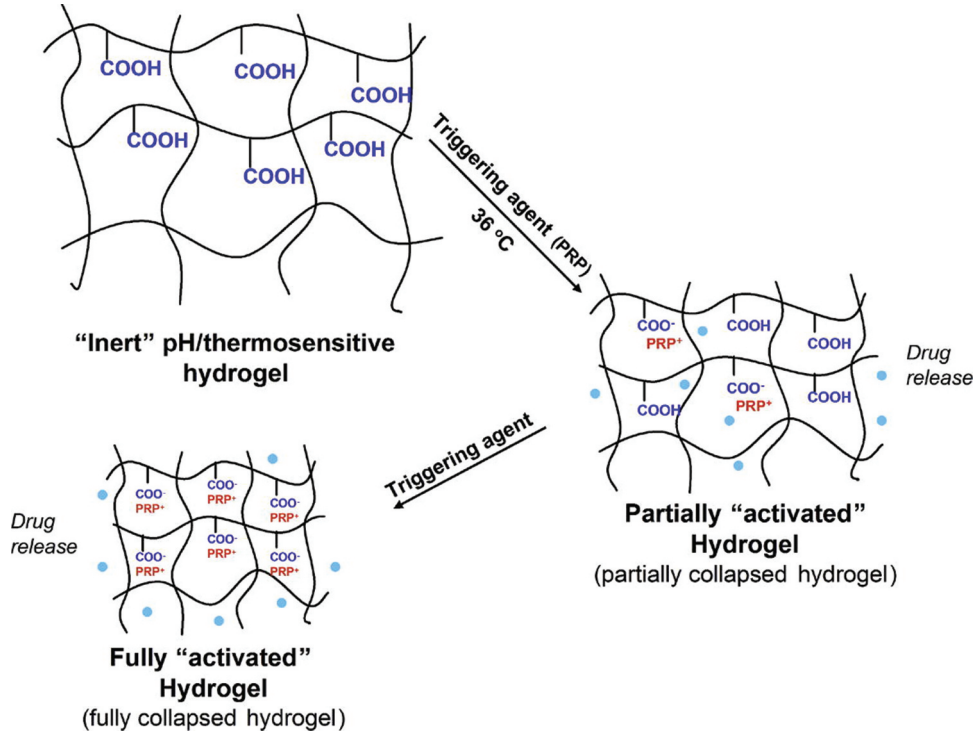

Figure 2. Schematic representation of the principle of operation of pH/thermosensitive poly(NIPAAm-co-MA) microgels in the presence of the triggering agent, under simulated physiological conditions. Reprinted with permission from Elsevier [46].

at low pH, the groups of MA are protonated, so are more hydrophobic and decrease the LCST of the copolymer. In this condition, the higher the MA content, the lower the LCST.

Not only the addition of monomers or drugs can influence the physical property of PNIPAM, but also the presence of other compounds such as peptides. Their use aims also to provide a therapeutic effect once loaded inside the hydrogel matrix. The research of Cao and coworkers [39] developed an injectable and reversible thermoresponsive peptide-PNIPAM hydrogel composed by peptides (I_3K) self-assembled in nanofibrils and PNIPAM able to perform a sol-gel transition around 33°C. The antibacterial peptide G(IIKK)$_3$I-NH$_2$ was encapsulated inside the hydrophobic region of peptide sites and its release from the hydrogel resulted linear over the first 10 h [39]. They showed that the sol-gel transition occurs only by mixing the I_3 K solution with PNIPAM; otherwise, the two separate solutions remained in sol phase also when temperature reached the 40°C. In particular, in presence of both the components and at temperature of 40°C, the PNIPAM molecules collapse and associate on the fibril surface acting as crosslinkers and leading to the packing of fibrils or the formation of junction points between fibrils (Figure 3). The consequence is the formation of a more strength materials with a stable three-dimensional network. Rheological tests at different concentrations of PNIPAM showed G′ and G″ values lower than 10 Pa at 25°C, whereas they assumed values between 10 and 1000 Pa at 40°C.

Because of its biostability, PNIMPAM is not cleared from the body in a fast way [33], but it can be used in combination with functional groups or other degradable polymers to improve its degradability [61]. As a consequence, also PNIPAm hydrogels hardly degrade, and so it is possible to link other degradable cross-linkers to enhance the rate of degradability. The research group of Gan [62] proposed a PNIPAm-based thermoresponsive and biodegradable hydrogel containing poly(ε-caprolactone) dimethacrylate (PCLDMA) and bisacryloylcystamine (BACy) as cross-linking agents.

In this case, the release of the levofloxacin drug molecule can be allowed both by the temperature and the degradation of the hydrogel. They tested the degradability of the hydrogel by studying the drug release behavior of the hydrogel with and without the presence of the reducing agent glutathione, which is able to break the disulfide linkage of BACy. The results revealed a complete release of levofloxacin after 120 h in 10 mM GSH PBS buffer solution instead of only 21% in pure PBS buffer solution, demonstrating the influence of degradation on the release kinetic of drug.

Regarding the use of other polymers, poly(lactic-co-glycolic acid) can be co-polymerized with PEG to obtain PLGA-PEG-based hydrogels that are synthetic, biodegradable, and biocompatible. These hydrogels are able to perform sol-to-gel transition, thanks to the presence of both hydrophobic and hydrophilic groups, which lead at the same time the possibility to deliver drug with different water affinity [56,57]. The physical characteristics of PEG-based hydrogel can be influence also by the presence of other molecules such as cyclodextrins (CDs). CDs are very attractive in developing supramolecular systems for biomedical application [63–65]. The α-CDs can be used in combination with PEG chain in different ratio in order to modulate the gel-sol transition temperature of the final hydrogel
($T_{gel\text{-}sol}$ = 30–60°C) [66]. For example, the transition temperature decreases with decreasing the length of PEG chains because the dethreading of α-CDs is more easy in case of short PEG chains at higher temperature. As expected, regarding the α-CDs concentration, the
$T_{gel\text{-}sol}$ decreases with the decrease of α-CDs and the gelation time increases with the decrease of α-CDs content.

All these aspects have a strong influence in drug release at physiological temperature: it resulted lower for hydrogels with high PEG chain length and α-CDs concentration due to the high $T_{gel\text{-}sol}$. Indeed, the appropriate formulation can be used to activate the drug release from thermosensitive hydrogels. Poly(ε-caprolactone) (PCL) is another polymer used for hydrogel formulation, thanks to its biodegradability and biocompatibility; it is approved by the FDA for application in health care [67]. When it is copolymerized with PEG, it is possible to obtain a thermosensitive copolymer (PCL-PEG) able to perform a sol-gel transition by increasing the temperature in a range between ambient temperature and 37°C [68,69]. PCL-PEG modified into poly(e-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ecaprolaone-co-1,4,8-trioxa[4.6]spiro-9-undecanone) (PECT) was developed as thermosensitive hydrogel to sustain and burst release paclitaxel (PTX) and doxorubicin (DOX), respectively, in the treatment of cancer [70]. PECE (PEG_{960}-PCL_{2448}- PEG_{960}) triblock

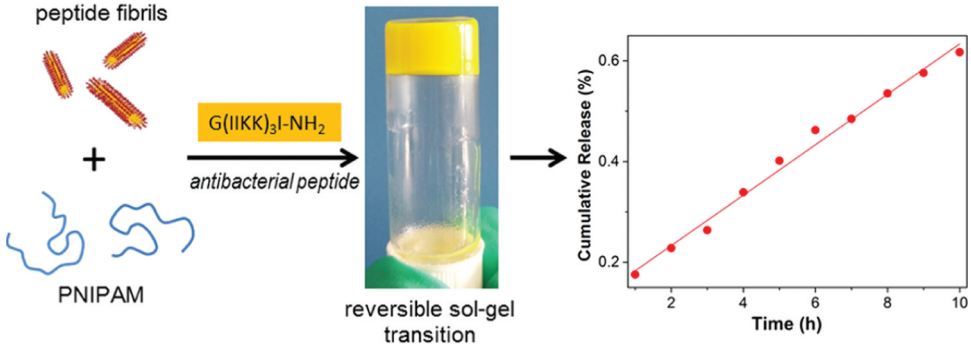

Figure 3. Schematic reperesentation of hydrogel drug delivery system based on PNIPAM and I_3K peptide and the cumulative release of G(IIKK)$_3$I-NH$_2$. Reprinted from [28] with permission. Copyright 2019 American Chemical Society.

copolymer composite hydrogel having a sol-gel transition at 37°C was studied for the release of 5-fluorouracil (5-FU) in the treatment of colorectal cancer and the results showed a controlled release of drug [71]. The research group of Yutao Ren prepared an injectable thermosensitive PCL-10R5-PCL (PCLR) hydrogel loaded with oxaliplatin (OXA) and tannic acid (TA) polymeric nanoparticles (OXA/TA NPs) that can be used for the treatment of colorectal peritoneal carcinoma [72]. Drug release experiment from OXA/TA NPs-H exhibited a slower release of OXA and TA compared to NPs alone and free drugs. Another thermoresponsive hydrogel was developed via radical copolymerization of 2-methylene-1,3-dioxepane (MDO) and 2-hydroxyethylacrylate (HEA). This hydrogel is also degradable because of the MDO, a hydrophobic cyclic monomer that after radical polymerization becomes a biodegradable polyester [73]. As PNIPAM-based hydrogel, its volume decreases with the increase of temperature and its VPTT can be varied by modifying the proportions of monomers. Other examples of synthetic polymers used for the synthesis of hydrogel are poloxamers, tri-block copolymer of PEO (polyethylene oxide), and PPO (polypropylene oxide), which have hydrophilic and hydrophobic sites and the sol-to-gel transition temperature that can vary with their concentration in water solution [74]. Thanks to their amphiphilic properties, poloxamers are able to rearrange into micellar packing when temperature increases leading to the formation of a gel [75]. Poloxamers such as P407 (poloxamer 407) and P188 (poloxamer 188) are widely used for the preparation of nasal, rectal, and ocular in situ gel due to their fast sol-gel transition at physiological temperature and mucoadhesive property [76–79]. For example, the P407 can be used together with other additives, which are able to improve its mechanical and physical properties, to deliver mometasone furoate via nasal route for the treatment of allergic rhinitis [80], quinine for the treatment of severe malaria in children via rectal delivery [81], tobramycin for the treatment of ocular infections [82], selegiline hydrochloride via nasal route for the treatment of Parkinson's disease [83], etc. In particular, poloxamers are studied together with heparin as vehicles for the sustained release of growth factors for tissue regeneration in the treatment of injured spinal cord [84,85]. A polymer which exhibits a UCST is the poly(N-acryloyl glycinamide) (PNAGA) and its value depends on the molar mass and concentration of the polymer [86]. For allowing the injection, it is important that the hydrogel presents a UCST higher than 37°C but not above 48°C, the maximum temperature tolerated by our cells for a short time. An optimal concentration can be designed in order to have gel-sol temperature between 35°C and 40°C, allowing the preparation of a versatile system that can work as carrier for the release of salts, drugs, charged macromolecules, and proteins. For the study of drug delivery in vivo, methylene blue was incorporated in the hydrogel and the coloration of local tissue and organ was evaluated in time. The coloration of peritoneum and abdominal organs remains until 52 h, underlining to be promising as drug delivery system. Despite the research done in many preclinical models, only two thermoresponsive hydrogels have reached clinical trials until now. In particular, Oncogel®, ReGel® solution loaded with paclitaxel, has been applied in clinical trials (NCT00479765, NCT00573131). However, these trials have been terminated due to sponsor decision (NCT00479765) or because the product did not show any impact on tumor regression (NCT00573131). Moreover, several trials of Pluronic® F127 (poloxamer 407) have been completed and/or are ongoing. Corresponding thermoresponsive hydrogels have been tested as a drug delivery matrix of simvastatin (NCT03400475) and anthralin (NCT03348462) for the treatment of mastitis and psoriasis, respectively.

3.2. Natural polymers

In the field of natural polymers, methyl cellulose has sol-to-gel transition near 37°C but the transition rate is too slow for having a drug release application, and so it can be used in combination with other polymers to have a faster gelation [87].

For example, the use of hyaluronic acid with methyl cellulose reduces the sol-to-gel transition temperature of methyl cellulose leading in a faster gelation once injected [87]. Gelatin and collagen are natural proteins mainly derived from animal tissue and can be used for hydrogel formation [88].

One of the disadvantages of using gelatin alone is that aqueous gelatin solution solidifies at a temperature of 25°C and returns to a liquid phase at 30°C. During the solidification, triple helices are formed leading to a more rigid structure, whereas above 30°C they become flexible coils [89]. For this reason, a suitable hydrogel for the delivery of protein drug bovine serum albumin with a sol-gel transition at physiological temperature was formed by mixing gelatin with chitosan [90]. The resulted hydrogel was injectable, biocompatible, biodegradable, and adhesive to human tissue. Similar to collagen and gelatin, agarose is a natural polysaccharide which once in solution can become gel via cooling below its UCST, which can vary between 35°C and 50°C depending on the origin and processing conditions [91]. It can be chemically modified in order to change its gelation point. For example, the higher the degree of carboxylation of primary hydrogel groups, the lower the temperature of gelation [92,93].

4. Thermoresponsive hydrogels made with non-intrinsically thermoresponsive polymers

Some hydrogels are not intrinsically thermo-responsive because of the absence of thermosensitive polymers, but their swelling/deswelling behavior can be achieved by incorporating specific particles, such as photosensitive molecules or nanoparticles. For example, photochromes such as azobenzene, spiropyran, spirooxazine, and fulgide derivatives undergo photoinduced isomerization, photodimerization, and photocleavage leading to sol-to-gel transition or vice-versa [94–96]. The research of Chiang and coworkers developed a β-cyclodextrin-grafted alginate hydrogel containing diazobenzene-modified PEG chains to have a UV-sensitive hydrogel. After UV-light irradiation, azobenzene units convert from the trans to cis isomerization leading to a low affinity with β-cyclodextrin-grafted alginate and causing the disruption of the gel structure [97].

Again, chitosan-based thermoresponsive hydrogels were made by combining chitosan with intrinsically thermoresponsive polymer such as pluronic or PEG polymers [98–100]. Chitosan is a biocompatible, non-toxic, and biodegradable material highly used in clinic for biomedical application [101], and its potential use in thermoresponsive hydrogel preparation is currently under studies. The research group of Abashzadeh *et al*. developed in situ gel forming system for hormonal therapy containing chitosan and its water-soluble derivatives, such as carboxy- methyl chitosan (CMCh), sodium carboxymethyl chitosan (NaCMCh), and opened ring polyvinyl pyrrolidone (OP-PVP), to deliver triptorelin acetate in controlled way [102,103]. In vitro release studies demonstrated a sustained release profile for about 192 h and in vivo tests on male rats, compared with the performance of the commercial delivery system Diphereline SR, confirmed the efficacy in decreasing the serum testosterone level for 35 days and its potential use for delivery of peptides. Hydrogel based on chitosan loaded with 5-Fluorouracil and cisplatin could be used for colorectal peritoneal carcinomatosis treatment [104]. This hydrogel was able to perform a sol-gel transition once injected in the body. Studies on mouse models revealed an inhibition of tumor growth and a prolonged survival time compared to other groups. Even with their high potential, a lot of stimuli-responsive hydrogels are not used in clinical test because of the drug security, mechanical strength, and not sustained release of drug molecules [105,106]. It is possible to overcome this problem by inserting another system inside the hydrogel that is able to encapsulate and release the drug, such as nanoparticles [107]. In this case, the drug release occurs at first from the micro- or nanoparticle and then through the hydrogel environment [108]. Moreover, the combination with molecules or nanoparticles in order to have a hybrid hydrogel leads to higher physical and mechanical properties. Polydopamine (PDA) is a biocompatible photothermal agent that can be used to convert a NIR into heat. Its use to form PDA nanoparticles allows morphological changes in the hydrogel network with consequent release of drug. In this direction, copolymer of polyetherimide and four-armed star-shape thermoresponsive poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) modified with tert- butyl acetoacetate (t-BAA) embedded with PDA nanoparticles can be used as drug delivery system for photothermal therapy in cancer treatment [109]. Tests of continuous stress scanning revealed a self-healing property of the hydrogels because of the recovery from sol to gel phase after three cycles of applied strain from 1% to 150%. By applying irradiation with 808 nm laser, it was seen that higher the power of intensity of the laser, higher the PDA NP content, higher the temperature in the hydrogel. Drug release of doxorubicin showed cell viability decrease with the increase of PDA (about 60% of cells died with 0.2 wt% PDA NPs for 5 min) and time of irradiation. In vivo test showed a higher temperature in the tissue for the nanocomposite gel (about 56°C) than only PDA (38°C) under the same irradiation conditions and the retention effect of the hydrogel leads to similar results also after some days from the first irradiation.

4.1. Gold nanoparticles

Regarding the use of NIR light as external source, gold nanoparticles are sensible to the near infrared region-light and can allow a gel-to-sol transition, as demonstrated by the work of Zhang [110].

Triblock copolymer of N-acrylamide (Aam), acrylonitrile (AN), and N,N′-dimethylacrylamide (P(AAm–co–AN)–b–PDMA–b–P(AAm–co–AN)) with UCST of about 37°C was loaded with gold nanorods (AuNRs) in order to have a gel-to-sol transition phase at a temperature higher than the UCST after the excitation with NIR light (785 nm) irradiation. In Figure 4, the scheme of the hybrid hydrogel that contains gold nanorods is presented. The cross-linkers of the 3D network are micelle cores derived from the aggregation of copolymers. For drug release experiment, fluorescein isothiocyanate conjugated bovine serum albumin was added and the hydrogel was put in the bottom of a cuvette covered by water solution. A 785-nm laser was applied to the system as represented in Figure 4a and 4b. As shown in Figure 4c, the emission intensity of the protein increased with the increase of exposure time. The same result is represented in Figure 4d where the release is compared with that from a hydrogel without nanoparticles confirming the thermal effect of gold NRs. In addition, on/off experiments were conducted and revealed a NIR-induced on-off release of the protein. In a recent study, a switchable dual light- and temperature-responsive drug carrier using gold nanoparticles (Au NPs)-grafted poly(dimethylacrylamide-co-acrylamide)/poly acrylic acid [P(DMA-co-AAm)/PAAc] hydrogel for a pulsatile release purpose was developed [111].

Moreover, a study of comparison between agarose-based hydrogel loaded with aggregated or PEGylated gold nanoparticles showed that aggregation of Au NPs [112] influences the release of therapeutic agents from the 3D hydrogel network. Graphs of cumulative release revealed no release from non-irradiated hydrogel, a release of about 25% from Au-PEG NPs (non-aggregating) hydrogel within the first hour without reaching 100% until 72 h, and a release of 100% within the first hour in the case of non-PEGylated Au NPs (aggregating) hydrogels. Hybrid hydrogels incorporating gold nanorods can also combine two different therapeutic effects in order to have a maximum efficacy for treating particular diseases. An innovative type of hydrogel used for minimal-invasive cancer treatment is represented by the combination of drug release function and chemo-photothermal therapy. Indeed, the generated heat is used for tumor ablation and drug release simultaneously [113]. One example is represented by hydrogel patch of alginate (Alg) and polyacrylamide (PAAm) [114]. Using a NIR radiation it was possible to stimulate polyvinylpyrrolidone functionalized graphene oxide nanosheets (PVP-nGO) and gold nanorods (AuNRs) for inducing a localized photothermal therapy (PTT) and drug release from the patch into the skin. The presence of gold nanorods was needed in order to exploit their optical property of surface plasmonic resonance and generate heat after an infrared irradiation. Its peak of absorbance is depending on the shape of the gold particles and in the case of nanorods there are two peaks in the NIR related to the transverse and longitudinal plasmonic

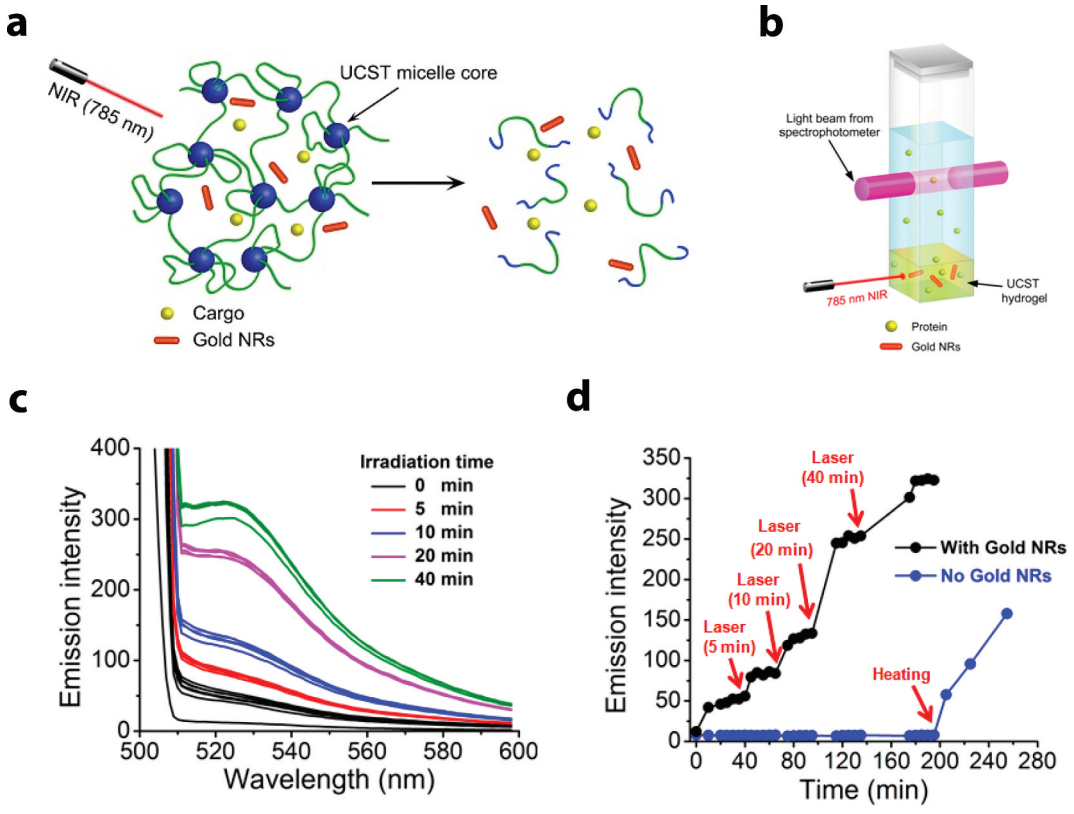

Figure 4. (a) Schematic illustration of NIR-light-triggered UCST gel–sol process due to heating by encapsulated AuNRs; (b) setup used to detect protein diffusing from the hydrogel into the aqueous solution after; 785 nm laser irradiation; (c) fluorescence emission spectra of the protein recorded after exposing the hydrogel to laser light (1 W) for a certain amount of time (indicated); (d) plots of the fluorescence emission intensity vs. NIR irradiation time showing a temporal control of the protein release by turning the NIR laser on and off. Adapted from [77] with permission. Copyright 2017 MDPI.

bands. Study of the photothermal response on the hydrogel patch after 10 min of infrared irradiation of 4.4 W/cm^2 showed a temperature next to 75°C whereas near 38°C for the same patch without nanorods. The cumulative release of methotrexate (water-insoluble anticancer drug) and rhodamine B (water-soluble drug mimetic) within 20 min reached about 30% and 43%, respectively, with NIR irradiation whereas about 9% and 20%, respectively, without NIR irradiation. Also, carbon nanotubes can be used as heater. As gold nanoparticles, they are activated by NIR light and generate heat, which in turn can provoke the swelling or deswelling of the hydrogel. For example, single-walled carbon nanotubes (SWNTs) embedded inside PNIPAM gel tube showed a deswelling behavior from an initial diameter of 240 μm to a final 80 μm after the NIR light application at 1064 nm (210 mW). In addition, repeated on/off-laser irradiation cycle showed a reversible phase transition behavior until more than 1200 cycles [115].

4.2. Magnetic nanoparticles

Instead of others stimuli sources, alternating magnetic field, used in MRI, can penetrate deeply into the human tissue and stimulate a system sensitive to magnetic field [116–118]. Superparamagnetic nanoparticles are able to convert an alternating magnetic field (AMF) into heat because of the phenomenon of Brownian and Néel relaxation [119]. Meenach and coworkers synthesized a thermo-responsive polyethylene glycol monomethacrylate (PEGMA) hydrogel containing iron oxide particles.

By using an external alternating magnetic field, an increment of internal temperature of the hydrogel is favored, leading to consequent deswelling of the network [120]. This phenomenon becomes interesting if related to a possible drug delivery route. The same idea of combining superparamagnetic iron oxide nanoparticles (SPIONs) within polymer network for having a thermoresponsive hydrogel was used by Crippa and coworkers [121]. They exploited the Brownian and Neel mechanism of SPIONs exited with alternative magnetic field to create an increment of temperature inside the hydrogel and a consequent modification of the swelling state. Other stimuli-responsive hydrogels can be made by thermoresponsive nanogels loaded inside the hydrogel [122]. In particular, they used magnetic NPs covered by a thermoresponsive poly(N-isopropylacrylamide-co-acrylamide) (poly(NIPAM-co-AM)) shell loaded inside a cross-linked gelatin network as drug reservoir. The aim of using gelatin hydrogel was to deliver locally the drug molecules by injection and allow tissue regeneration by slow degradation of the hydrogel during time. DLS analysis confirmed a change in hydrodynamic diameter from about 255 nm at low temperatures (25–40°C) to about 90 nm at 55°C and from the derivative of DLS temperature sweep 45°C was determined as the VPTT. To demonstrate the effect of using magnetic NPs, studies about drug release showed a significant higher value of cumulative drug release (23%) by using an alternating magnetic field of 0.0375 T for 1 h instead of exposing

hydrogels to thermal stimuli (<10%). The inclusion of nanomaterials inside hydrogel network can limit their clearance from the body and enhance their functionality. In this direction, the research of Campbell [123] developed microgel-SPION within hydrogel in order to reduce the typical sequestration of microgels by the lymphatic system [124]. In addition, SPIONs are used to generate heat and induce the deswelling of microgels (Figure 5). Microgels were prepared by a copolymerization of NIPAM with N-isopropylmethacrylamide (NIPMAM) and exhibit 90% decrease in volume passing from 37°C–43°. This leads to the formation of free volume in the hydrogel through which the drug diffused to the external environment. Magnetic NPs work as thermal sources after the application of magnetic field and this property can be used for an on-off treatment in order to control the release of drug [125].

Pulsatile experiment using AMF in an on/off mode were performed and the results revealed an enhanced release of drug mimetic after each application of AMF impulse and a return to the baseline release rate when it was shut off.

4.3. Wearable thermosensitive device

Thermoresponsive hydrogels can be used also for wound-healing applications. In this case, dressing can protect from the damage, contamination, and others factors, which can lead to scar formation, allowing a healing process and possibly tissue regeneration [126–128]. Alginate hydrogels are known as biocompatible dressing material with high absorbency and moisture retention [129,130]. One recent work tried to combine different applications in a single multifunctional dressing hydrogel able to perform drug delivery, stem cell-based therapy, tissue engineering, and regenerative medicine [131]. The hydrogel is the result of the combination of Fe_3O_4@SiO_2-IPN microfibers and hUMSC-laden microfibers. The firsts are used to have a magnetothermal heating (MTH) effect in order to have a controlled release of antibiotics from the thermoresponsive interpenetrating polymer network (INP) hydrogel, whereas the other microfibers allow a cell proliferation to enhance tissue regeneration. Human umbilical cord mesenchymal stem cells (hUMSCs) are very interesting from the point of view of regenerative medicine and clinical use compared to other types of stem cells due to their availability, proliferation capacity, low immunogenicity, and ethical aspects [132]. Regarding the wearable device for the treatment of skin damages, patch with flexible heating system for on-demand drug release was developed [133]. In particular, micropatterned gold heating elements are used within Ca-alginate hydrogel sheet loaded with thermoresponsive NIPAM-based drug microcarriers. The device was also composed by a controller and a power source used to adjust the generated heat. The studies of model drug release at 25°C and 37°C revealed a temperature-drug release behavior from the patch due to the phase transition and consequent release of drug from the thermoresponsive NIPAM particles.

4.4. Polymer-nanoparticle hydrogels

Nanocomposite hydrogels include also those derived from the physical or chemical interaction between the hydrogel and the polymeric nanoparticles; their presence can control the swelling/deswelling behavior and the mechanical property of the final gel. PNIPAM hydrogels containing cross-linked poly(acrylamide) nanoparticles showed larger equilibrium water uptake and faster swelling/deswelling rate compared with conventional hydrogels. Moreover, the volume phase transition temperature is dependent on the nanoparticle content: the higher the nanoparticles amount, the higher the volume phase transition temperature [134]. Polymeric nanoparticles can be used not only to improve the mechanical property of the gel, but also as a thermo-responsible system for the drug delivery compensating a low or absence of thermo-sensitivity of the hydrogel itself. For example, a composite hydrogel characterized by a poly(ethylene glycol) diacrylate (PEGDA) matrix containing thermo-responsive poly(N-isopropylacrylamide-co-acrylamide) (PNIPAM-Aam) nanoparticles can work in this direction [135]. The hydrogel is able to photopolymerize in situ by using an ultraviolet (UV) light and release drug and/or protein only by changing the temperature locally above the LCST of the nanoparticles (39–40°C). Protein release study showed quicker release of the model protein (bovine serum albumin) from the hydrogel at

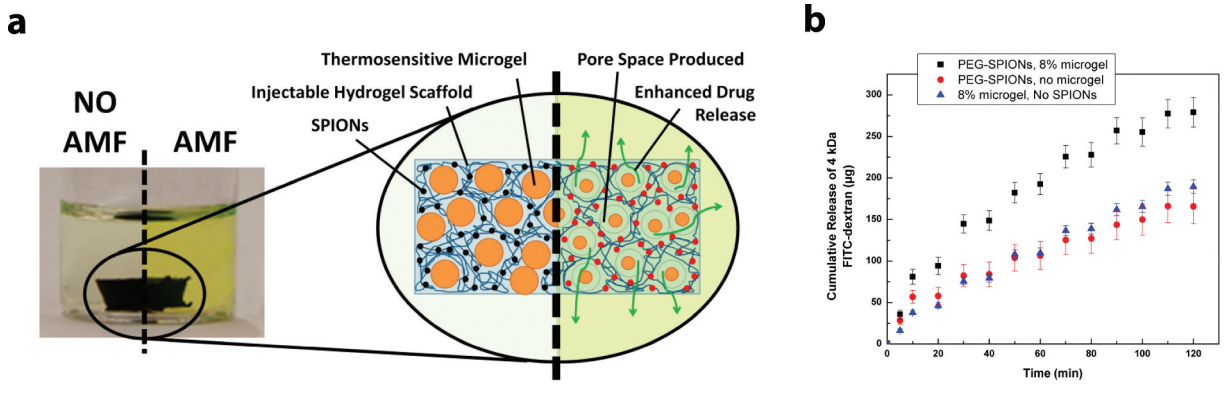

Figure 5. (a) Nanocomposites and their proposed mechanism of externally AMF-controlled enhanced drug release; (b) cumulative release of drug mimetic over 2 h of AMF exposure from a nanocomposite with 5% PEG-SPION and 8% p(NIPAM-NIPMAM) microgel content compared to control composites prepared without SPIONs and without microgel, respectively. Reprinted with permission from [90]. Copyright 2015 American Chemical Society.

40°C compared with that at 23°C, because of the collapse of PNIPAM at temperature higher than LCST and consequent compression, which leads to the release of protein.

In addition, a factorial analysis was performed to estimate the influence of different factors on protein delivery. It resulted that the increase in PNIPAM-AAm nanoparticle concentration and temperature allowed higher protein release in the initial burst and sustained burst region, whereas a higher MW of PEGDA allowed a higher release in the plateau region. In another study, chitosan hydrogel embedded with p-(NIPAAm) nanogels was developed for the thermo-responsive release of the antibacterial model drug levofloxacin (LFX) [108]. In this case, p(NIPAAm) hydrogels were synthesized by free radical emulsion polymerization and then added to a methacrylamide functionalized chitosan solution.

Free radical polymerization between methacrylic groups occurred leading to a thermo-responsive nanocomposite hydrogel. Studies about the LFX release revealed that not only the nanocomposite hydrogel presents drug loading capacity higher than hydrogel without nanogels, but also that there is big difference in cumulative drug release behavior. Indeed, while a huge difference in percentage of cumulative drug release was seen for the nanocomposite hydrogels below and above the LCST of NIPAAm, respectively, 25°C and 37°C; no significant difference was seen from the hydrogel without nanoparticles. In addition, the study demonstrated that higher the quantity of nanogels, higher the loading and release of drug.

5. Conclusions

Most of the principal side effects of therapeutic drugs are related to the route of administration, which influences the half-life of drug and its efficacy. New strategies involve the use of thermoresponsive hydrogels to overcome the limitation of commercial drugs. The main advantages of the use of thermo-responsive hydrogels are related to the possibility of being injected in the damaged tissue and release drug locally for a prolonged period. The development of thermoresponsive hydrogels can be performed by using different type of polymers that are intrinsically and not intrinsically thermosensitive. In the second case, particular compound or nanoparticles are used to achieve the same results. Moreover, the addition of nanoparticles inside the hydrogel can allow a local increment of temperature by using different types of sources, which guarantee a non-invasive way of drug administration.

6. Expert opinion

In the recent years, the research is trying to develop innovative systems based on the use of hydrogels to overcome some limitations related to commercial drugs.

Some of the principal disadvantages of commercial drugs are the short circulation time, the fast clearance from the body, and the immunological response. All these side effects are also a consequence of the type of administration. In fact, the route of administration influences the pharmacokinetics, absorption, distribution, and metabolism, and so the safety and efficacy of the drug [136]. This leads to repeated administrations of the drug by the patient along with all negative side effects. For these reasons it is important to provide a controlled, prolonged, and local drug release. Hydrogels represent promising systems for controlled and local drug release. They can be easily injected in a specific site of the body and act as a reservoir able to contain a large quantity of drug and release it in a controlled way. They can allow sustained release of drug in the surrounding environment allowing to avoid drug's circulation in the body [37] and limiting the adverse effect on healthy tissues. Moreover, their ability to provide a prolonged release of drug in a targeted location allows to reduce the time of administration by maintaining a high level of drug in the specific area. Among hydrogels, some of them are made by 'smart polymers' able to respond to stimuli from external environment such as pH, light, or temperature. The main advantage of this polymers is the ability to release drug on demand by simply applying an external stimulus. PNIPAM is the most studied polymer used for the synthesis of thermoresponsive drug delivery systems. It can be copolymerized with other polymers to change the chemical and physical properties of the final system and make it adequate for a specific therapeutic purpose. Other polymers are not intrinsically thermoresponsive but can be used together with organic or inorganic nanoparticles sensitive to external stimuli such as temperature, light, or magnetic field to form a final thermoresponsive hydrogel. In particular, gold nanorods, thanks to their surface plasmonic resonance property, can convert an incident light in the NIR into heat. The increase of temperature in the hydrogel leads to a structural deformation of hydrogel or of organic nanoparticles and the release of drug encapsulated inside. The same effect can be achieved by using alternating magnetic field on iron nanoparticles. In this case, the magnetic field can penetrate deeper into the biological tissues [116–118] compared to the NIR light and have a therapeutic effect in organs or internal region of the body.

In summary, by using thermo-responsive hydrogels for drug delivery it is possible to have an on-demand release drug in a specific region of the body. Moreover, the use of an external stimulus allows a non-invasively route administration of drug and a local distribution of it without damaging healthy tissues. Despite the very promising results, some issues should be solved before reaching clinics [137,138]. First of all, toxicity. Detailed studies are necessary to be sure about the degradation of hydrogels in non-toxic by-products. Moreover, other challenges should be overcome during the translation process, such as hydrogel fabrication and storage, cost, and regulatory complexity. Indeed, their high water content makes sterilization extremely difficult and sterility should be ensured for all manufacturing processes and raw materials. If stored in dry state, to prevent premature degradation, treatment used must guarantee that both its structure and drug bioactivity are unaltered. On the contrary, if maintained in wet state, the storage and transport conditions should minimize water evaporation and unwanted drug loss. Moreover, regulatory concerns can be a big obstacle. Indeed, a hydrogel releasing drug is considered ad a combination product and its regularity approval often take longer time respect to

the neat one. So, the high costs together with limited patent protection can be an issue for their commercial viability.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Klouda L, Mikos AG. Thermoresponsive hydrogels in biomedical applications - a review. Eur J Pharm Biopharm. 2008;68(1):34.
2. Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev. 2012;64:18–23.
3. Hoffman AS. Hydrogels for biomedical applications. Ann N Y Acad Sci. 2001;944(1):62–73.
4. Øvrebø Ø, Perale G, Wojciechowski JP, et al. Design and clinical application of injectable hydrogels for musculoskeletal therapy. Bioeng Transl Med. 2022;7:e10295.
5. Mauri E, Papa S, Masi M, et al. Novel functionalization strategies to improve drug delivery from polymers. Expert Opin Drug Deliv. 2017;14(11):1305–1313.
6. Caron I, Rossi F, Papa S, et al. A new three dimensional biomimetic hydrogel to deliver factors secreted by human mesenchymal stem cells in spinal cord injury. Biomaterials. 2016;75:135–147.
7. Munoz-Robles BG, Kopyeva I, DeForest CA. Surface patterning of hydrogel biomaterials to probe and direct cell–matrix interactions. Adv Mater Interfaces. 2020;7(21):2001198.
8. Webber MJ, Tibbitt MW. Dynamic and reconfigurable materials from reversible network interactions. Nat Rev Mater. 2022;1–16. DOI:10.1038/s41578-021-00412-x.
9. Chai Q, Jiao Y, Yu X. Hydrogels for biomedical applications: their characteristics and the mechanisms behind them. Gels. 2017;3:6.
10. Simões S, Figueiras A, Veiga F, et al. Modular hydrogels for drug delivery. J Biomater Nanobiotechnol. 2012;3(2):185–199.
11. Peppas NA, Langer R. New challenges in biomaterials. Science. 1994;263(5154):1715–1720.
12. Ossipov DA, Hilborn J. Poly(vinyl alcohol)-based hydrogels formed by "click chemistry. Macromolecules. 2006;39(5):1709–1718.
13. Kuo CK, Ma PX. Ionically crosslinked alginate hydrogels as scaffolds for tissue engineering: part 1. Structure, gelation rate and mechanical properties. Biomaterials. 2001;22(6):511–521.
14. Burdick JA, Frankel D, Dernell WS, et al. An initial investigation of photocurable three-dimensional lactic acid based scaffolds in a critical-sized cranial defect. Biomaterials. 2003;24(9):1613–1620.
15. Peppas NA, Bures P, Leobandung W, et al. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000;50(1):27–46.
16. Xu MM, Liu RJ, Yan Q. Biological Stimuli-responsive polymer systems: design, construction and controlled self-assembly. Chinese J Polym Sci. 2017;36(3):347–365. 363. 2017.
17. Sun X, Agate S, Salem KS, et al. Hydrogel-based sensor networks: compositions, properties, and applications - a review. ACS Appl Bio Mater. 2021;4(1):140–162.
18. Jochum FD, Theato P. Temperature- and light-responsive smart polymer materials. Chem Soc Rev. 2013;42(17):7468–7483.
19. Nicoletta FP, Cupelli D, Formoso P, et al. Light responsive polymer membranes: a review. Membranes (Basel). 2012;2(1):134–197.
20. Katsuno C, Konda A, Urayama K, et al. Pressure-responsive polymer membranes of slide-ring gels with movable cross-links. Adv Mater. 2013;25(33):4636–4640.
21. Reinhardt M, Dzubiella J, Trapp M, et al. Fine-tuning the structure of stimuli-responsive polymer films by hydrostatic pressure and temperature. Macromolecules. 2013;46(16):6541–6547.
22. Kim SJ, Kim HI, Park SJ, et al. Behavior in electric fields of smart hydrogels with potential application as bio-inspired actuators. Smart Mater Struct. 2005;14(4):511–514.
23. Wang M, Singh H, Hatton TA, et al. Field-responsive superparamagnetic composite nanofibers by electrospinning. Polymer. 2004;45(16):5505–5514.
24. Thévenot J, Oliveira H, Sandre O, et al. Magnetic responsive polymer composite materials. Chem Soc Rev. 2013;42(17):7099–7116.
25. Tagliazucchi M, Azzaroni O, Szleifer I. Responsive polymers end-tethered in solid-state nanochannels: when nanoconfinement really matters. J Am Chem Soc. 2010;132(35):12404–12411.
26. Tagliazucchi M, Szleifer I. Stimuli-responsive polymers grafted to nanopores and other nano-curved surfaces: structure, chemical equilibrium and transport. Soft Matter. 2012;8(28):7292–7305.
27. Xu MM, Liu RJ, Yan Q. Biological stimuli-responsive polymer systems: design, construction and controlled self-assembly. Chinese J Polym Sci. 2018;36(3):347–365.
28. Dan Z, Cao H, He X, et al. Biological stimuli-responsive cyclodextrin-based host-guest nanosystems for cancer therapy. Int J Pharm. 2015;483(1–2):63–68.
29. Bikram M, West JL. Thermo-responsive systems for controlled drug delivery. Expert Opin Drug Deliv. 2008;5(10):1077–1091.
30. Sponchioni M, Capasso Palmiero U, Moscatelli D. Thermo-responsive polymers: applications of smart materials in drug delivery and tissue engineering. Mater Sci Eng C. 2019;102:589–605.
31. Ward MA, Georgiou TK. Thermoresponsive polymers for biomedical applications. Polym. 2011;3(3):1215–1242.
32. Ebara M, Kotsuchibashi Y, Uto K, et al. Smart Biomaterials. Tokyo: Springer. 2014; p. 9–65.
33. Schild HG. Poly(N-isopropylacrylamide): experiment, theory and application. Prog Polym Sci. 1992;17(2):163–249.
34. Southall NT, Dill KA, Haymet ADJ. A view of the hydrophobic effect. J Phys Chem B. 2001;106(3):521–533.
35. Matanović MR, Kristl J, Grabnar PA. Thermoresponsive polymers: insights into decisive hydrogel characteristics, mechanisms of gelation, and promising biomedical applications. Int J Pharm. 2014;472(1–2):262–275.
36. Kasiński A, Zielińska-Pisklak M, Oledzka E, et al. Smart hydrogels – synthetic stimuli-responsive antitumor drug release systems. Int J Nanomedicine. 2020;15:4541–4572.
37. Norouzi M, Nazari B, Miller DW. Injectable hydrogel-based drug delivery systems for local cancer therapy. Drug Discov Today. 2016;21(11):1835–1849.
38. Agarwal P, Rupenthal ID. Injectable implants for the sustained release of protein and peptide drugs. Drug Discov Today. 2013;18(7–8):337–349.
39. Cao M, Wang Y, Hu X, et al., Reversible thermoresponsive peptide-PNIPAM hydrogels for controlled drug delivery. Biomacromolecules. 2019;20(9):3601–3610.

•• **This study provides a useful understanding on how to influence the physical properties of PNIPAM**

40. Tang S, Zhao L, Yuan J, et al. Physical hydrogels based on natural polymers. Hydrogels Based Nat Polym 2020; 51–89
41. Perale G, Rossi F, Sundstrom E, et al. Hydrogels in spinal cord injury repair strategies. ACS Chem Neurosci. 2011;2(7):336–345.

42. Vihola H, Laukkanen A, Tenhu H, et al. Drug release characteristics of physically cross-linked thermosensitive poly(N-vinylcaprolactam) hydrogel particles. J Pharm Sci. 2008;97(11):4783–4793.
43. Vihola H, Laukkanen A, Valtola L, et al. Cytotoxicity of thermosensitive polymers poly(N-isopropylacrylamide), poly (N-vinylcaprolactam) and amphiphilically modified poly (N-vinylcaprolactam). Biomaterials. 2005;26(16):3055–3064.
44. Bütün V, Armes SP, Billingham NC. Synthesis and aqueous solution properties of near-monodisperse tertiary amine methacrylate homopolymers and diblock copolymers. Polymer. 2001;42 (14):5993–6008.
45. Becer CR, Hahn S, Fijten MWM, et al. Libraries of methacrylic acid and oligo(ethylene glycol) methacrylate copolymers with LCST behavior. J Polym Sci Part A Polym Chem. 2008;46(21):7138–7147.
46. Pakulska MM, Ballios BG, Shoichet MS. Injectable hydrogels for central nervous system therapy. Biomed Mater. 2012;7(2):024101.
47. Kim S, Nishimoto SK, Bumgardner JD, et al. A chitosan/β-glycerophosphate thermo-sensitive gel for the delivery of ellagic acid for the treatment of brain cancer. Biomaterials. 2010;31 (14):4157–4166.
48. Ashraf S, Park HK, Park H, et al. Snapshot of phase transition in thermoresponsive hydrogel PNIPAM: role in drug delivery and tissue engineering. Macromol Res. 2016;24(4):297–304.
49. Okuyama Y, Yoshida R, Sakai K, et al. Swelling controlled zero order and sigmoidal drug release from thermo-responsive poly (N-isopropylacrylamide-co-butyl methacrylate) hydrogel. J Biomater Sci Polym Ed. 1993;4(5):545–556.
50. Bellotti E, Schilling AL, Little SR, et al. Injectable thermoresponsive hydrogels as drug delivery system for the treatment of central nervous system disorders: a review. J Control Release. 2021;329:16–35.
51. Kim S, Lee K, Cha C. Refined control of thermoresponsive swelling/deswelling and drug release properties of poly (N-isopropylacrylamide) hydrogels using hydrophilic polymer crosslinkers. J Biomater Sci Polym Ed. 2016;27(17):1698–1711.
52. Chen S, Zhong H, Gu B, et al. Thermosensitive phase behavior and drug release of in situ N-isopropylacrylamide copolymer. Mater Sci Eng C. 2012;32(8):2199–2204.
53. Alexander A, Ajazuddin KJ, Khan J, et al. Polyethylene glycol (PEG)–Poly(N-isopropylacrylamide) (PNIPAAm) based thermosensitive injectable hydrogels for biomedical applications. Eur J Pharm Biopharm. 2014;88(3):575–585.
54. Kang Derwent JJ, Mieler WF. Thermoresponsive hydrogels as a new ocular drug delivery platform to the posterior segment of the eye. Trans Am Ophthalmol Soc. 2008;106:206–213.
55. Alvarez-Lorenzo C, Concheiro A, Dubovik AS, et al. Temperature-sensitive chitosan-poly(N-isopropylacrylamide) interpenetrated networks with enhanced loading capacity and controlled release properties. J Control Release. 2005;102(3):629–641.
56. Park SY, Kim SY, Kang JH, et al., Design of thermoresponsive hydrogels by controlling the chemistry and imprinting of drug molecules within the hydrogel for enhanced loading and smart delivery of drugs. Mol Syst Des Eng. 2021;6(4):286–292.
•• **This study provides a good strategy for temperature-dependent release of drug from the hydrogel**
57. Mai-ngam K, Boonkitpattarakul K, Sakulsombat M, et al. Synthesis and phase separation of amine-functional temperature responsive copolymers based on poly(N-isopropylacrylamide). Eur Polym J. 2009;45(4):1260–1269.
58. Lue SJ, Chen CH, Shih CM, et al. Grafting of poly (N-isopropylacrylamide-co-acrylic acid) on micro-porous polycarbonate films: regulating lower critical solution temperatures for drug controlled release. J Memb Sci. 2011;379(1–2):330–340.
59. Yoo MI, Sung YK, Cho SC, et al. Effect of polymer complex formation on the cloud-point of poly(N-isopropyl acrylamide) (PNIPAAm) in the poly(NIPAAm-co-acrylic acid): polyelectrolyte complex between poly(acrylic acid) and poly(allylamine). Polymer. 1997;38 (11):2759–2765.
60. Constantin M, Bucatariu S, Harabagiu V, et al. Poly (N-isopropylacrylamide-co-methacrylic acid) pH/thermo-responsive porous hydrogels as self-regulated drug delivery system. Eur J Pharm Sci. 2014;62:86–95.
61. Ohya S, Nakayama Y, Matsuda T. Thermoresponsive artificial extracellular matrix for tissue engineering: hyaluronic acid bioconjugated with poly(N -isopropylacrylamide) grafts. Biomacromolecules. 2001;2(3):856–863.
62. Gan J, Guan XX, Zheng J, et al. Biodegradable, thermoresponsive PNIPAM-based hydrogel scaffolds for the sustained release of levofloxacin. RSC Adv. 2016;6(39):32967–32978.
63. Li J, Yang C, Li H, et al. Cationic supramolecules composed of multiple oligoethylenimine-grafted β-cyclodextrins threaded on a polymer chain for efficient gene delivery. Adv Mater. 2006;18 (22):2969–2974.
64. Li J, Li X, Ni X, et al. Self-assembled supramolecular hydrogels formed by biodegradable PEO-PHB-PEO triblock copolymers and alpha-cyclodextrin for controlled drug delivery. Biomaterials. 2006;27(22):4132–4140.
65. Chen G, Jiang M. Cyclodextrin-based inclusion complexation bridging supramolecular chemistry and macromolecular self-assembly. Chem Soc Rev. 2011;40(5):2254–2266.
66. Ha W, Yu J, Song X-Y, et al., Tunable temperature-responsive supramolecular hydrogels formed by prodrugs as a codelivery system. ACS Appl Mater Interfaces. 2014;6(13):11.
• **This study provides a good strategy to modulate the sol-gel transition temperature**
67. Dabbaghi A, Ramazani A, Farshchi N, et al. Synthesis, physical and mechanical properties of amphiphilic hydrogels based on polycaprolactone and polyethylene glycol for bioapplications: a review. J Ind Eng Chem. 2021;101:307–323.
68. Mishra GP, Tamboli V, Mitra AK. Effect of hydrophobic and hydrophilic additives on sol-gel transition and release behavior of timolol maleate from polycaprolactone-based hydrogel. Colloid Polym Sci. 2011;289(14):1553–1562.
69. Boffito M, Sirianni P, Di Rienzo AM, et al. Thermosensitive block copolymer hydrogels based on poly(ε-caprolactone) and polyethylene glycol for biomedical applications: state of the art and future perspectives. J Biomed Mater Res Part A. 2015;103 (3):1276–1290.
70. Xu S, Wang W, Li X, et al. Sustained release of PTX-incorporated nanoparticles synergized by burst release of DOX·HCl from thermosensitive modified PEG/PCL hydrogel to improve anti-tumor efficiency. Eur J Pharm Sci. 2014;62:267–273.
71. Yan TD, Black D, Savady R, et al. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24(24):4011–4019.
72. Ren Y, Li X, Han B, et al. Improved anti-colorectal carcinomatosis effect of tannic acid co-loaded with oxaliplatin in nanoparticles encapsulated in thermosensitive hydrogel. Eur J Pharm Sci. 2019;128:279–289.
73. Komatsu S, Asoh TA, Ishihara R, et al. Fabrication of thermoresponsive degradable hydrogel made by radical polymerization of 2-methylene-1,3-dioxepane: unique thermal coacervation in hydrogel. Polymer. 2019;179:121633.
74. Russo E, Villa C. Poloxamer hydrogels for biomedical applications. Pharm. 2019;11:671.
75. Attwood D, Collett JH, Tait CJ. The micellar properties of the poly-(oxyethylene) - poly(oxypropylene) copolymer Pluronic F127 in water and electrolyte solution. Int J Pharm. 1985;26(1–2):25–33.
76. Agrawal M, Saraf S, Saraf S, et al. Stimuli-responsive In situ gelling system for nose-to-brain drug delivery. J Control Release. 2020;327:235–265.
77. Giuliano E, Paolino D, Fresta M, et al. Mucosal applications of poloxamer 407-based hydrogels: an overview. Pharm. 2018;10:159.
78. Habeck M. Temperature-sensitive gels: from tissue engineering to drug delivery. Drug Discov Today. 2001;6(11):553–554.
79. Alexander A, Saraf S, Saraf S. Understanding the role of poloxamer 407 based thermoreversible in situ gelling hydrogel for delivery of pegylated melphalan conjugate. Curr Drug Deliv. 2016;13 (4):621–630.

80. Altuntaş E, Yener G. Formulation and evaluation of thermoreversible in situ nasal gels containing mometasone furoate for allergic rhinitis. AAPS PharmSciTech. 2017;18(7):2673–2682.
81. Koffi AA, Agnely F, Ponchel G, et al. Modulation of the rheological and mucoadhesive properties of thermosensitive poloxamer-based hydrogels intended for the rectal administration of quinine. Eur J Pharm Sci. 2006;27(4):328–335.
82. Khan S, Warade S, Singhavi DJ. Improvement in ocular bioavailability and prolonged delivery of tobramycin sulfate following topical ophthalmic administration of drug-loaded mucoadhesive microparticles incorporated in thermosensitive in situ gel. J Ocul Pharmacol Ther. 2018;34(3):287–297.
83. Sridhar V, Wairkar S, Gaud R, et al. Brain targeted delivery of mucoadhesive thermosensitive nasal gel of selegiline hydrochloride for treatment of Parkinson's disease. J Drug Target. 2017;26:150–161.
84. Zhao YZ, Jiang X, Xiao J, et al. Using NGF heparin-poloxamer thermosensitive hydrogels to enhance the nerve regeneration for spinal cord injury. Acta Biomater. 2016;29:71–80.
85. Wang Q, He Y, Zhao Y, et al. A thermosensitive heparin-poloxamer hydrogel bridges AFGF to treat spinal cord injury. ACS Appl Mater Interfaces. 2017;9(8):6725–6745.
86. Boustta M, Colombo PE, Lenglet S, et al. Versatile UCST-based thermoresponsive hydrogels for loco-regional sustained drug delivery. J Control Release. 2014;174:1–6.
87. Zhao X, Wang H, Zou Y, et al. Injectable hydrogel materials for spinal cord regeneration: a review. Biomed Mater. 2012;7(1):012001.
88. Chatterjee S, Hui PCL, wai KC. Thermoresponsive hydrogels and their biomedical applications: special insight into their applications in textile based transdermal therapy. Polym. 2018;10(5):480.
89. Joly-Duhamel C, Hellio D, Djabourov M. All gelatin networks: 1. biodiversity and physical chemistry. Langmuir. 2002;18(19):7208–7217.
90. Chang Y, Xiao L, Tang Q. Preparation and characterization of a novel thermosensitive hydrogel based on chitosan and gelatin blends. J Appl Polym Sci. 2009;113(1):400–407.
91. Normand V, Lootens DL, Amici E, et al. New insight into agarose gel mechanical properties. Biomacromolecules. 2000;1(4):730–738.
92. Graham S, Marina PF, Blencowe A. Thermoresponsive polysaccharides and their thermoreversible physical hydrogel networks. Carbohydr Polym. 2019;207:143–159.
93. Forget A, Christensen J, Lüdeke S, et al. Polysaccharide hydrogels with tunable stiffness and provasculogenic properties via α-helix to β-sheet switch in secondary structure. Proc Natl Acad Sci U S A. 2013;110(32):12887–12892.
94. Schattling P, Jochum FD, Theato P. Multi-stimuli responsive polymers – the all-in-one talents. Polym Chem. 2013;5(1):25–36.
95. Van Hoorick J, Ottevaere H, Thienpont H, et al. Polymer and photonic materials towards biomedical breakthroughs. polym photonic mater towar biomed break. Cham, Switzerland: Springer. 2018; pp. 3–49.
96. Zhao YL, Fraser Stoddart J. Azobenzene-based light-responsive hydrogel system. Langmuir. 2009;25(15):8442–8446.
97. Chiang CY, Chu CC. Synthesis of photoresponsive hybrid alginate hydrogel with photo-controlled release behavior. Carbohydr Polym. 2015;119:18–25.
98. Park KM, Lee SY, Joung YK, et al. Thermosensitive chitosan-Pluronic hydrogel as an injectable cell delivery carrier for cartilage regeneration. Acta Biomater. 2009;5(6):1956–1965.
99. Bhattarai N, Matsen FA, Zhang M. PEG-grafted chitosan as an injectable thermoreversible hydrogel. Macromol Biosci. 2005;5(2):107–111.
100. Alexander A, Saraf S, Saraf S, et al. A comparative study of chitosan and poloxamer based thermosensitive hydrogel for the delivery of PEGylated melphalan conjugates. Drug Dev Ind Pharm. 2015;41(12):1954–1961.
101. Mu M, Li X, Tong A, et al. Multi-functional chitosan-based smart hydrogels mediated biomedical application. Expert Opin Drug Deliv. 2019;16(3):239–250.
102. Abashzadeh S, Dinarvand R, Sharifzadeh M, et al. Formulation and evaluation of an in situ gel forming system for controlled delivery of triptorelin acetate. Eur J Pharm Sci. 2011;44(4):514–521.
103. Saraf S, Ajazuddin AA, Khan J, et al. Advancement in stimuli triggered in situ gelling delivery for local and systemic route. Expert Opin Drug Deliv. 2012;9(12):1573–1592.
104. Yun Q, Wang SS, Xu S, et al. Use of 5-fluorouracil loaded micelles and cisplatin in thermosensitive chitosan hydrogel as an efficient therapy against colorectal peritoneal carcinomatosis. Macromol Biosci. 2017;17:1600262.
105. Muzzarelli RAA. Human enzymatic activities related to the therapeutic administration of chitin derivatives. Cell Mol Life Sci C 532. 1997;53(2):131–140.
106. Liu F, Urban MW. Recent advances and challenges in designing stimuli-responsive polymers. Prog Polym Sci. 2010;35(1–2):3–23.
107. Leach JB, Schmidt CE. Characterization of protein release from photocrosslinkable hyaluronic acid-polyethylene glycol hydrogel tissue engineering scaffolds. Biomaterials. 2005;26(2):125–135.
108. Shin B, Kim J, Vales TP, et al. Thermoresponsive drug controlled release from chitosan-based hydrogel embedded with poly(N -isopropylacrylamide) nanogels. J Polym Sci Part A Polym Chem. 2018;56(17):1907–1914.
109. Wang C, Zhao N, Yuan W. NIR/thermoresponsive injectable self-healing hydrogels containing polydopamine nanoparticles for efficient synergistic cancer thermochemotherapy. ACS Appl Mater Interfaces. 2020;12(8):9118–9131.
110. Zhang H, Guo S, Fu S, et al., A near-infrared light-responsive hybrid hydrogel based on UCST triblock copolymer and gold nanorods. Polym. 2017;9(12):238.

•• **This study provides a good strategy to modulate delivery from hydrogels**

111. Basuki JS, Qie F, Mulet X, et al. Photo-modulated therapeutic protein release from a hydrogel depot using visible light. Angew Chem Int Educ. 2017;56(4):966–971.
112. Moretti L, Mazzanti A, Rossetti A, et al. Plasmonic control of drug release efficiency in agarose gel loaded with gold nanoparticle assemblies. Nanophotonics. 2021;10(1):247–257.
113. Li Z, Chen Y, Yang Y, et al. Recent advances in nanomaterials-based chemo-photothermal combination therapy for improving cancer treatment. Front Bioeng Biotechnol. 2019;7:293.
114. Matai I, Kaur G, Soni S, et al. Near-infrared stimulated hydrogel patch for photothermal therapeutics and thermoresponsive drug delivery. J Photochem Photobiol B Biol. 2020;210:111960.

• **This study provides a new way to induce localized photothermal therapy**

115. Fujigaya T, Morimoto T, Niidome Y, et al. NIR laser-driven reversible volume phase transition of single-walled carbon nanotube/poly(N-isopropylacrylamide) composite gels. Adv Mater. 2008;20(19):3610–3614.
116. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013;12(11):991–1003.
117. Pankhurst QA, Connolly J, Jones SK, et al. Applications of magnetic nanoparticles in biomedicine. J Phys D Appl Phys. 2003;36(13):R167.
118. Stuart MAC, Huck WTS, Genzer J, et al. Emerging applications of stimuli-responsive polymer materials. Nat Mater. 2010;9(2):101–113.
119. Bedanta S, Kleemann W. Supermagnetism. J Phys D Appl Phys. 2008;42(1):013001.
120. Meenach SA, Anderson KW, Hilt JZ. Synthesis and characterization of thermoresponsive poly(ethylene glycol)-based hydrogels and their magnetic nanocomposites. J Polym Sci Part A Polym Chem. 2010;48(15):3229–3235.
121. Crippa F, Moore TL, Mortato M, et al. Dynamic and biocompatible thermo-responsive magnetic hydrogels that respond to an alternating magnetic field. J Magn Magn Mater. 2017;427:212–219.
122. Jalili NA, Jaiswal MK, Peak CW, et al. Injectable nanoengineered stimuli-responsive hydrogels for on-demand and localized therapeutic delivery. Nanoscale. 2017;9(40):15379–15389.

123. Campbell S, Maitland D, Hoare T. Enhanced pulsatile drug release from injectable magnetic hydrogels with embedded thermosensitive microgels. ACS Macro Lett. 2015;4(3):312–316.
•• **This study provides a good strategy to induce delivery by using an alternating magnetic field.**
124. Hendrickson GR, Andrew Lyon L. Microgel translocation through pores under confinement. Angew Chem Int Educ. 2010;49:2193–2197.
125. Knecht LD, Ali N, Wei Y, et al. Nanoparticle-mediated remote control of enzymatic activity. ACS Nano. 2012;6(10):9079–9086.
126. Naseri-Nosar M, Ziora ZM. Wound dressings from naturally-occurring polymers: a review on homopolysaccharide-based composites. Carbohydr Polym. 2018;189:379–398.
127. Hu M, Korschelt K, Daniel P, et al. Fibrous nanozyme dressings with catalase-like activity for H 2 O 2 reduction to promote wound healing. ACS Appl Mater Interfaces. 2017;9(43):38024–38031.
128. Gao W, Jin W, Li Y, et al. A highly bioactive bone extracellular matrix-biomimetic nanofibrous system with rapid angiogenesis promotes diabetic wound healing. J Mater Chem B. 2017;5(35):7285–7296.
129. Pereira RF, Bártolo PJ. Traditional therapies for skin wound healing. Adv Wound Care. 2016;5(5):208–229.
130. Neibert K, Gopishetty V, Grigoryev A, et al. Wound-healing with mechanically robust and biodegradable hydrogel fibers loaded with silver nanoparticles. Adv Healthc Mater. 2012;1(5):621–630.
131. Zhang X, Tian C, Chen Z, et al. Hydrogel-based multifunctional dressing combining magnetothermally responsive drug delivery and stem cell therapy for enhanced wound healing. Adv Ther. 2020;3(9):2000001.
132. Wang S, Yang H, Tang Z, et al. Wound dressing model of human umbilical cord mesenchymal stem cells-alginates complex promotes skin wound healing by paracrine signaling. Stem Cells Int. 2016;2016:1–8.
133. Bagherifard S, Tamayol A, Mostafalu P, et al. Dermal patch with integrated flexible heater for on demand drug delivery. Adv Healthc Mater. 2016;5(1):175–184.
134. Fernández VVA, Aguilar J, Becerra F, et al. Tailoring thermoresponsive nanostructured poly(N-isopropylacrylamide) hydrogels made with poly(acrylamide) nanoparticles. Colloid Polym Sci. 2013;291(8):1829–1842.
135. Sabnis A, Wadajkar AS, Aswath P, et al. Factorial analyses of photopolymerizable thermoresponsive composite hydrogels for protein delivery. Nanomedicine. 2009;5(3):305.
136. Park K. The controlled drug delivery systems: past forward and future back. J Control Release. 2014;190:3.
137. Li J, Paulson JA. Designing hydrogels for controlled drug delivery Nat Rev Mater . 2016;1:16071.
138. Bernhard S, Tibbitt MW. Supramolecular engineering of hydrogels for drug delivery. Adv Drug Deliv Rev. 2021;171:240–256.