



Molecular design, synthesis and biomedical applications of stimuli-responsive shape memory hydrogels

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ABSTRACT

The review article encompasses an overview of the contemporary research related to an arsenal of smart materials i.e., shape memory hydrogels (SMHs). SMHs are instrumental in fixing temporary shapes or recovering permanent ones in response to external stimuli and are playing an increasingly important role in a diverse range of applications including soft robots, artificial mussels, embolic agents and so forth. As cynosure of smart materials, SMHs have attracted considerable attention in recent years owing to their unique functionality. We highlighted the mechanism of the shape memory effect (SME) and the design principle of SMHs coupled with recent advances in four distinct classes of SMHs where SME is triggered in response to temperature, pH, chemicals, and light. Besides, the progress in biomedical applications of SMHs has also been presented.

1. Introduction

Polymers exhibiting shape memory effect, in which the materials are capable of fixing one or more temporary shapes and recovering to their remembered permanent shape under suitable stimuli, can be defined as shape memory polymers (SMPs) [1]. As one of the most important classes of stimuli-responsive polymers, SMPs have made significant progress [2]. The shape memory ability of a classical SMP is generally achieved based on thermal transition (T_{trans} , commonly glass transition temperature T_g or melting temperature T_m) which could determine chain mobility or crystallization [3,4]. Thereby, thermal-induced shape memory effect (SME) can be considered as an intrinsic property for most dried polymers [5]. Inspired by hydrophobic SMPs, a series of shape memory hydrogels (SMHs) were developed by grafting hydrophobic crystallizable side chains onto the hydrophilic backbones of polymer networks in the early days [6–8]. The order-disorder transition of the hydrophobic domains can serve as a temperature sensitive physical crosslinking and thereby endows the hydrogel with thermal-responsive SME. SMHs have a great potential in application areas, such as tissue engineering scaffold, actuators, soft robots, biomedical fields, textiles and information carriers, owing to their soft and wet nature [9–13]. Due to the promising potential applications, SMHs have gained more and more attention from researchers in recent years. The unique aqueous nature and permeability of hydrogel network endow SMHs with the ability to respond to various stimuli which may not easily be applied on hydrophobic SMPs, like pH, chemical and even ultrasound

[13–16]. Thus, in contrast to hydrophobic SMPs, the realization of SME in hydrophilic hydrogel network is more versatile and flexible. In addition, the combination of supramolecular chemistry and functionalization of hydrogel has promoted greatly the development of SMHs, thereby many SMHs with various or multiple functions were fabricated in the past decade [17–19].

Although the research of SMHs has been improved dramatically in recent years, the reported reviews are quite scarce. Additionally, most of them have been aimed at the preparation and general mechanism of SMHs, while their multi-functionalization and the potential applications are rarely reported [17,20,21]. In this review, we recapitulate the advances in SMH research including design, synthesis and potential applications. Moreover, some new viewpoints about the design strategy of responsive SMHs with enhanced functionality have also been provided.

2. The basic mechanism and design principle of stimuli-responsive SMHs

Stimuli-responsive SMHs involve the fixation of programmed temporary shapes and recovery of the permanent shape. Compared to the swelling-induced shape change effect in which complex shape change could be obtained by anisotropic swelling (e.g. bi-layer hydrogels based on poly(*N*-isopropylacrylamide)), the SME is different not only in the mechanisms underlying the active movement but also in the energy barriers [22–26].

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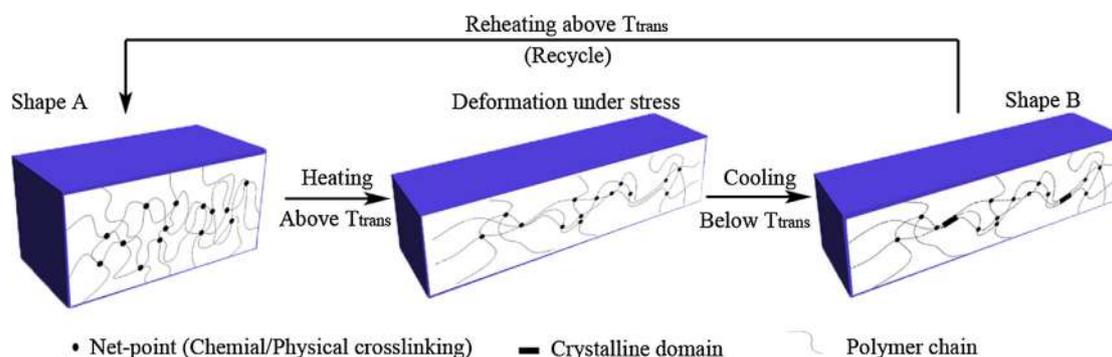


Fig. 1. The shape memory cycle of typical thermally induced dual-SME for typical hydrophobic semi-crystalline hydrophobic SMPs.

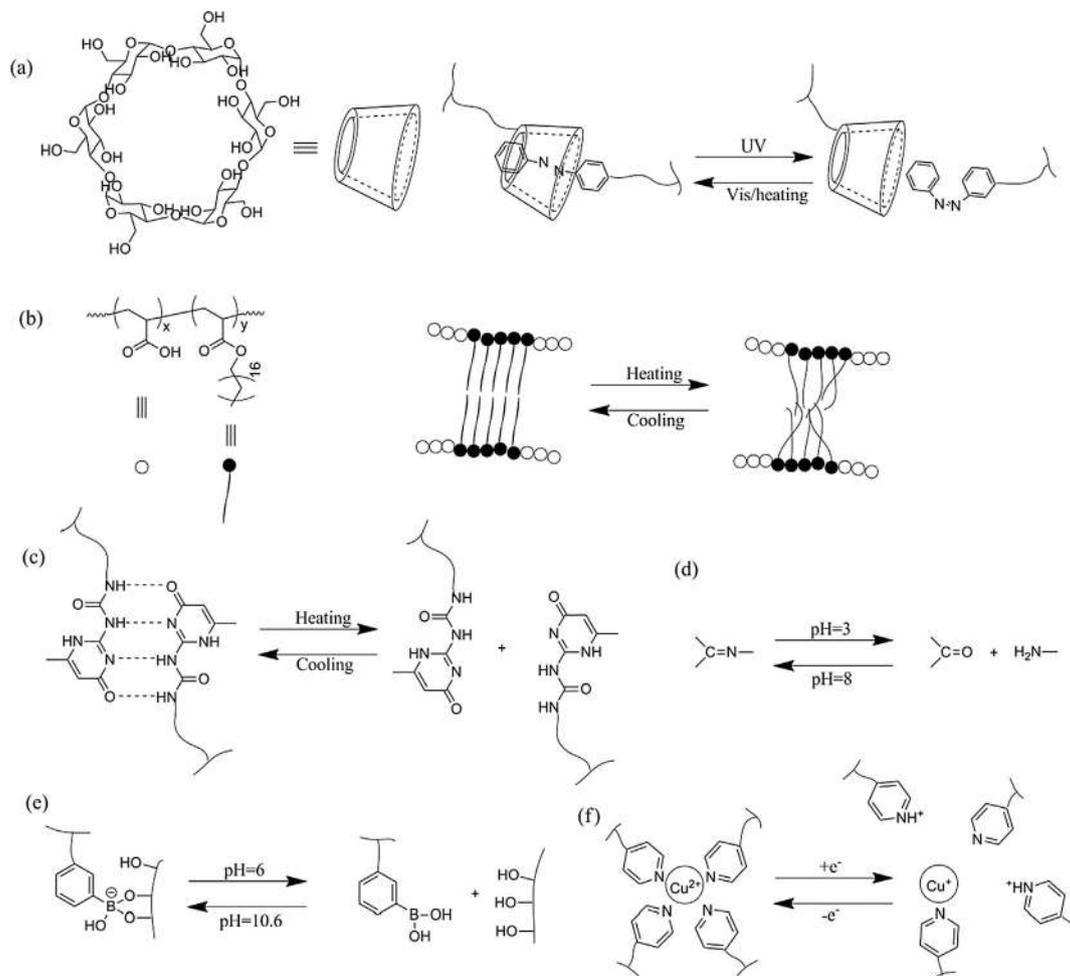


Fig. 2. Selective examples of supramolecular interactions and dynamic covalent bonds that are used as stimuli-responsive molecular switches: (a) α -CD/Azo host-guest interactions; (b) order-disorder transition of crystalline domains from hydrophobic n-alkyl acrylate units; (c) self-complementary quadruple hydrogen bonds of Upy couple; (d) Schiff base bonds; (e) PBA-diol ester bond; (f) pyridine- Cu^{2+} coordination. (Reproduced from Ref. [36] with permission from the the American Chemical Society.)

Overall, similar to hydrophobic SMPs, the design of a SMH should also meet two structural requirements. One is the hard segment, and another is the “switching segment” [27,28]. The hard segment we define here is not just the concept of “hard segment” in the early SMPs like shape memory polyurethane. It represents a stable network constructed by net-points which remain stable during the actuation of SME. Hard segment defines the permanent shape and is responsible for driving the recovery of the deformation from the temporary shape to the original shape (or permanent shape), whereas the switching segment serves as a stimuli-sensitive switch to fix or recover the temporary shapes [13,20].

It is worth pointing out that the switching segment is responsible for stabilizing the temporary shape, however, the final state or the morphology of the temporary shape that stably display is the result of the combined effect of the two segments since both segments contribute to the network architecture of the hydrogel with the formed temporary shape [29–31].

Typically, chain segments or domains with transition temperature, T_{trans} , can serve as switching segment to endow a polymeric network with the ability of SME. T_{trans} can either be a glass transition, T_g , for an amorphous polymer or a melting temperature T_m for a crystalline

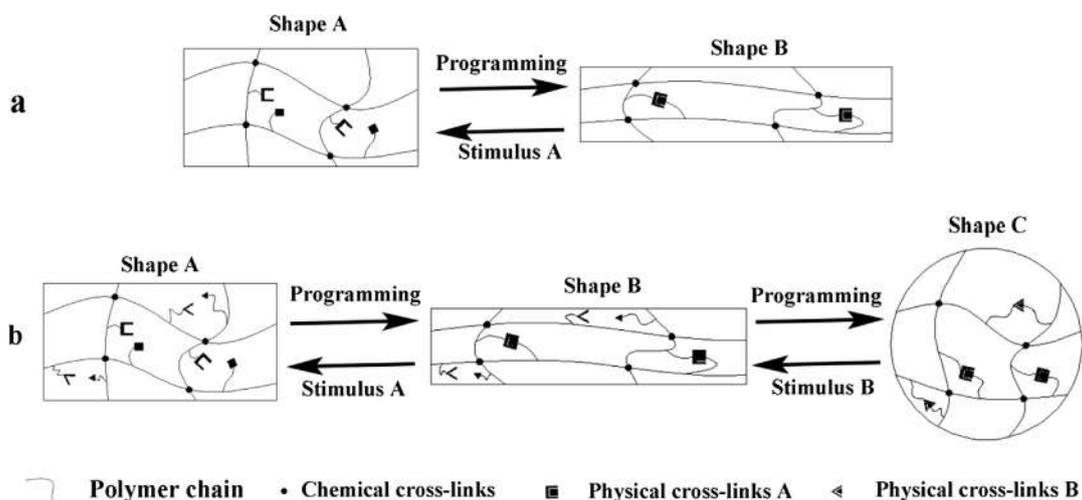


Fig. 3. Typical polymeric network architectures with (a) dual-SME and (b) triple-SME for SMHs.

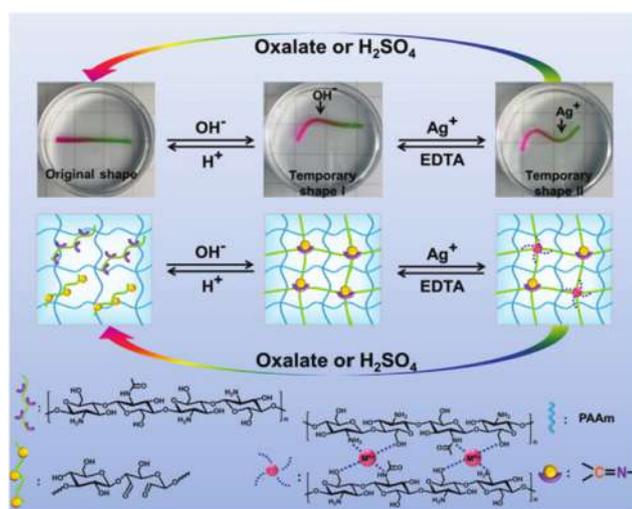


Fig. 4. Triple-SME of the SMH fabricated including Schiff base bonds and CS-Ag⁺ coordination interactions as molecular switches. (Reproduced from Ref. [38] with permission from the Royal Society of Chemistry.)

polymer. An intact shape memory cycle for a semi-crystalline hydrophobic SMP with dual-SME has been described in Fig. 1. As shown, the permanent shape (shape A) is supported by the net-points which may be from chemical crosslinking or even physical crosslinking like chain entanglement, while the generated crystalline domains can serve as temporary crosslinking to fix the polymer at a temporary shape (shape B). The sample is heated at the start and deformed under programming stress above the T_{trans} , and then temperature is cooled down to fix the deformation owing to the formation of the crystalline domain which serves as temporary crosslinking. Consequently, a temporary shape B can be obtained. The temporary shape is stable after removing the programming stress as a result of the formation of temporary crosslinking. Reheating the sample above the T_{trans} induces the melting of the crystalline domains, thereby leads to the release of the entropic energy at molecular level and the shape recovery at macroscopic level.

In the early days, many SMHs were developed inspired by conventional thermal-induced hydrophobic SMPs [6–8]. Although the SME mechanism of the SMHs is similar to that of hydrophobic SMPs, their molecular structure is largely different [21]. In contrast to hydrophobic SMPs, the design of SMHs has to take the aqueous environment into account. For example, many crystalline domains from the hydrophilic chains may not form in the presence of water [21]. By incorporating hydrophobic side chains (typically, long alkyl chain segments) into the

hydrophilic network of hydrogel, thermal-responsive SME could be realized easily via the temperature sensitive order-disorder transition of the hydrophobic domain [6].

Compared to dried hydrophobic polymers, the 3D polymeric network of a hydrogel allows the penetration of molecules, making the realization of SME to be more flexible. In light of the high binding energy of covalent bonds, chemical cross-linking usually plays a very important role in the design of the hard segment [32,33]. However, physical crosslinking tends to be more favored by researchers in recent years, because of its functionality to the network [34,35]. In all events, the net-point which is responsible for permanent shape should be kept stable enough to certain stimuli to ensure the structure of “hard segment” is not affected during the SME cycle. Otherwise, the original shape (or permanent shape) can be disturbed or shifted.

Switching segment involves the fixing of deformed shape and the releasing of deformation energy through the reversible formation-breakage of temporary net-point. In the past years, methods based on covalent bonds and physical interactions ranging from reversible covalent bond to supramolecular interactions including metal-ligand coordination [36], phenylboronic acid (PBA)-diol ester bonds [37], Schiff base bonds [38], hydrogen bonds [18,39], host-guest interactions [40], hydrophobic interactions [32,41], etc., are widely used as molecular switches (switching segments at molecular level) in the designing of the switching segment to enable shape switching of hydrogel networks. Fig. 2 provides some selective examples of molecular switches that endow hydrogels with SME. Due to the reversible nature, the crosslinks formed by different molecular switches in the SMHs are switchable (on-off) when exposed to corresponding stimuli such as light, heat, ion species and pH [13,32,42].

Generally, a typical dual-SMH contains only one switching segment [32,33], while integrating two or more types of switching segments into one ensemble allows the hydrogel to be capable of fixing two or more temporary shapes via applying non-interfering stimuli to exhibit triple or multiple SME [41]. As illustrated in Fig. 3a hydrogel with a single network constructed via chemical cross-links and physical cross-links A could exhibit a dual-SME, while triple SME will be realized when two non-interfering physical cross-links, A and B, are employed in the network (Fig. 3b). Similarly, introducing more non-interfering switching segments can endow the hydrogel with multi-SME. For instance, a SMH that was fabricated with two types of molecular switches-Schiff base bonds and chitosan-Ag⁺ (CS-Ag⁺) coordination interactions, showed a triple-SME (Fig. 4) [38]. As shown, the strip hydrogel was firstly immersed into an alkaline buffer solution (pH = 8), a temporary shape I was fixed as a result of the formation of Schiff base bonds. After that the immersion in AgNO₃ aqueous solution induced the formation of CS-

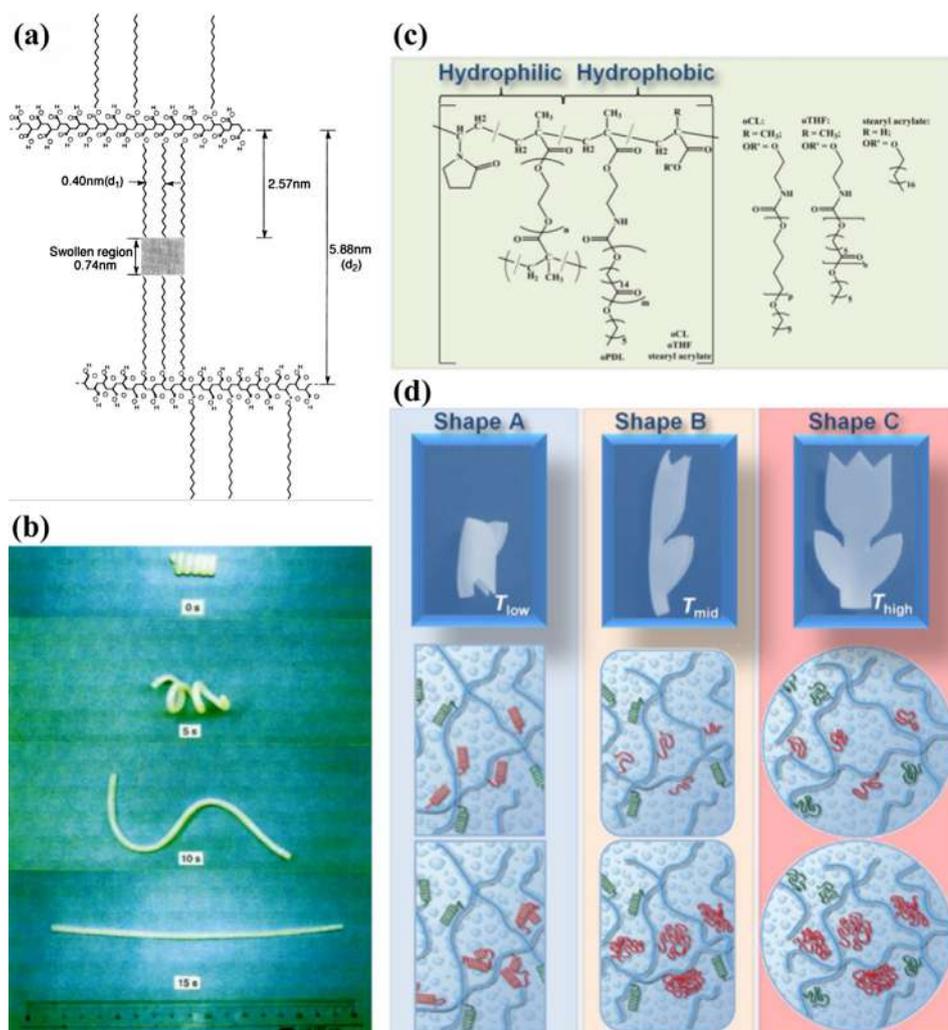


Fig. 5. Thermal responsive SMHs fabricated using crystallizable hydrophobic side chains. (a) Chemical structure of poly(SA-co-AA) (Adapted from Ref. [8] with permission from the the American Chemical Society); (b) an illustration of shape memory effect for the hydrogel with the long alkyl chains incorporated in the network (Reproduced from Ref. [6] with permission from the Nature Publishing Group); (c) chemical structure of the SMH with various types of monofunctionalized oligomers in the network; and (d) the triple-shape memory effect in response to temperature. (Reproduced from Ref. [27] with permission from the American Chemical Society.)

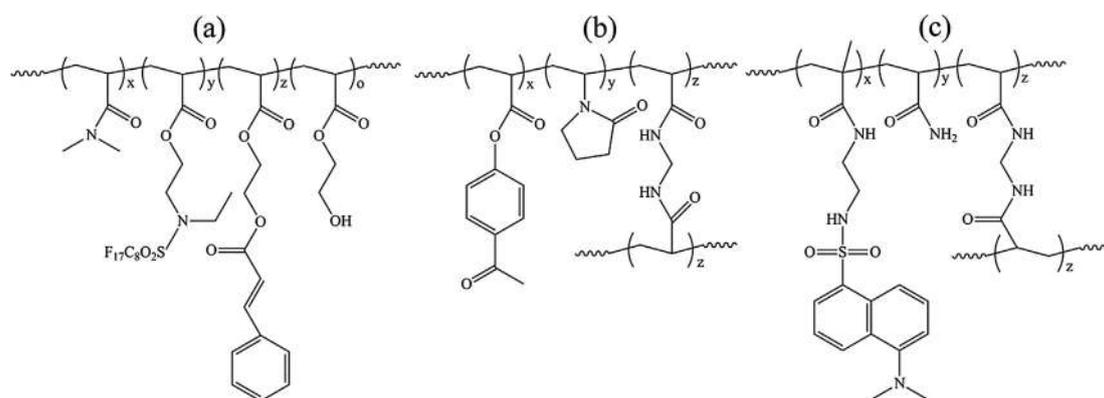


Fig. 6. Chemical structures of SMHs based on hydrophobic interactions of (a) FOSM, (b) AAP and (c) dansyl groups. (Reproduced from Refs. [32,33,51] with permission from the American Chemical Society.)

Ag^+ coordination interactions, as a consequence the second temporary shape can be fixed. Both the two types of temporary crosslinking contributed to the formation of the final “N” shape. After transferring the “N” shaped hydrogel into the aqueous solutions of EDTA and acetic acid–sodium acetate (pH = 3) sequentially, the “N” shape gradually recover to the temporary shape I and finally the original shape was observed. Moreover, the “N” shape can also be recovered by using oxalate or H_2SO_4 as stimuli due to the acidic nature and the strong binding ability of oxalate and H_2SO_4 to Ag^+ [38]. Thus, it is possible for researchers to design their expected SMHs through a modular way. For

example, integrating molecular switches like α -CD/Azo host-guest interaction and PBA-diol ester bond into one hydrogel network in the present of chemical crosslink as permanent net-point may endows the hydrogel with a triple-SME in response to UV and pH.

3. Molecular design and synthesis of stimuli-responsive SMHs

The SME of a SMH is highly dependent on the switching segments introduced in the network as was already been described [21]. The type of switching segment plays a dominant role in determining which types

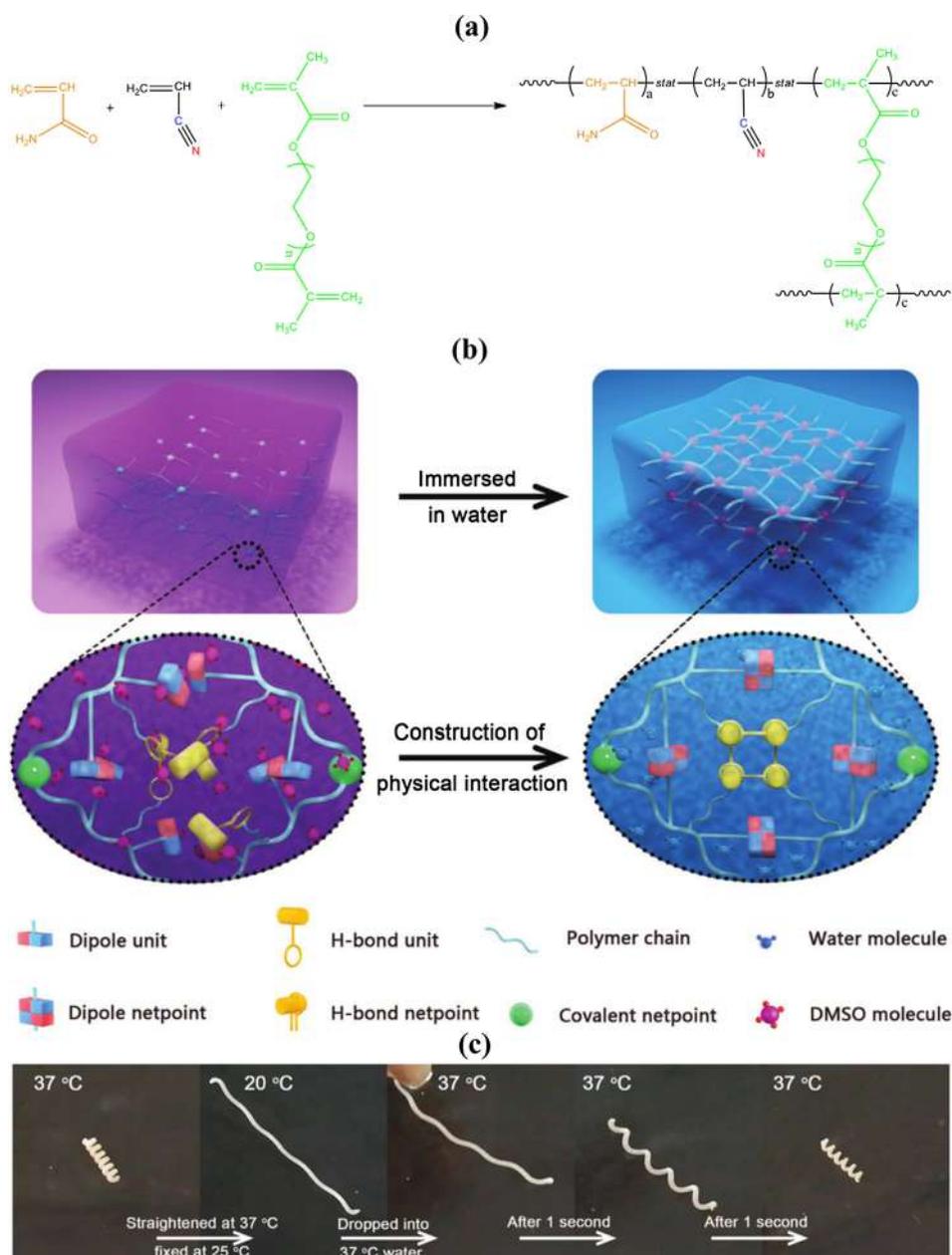


Fig. 7. SMH fabrication based on dipole-dipole interactions and hydrogen bonds and the SME in response to temperature. (a) The copolymerization of the crosslinked PAN-PAAm-PEG3kMDA hydrogel; (b) schematic illustration of the synergistic effect of the dipole-dipole interactions and hydrogen bonds in the hydrogel and the formation of dual physical crosslinking construction on immersing the as-prepared hydrogel into water; (c) the depiction of the shape memory cycle of the hydrogel in response to temperature. (Reproduced from Ref. [55] with permission from John Wiley and Sons.)

of applied stimuli can activate the SME [17]. In this section, we will focus on the molecular design and synthesis of SMHs that activate in response to temperature, pH, chemicals, and light. These stimuli have attracted the scientific interest due to their facile fabrication, potential application in physiological conditions, and easier manipulation [36–38].

3.1. Thermal-responsive SMHs

Generally, thermal-responsive SMHs can be classified into two parts. Thermally induced SME of SMHs, particularly in early stage, is in most situations realized by direct temperature action [13,33,43–45]. Additionally, SME realized in response to indirect heating that employs other forms of energy including photo, electric, magnetic and ultrasonic energy etc., as heat sources has already attracted more attention in

recent years [14,30,42,46,47]. Compared to the SME that is induced by direct heating, the indirect mode is more flexible in context to application due to its abilities of response to versatile stimuli. However, in this case, the fabrication process is more complex because functional fillers such as nanogold, nano platinum, graphene oxide (GO) and Fe₃O₄ particles, acting as energy conversion medium, are required to incorporate into the SMHs [20,46,48].

As one of the most important classes of SMHs, thermal-responsive SMHs have been investigated in depth [32,46]. The design of reversible segment based on T_{trans} (T_g , T_m) [33,49] and some temperature sensitive interactions like hydrogen bonds [43,50], dipole-dipole interaction [45], coil-helix transition [13] hydrophobic interactions [51] enrich the family of thermal-responsive SMHs.

Inspired by conventional hydrophobic SMPs based on T_{trans} , SMHs can be developed by introducing switching segments in which long

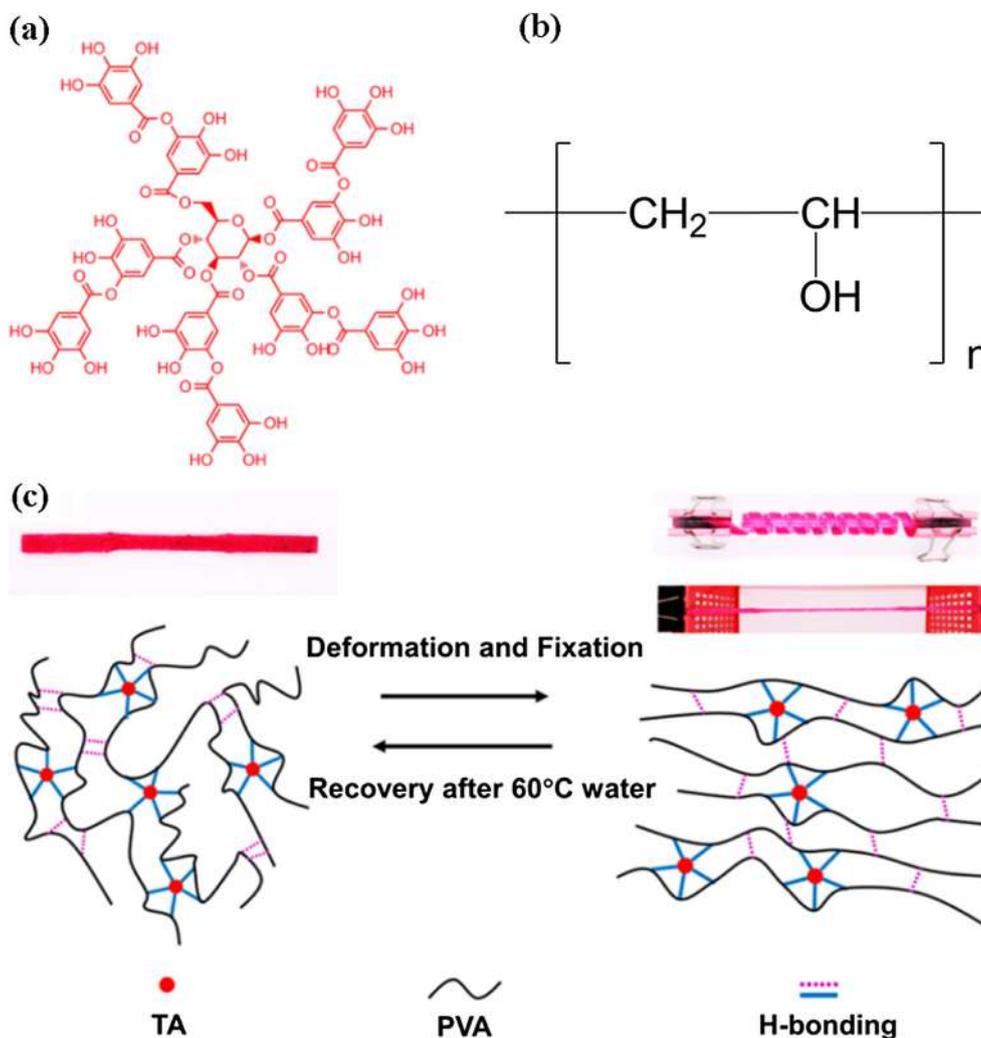


Fig. 8. The PVA-TA hydrogel network and its thermal-responsive SME. (a, b) The chemical structure of TA and PVA; (c) the thermal-responsive SME. (Reproduced from Ref. [59] with permission from the American Chemical Society.)

crystallizable hydrophobic side chains are grafted on the hydrophilic backbone [52]. These long hydrophobic side chains tend to aggregate to form temperature sensitive crystalline domains which act as reversible temporary cross-links [53]. Osada et al. [6,8] synthesized a thermal-responsive SMH (Fig. 5a, b) by the copolymerization of acrylic acid and *n*-stearyl acrylate. The long alkyl side chains of the *n*-stearyl acrylate units adopted a crystalline aggregate structure from an amorphous state due to the interactions between the long alkyl side chains when temperature was decreased from 50 °C to 25 °C, making its Young's modulus increase drastically by about two orders of magnitude. The drastic change in Young's modulus rendered the copolymer material with the ability to retain the deformation energy below 25 °C. However, the deformation energy was released completely when the temperature reached above 50 °C. Similar to triple- or multi-SMPs that can fix two or more temporary shapes under different temperatures *via* distinct T_{trans} , SMHs with different types of hydrophobic side chains that possess different T_{trans} in the hydrophilic network also exhibit triple- or multi-SME, accordingly. Lendlein et al. [27] developed a triple-SMH in response to the temperature by cooperating different crystallizable segments. In their work, stearyl acrylate and various types of monofunctionalized oligomers with distinct T_m (with at least 20 K of difference in temperature) in the order of oligotetrahydrofuran (σ THF) < oligo(ϵ -caprolactone) (OCL) < oligo(ω -pentadecalactone) (OPDL) as side chains grafted on the hydrophilic backbone of the hydrogel network were used to fabricate a series of SMHs as shown in

Fig. 5c, d. Each SMH had two switching segments consisting of OPDL and another hydrophobic side chain, thereby exhibiting two different T_{trans} ($T_{trans1} < T_{trans2}$). In order to realize the triple-SME, the two temporary shapes could be systematically programmed by gradually decreasing the surrounding temperature from T_{high} to T_{mid} ($T_{mid} < T_{trans2} < T_{high}$) and from T_{mid} to T_{low} ($T_{low} < T_{trans1} < T_{mid}$). The temporary shapes were fixed owing to the formation of physical cross-links by the crystallization of the two distinct switching segments. The shape fixity ratios (R_f) of the temporary shapes were dependent on the weight content of the related switching domains [27].

Hydrophobic motifs or non-polar portions of molecules are tended to aggregate spontaneously in the aqueous environment, which is known as hydrophobic interactions in stabilizing protein structure, providing an inspiration of reversible cross-linking formation for SMHs [32,54]. Hao et al. [33] used a random copolymerization of four monomers including hydrophilic monomers *N,N*-dimethylacrylamide (DMA) and hydroxyethyl acrylate, hydrophobic monomer 2-(*N*-ethylperfluoro-octanesulfonamido) ethyl methacrylate (FOSM) and chemical crosslinker 2-cinnamoyloxyethyl to synthesize SMHs with a dual thermal-responsive SME (Fig. 6a). The temporary shape could be fixed by the strong hydrophobic interactions of the FOSM species at a temperature below T_g (about 45 °C) of the formed hydrophobic nanodomains. In contrast to many SMHs fabricated based on crystallizable *n*-stearyl acrylate, the hydrogels prepared in this work remain their soft

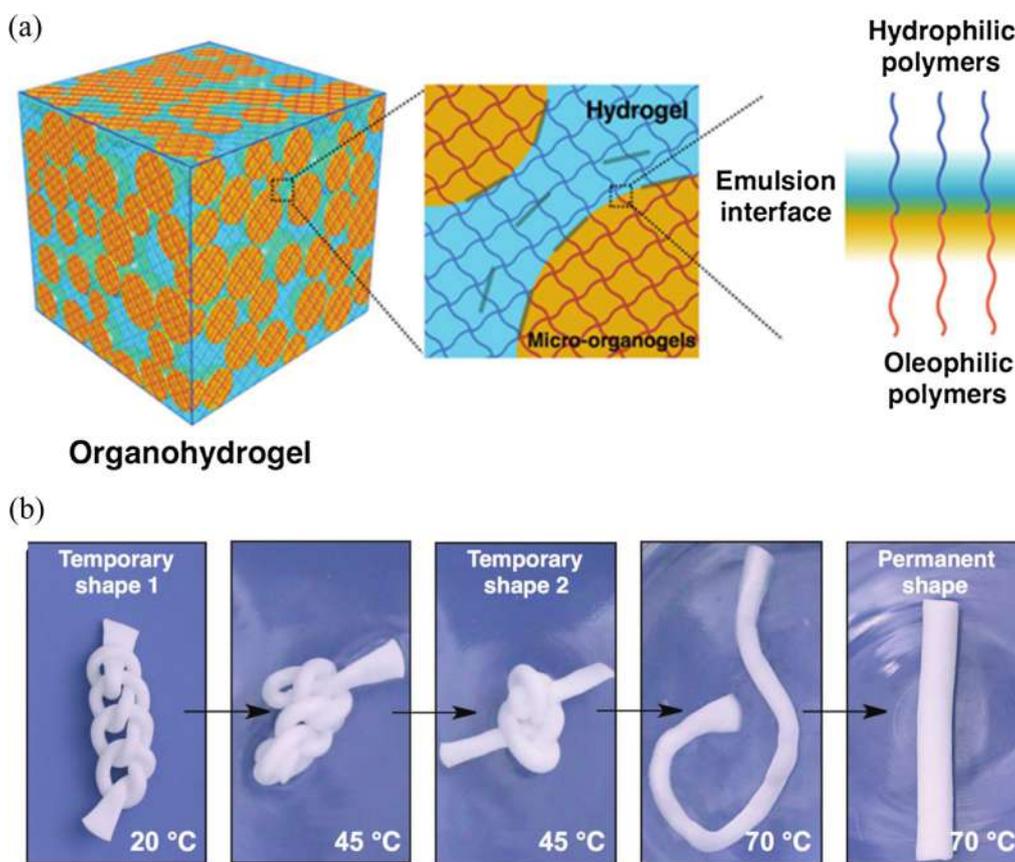


Fig. 9. The network architecture and SME of the organohydrogel. (a) Schematic illustration of the structure of the organohydrogels. (b) Photographs demonstrate the triple-SME of the organohydrogel including two different oil phases with distinct T_m in microorganogel domains (oil phase: octadecane with $T_m = 28^\circ\text{C}$ and paraffin wax with $T_m = 65^\circ\text{C}$, same ratio). (Reproduce from Ref. [64] with permission from John Wiley and Sons.)

state in both permanent and temporary shapes (i.e., the states of association and dissociation of hydrophobic FOSM species). Similar to this work, hydrophilic network bearing hydrophobic acetophenone moieties [51] (Fig. 6b) and dansyl groups [32] (Fig. 6c) also exhibited excellent thermal-responsive SME. The acetophenone moieties form strong hydrophobic interactions and possibly π - π stacking in aqueous environment, acting as temperature-sensitive physical crosslinking. The hydrogel prepared with same mole ratio of acryloxy acetophenone (AAP) and N-vinyl-pyrrolidone (NVP) showed a value of R_f almost 100% and a value of R_r about 90%. In this system, temporary shapes could be fixed at 25°C , and the shape recovery rate was strongly dependent on temperature. The dansyl groups attached on the covalent crosslinked polyacrylamide chain tend to aggregate in aqueous solution of pH above 5 because of the pH triggered hydrophilic-hydrophobic transition. Therefore, it can be concluded that SMHs prepared based on dansyl groups will exhibit SME in response to both temperature and pH [32] (pH-responsive SME will be discussed in the following section.)

In addition, supramolecular interactions like dipole-dipole interactions, host-guest interactions and hydrogen bonds have become a technology-push in designing SMHs nowadays. Zhang et al. [55] reported a thermal-responsive SMH based on reversible hydrophobic dipole-dipole interactions from cyano dipole pairings. The hydrogels were synthesized using acrylonitrile (AN), acrylamide (AAM), long flexible PEG-3kDMA as dipole monomer, hydrogen-bonding monomer and chemical cross-linker (Fig. 7a). Polymerizations were carried out by free radical thermal initiation using dimethyl sulfoxide (DMSO) as solvent to produce organogels. The as-prepared organogels displayed very weak mechanical properties due to the dissociation of cyano dipole pairings and amide hydrogen bonds in DMSO. However, the tensile strength increased about 300-fold after replacing the DMSO by immersing the organogel in water to form strong hydrophobic dipole-dipole interactions and weak hydrophilic hydrogen bonds (Fig. 7b). As expected, dipole-dipole pairing microdomains formed due to the

interactions between cyano dipole pairings from polyacrylonitrile and stabilized the hydrogen bonds of AAM, leading to a drastic increase in Young's modulus of the hydrogels. Owing to the strong temperature-dependence of the physical cross-links, the hydrogel sample could be softened by heating or even applying temperature of the fingers, hinting at a body-temperature responsive SME. As shown in Fig. 7c, a temporary strip shape was fixed at 20°C from the permanent coil shape, and the temporary shape was released after a few seconds at 37°C due to the temperature induced dissociation of dipole-dipole interactions. The study on the shape memory behavior showed that the R_f of the hydrogels fabricated in this work were as high as 97.5%.

Hydrogen bonding, an important interaction playing a key role in chemical, physical, and biochemical processes, which shows strong temperature dependence to its strength [56–58]. Due to the temperature sensitive nature, polymeric network with the groups or polymer segment which are capable of forming hydrogen bonds may be employed in SMHs. One of the most typical examples is the polyvinyl alcohol (PVA) based polymeric network [59,60]. By using a repeated freezing-thawing (FT) method, a PVA hydrogel can be easily obtained from a liquid solution state due to the formation of crystalline domains which serve as physical cross-links produced by the enhanced hydrogen bonds between the hydroxyl groups after each freezing-thawing cycle [61,62]. Crystalline domains and hydrogen bonds can be dissociated easily under elevated temperature. Thereby, they can be introduced in SMHs as switching segments. Li et al. [60] fabricated a SMH with a double network composed of poly(ethylene glycol) (PEG) and PVA. The double network was obtained via chemical cross-linking of PEG chain in the presence of dissolved PVA following by freezing-thawing treatment to form the physical cross-links. The crystalline domains of PVA served as switching molecules to stabilize the deformation after removing the external force. The subsequent heating led to the melting of crystalline domains, causing the recovery of the permanent shape. Shape memory behavior showed that more cycles of freezing/thawing resulted in a

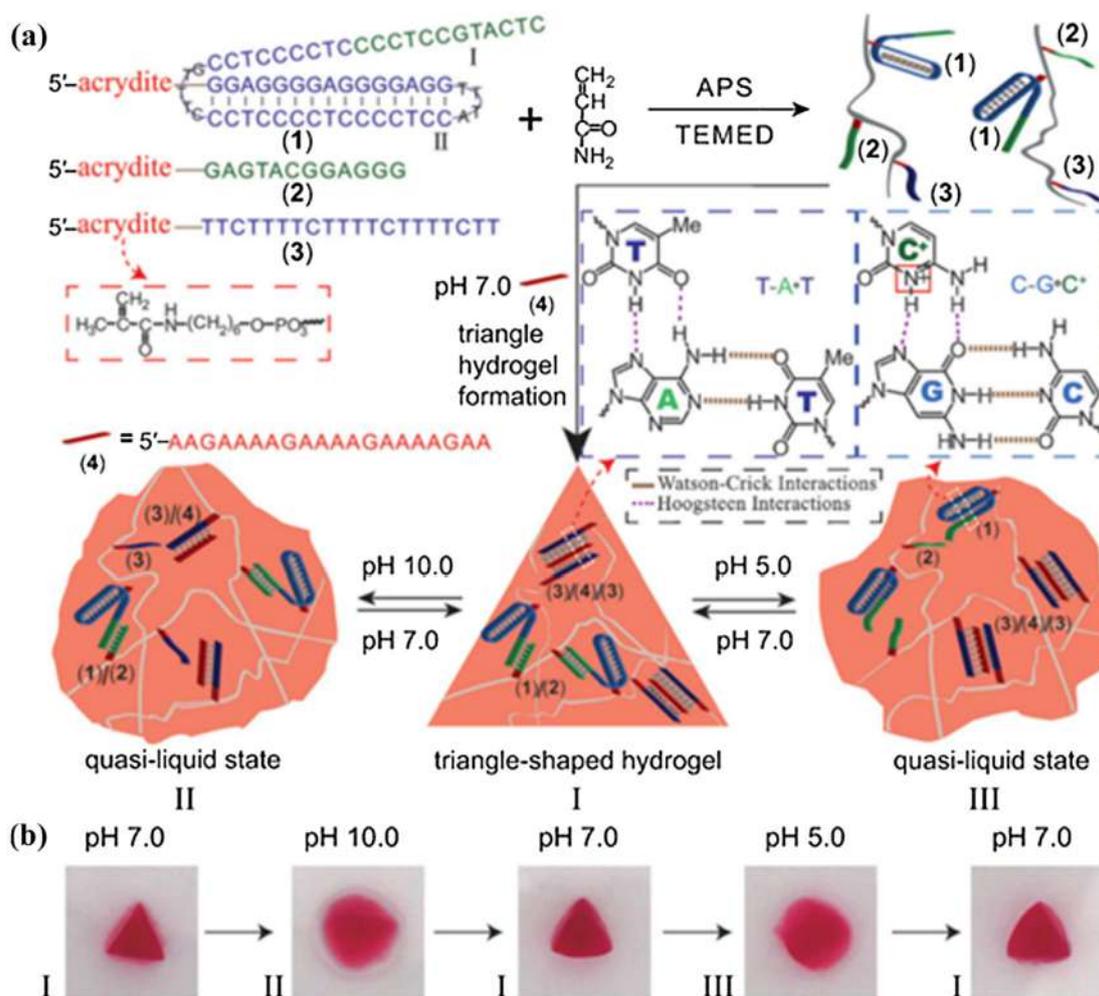


Fig. 10. (a) Synthesis of the DNA hydrogel with the network formed by the polyacrylamide backbone and two different pH-responsive cross-linking motifs. Both of the cross-linking elements stabilize the triangle-shaped hydrogel structure at pH 7, while the pH sensitivity of the two cross-linking units to acidic and alkaline environment, respectively, causes the reversible gel-quasi-liquid transition. (b) The photographs display the SME of the DNA hydrogel in response to pH change. (Adapted from Ref. [69] with permission from John Wiley and Sons.)

better R_f and higher shape recovery temperature, which was likely attributed the formation of more stable crystalline microdomains.

Similar work was reported by Chen et al. [59] as illustrated in Fig. 8. Tannic acid (TA), a compound bearing many functional groups that can form hydrogen bonds, was introduced into the PVA network by physical mixing. There were two sets of hydrogen bonds existing in the hydrogel network: a stronger one formed by TA with PVA and a weaker one formed by the hydroxyl groups between PVA chains. XRD patterns didn't show the typical peaks of PVA crystallites for the PVA-TA hydrogel, revealing that the formation of crystalline microdomains was inhibited by the formation of strong H-bonding between PVA and TA. Thereby, the stronger hydrogen bonds between TA and PVA were considered as permanent net-points to stabilize the permanent shape, while the weaker one served as temperature sensitive switching segments to fix the deformed shape at low temperature. The permanent shape could be recovered by immersing the hydrogel in 60 °C water, which is attributed to the heat triggered breakage of physical cross-links from the weak hydrogen bonds between PVA chains.

Recently, the reported shape memory organohydrogels brought a new perspective for the design and fabrication of shape memory hydrogel materials [63,64]. In their work, an *in situ* heterophase emulsion polymerization technique was employed to produce a heteronetwork which features binary cooperative phase. A representative architecture of the organohydrogel network is illustrated in Fig. 9a. The network was constructed with distributed micro-organogels and an elastic

hydrogel framework, in which the hydrophilic and oleophilic polymer chains were covalently linked at the emulsion interface. The oil phase in the micro-organogel domains acted as a temperature-sensitive switch to fix or recover the programmed temporary shapes *via* phase transition. The trigger temperature of the SME is relative to the T_m of the oil phase, thereby a triple-SME could be easily realized by applying two different oil phases with distinct T_m (Fig. 9b).

3.2. pH-responsive SMHs

As a fundamental physiological parameter, pH plays a vital role in biological system. It is well known that physiological pH in different sites of the human body varies greatly under physiological and pathological conditions, and pH therefore becomes a significant parameter for detecting diseases [65,66]. Because of the promising applications in the healthcare and biomedicine, pH-responsive SMHs have attracted substantial interest [13,15,32,37,41,67,68]. pH-responsive SMHs can realize SME in response to the pH variation of the environment by introducing pH sensitive “elements” in their polymeric networks. These “elements” can be any groups or motifs of molecules by which temporary cross-links can reversibly break and reform in response to pH, such as some host-guest interactions [67], phenylboronic acid (PBA)-diol ester bonds [37], some acid or alkaline groups [41], pH-sensitive duplex DNAs and i-motif units [15,68,69] and even metal-ligand coordination [70], and so forth.

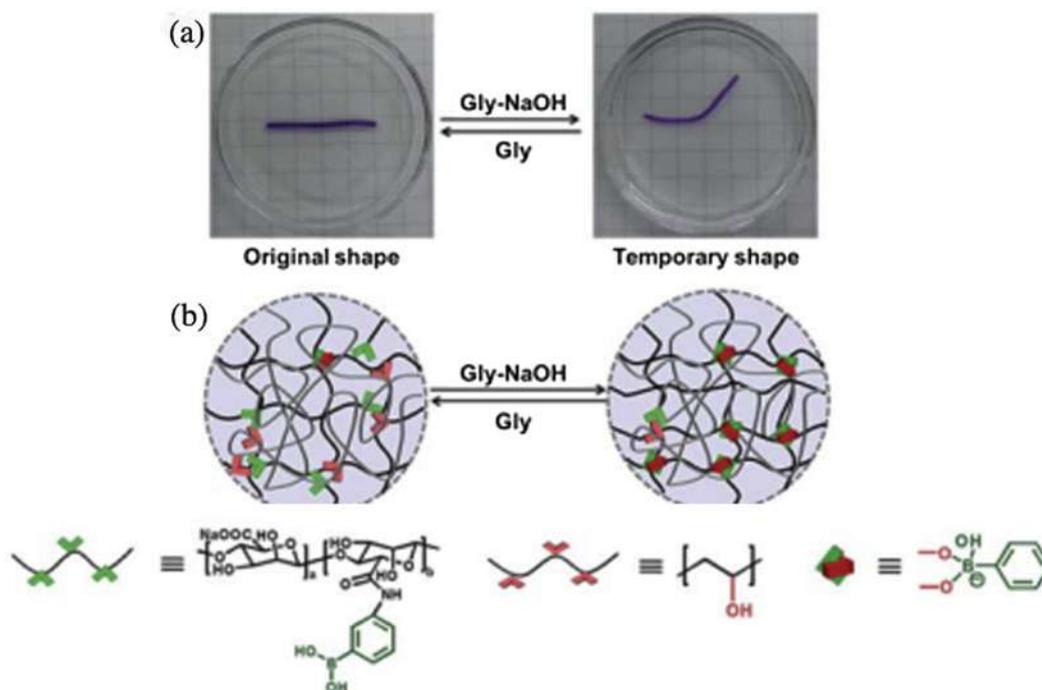


Fig. 11. (a) The PBA-diol ester bonds formed by PBA and hydroxyl groups of PVA in Gly-NaOH (pH = 10.6) are strong enough to stabilize the deformed shape, and the recovery of the permanent shape was observed after immersing the hydrogel in a weakly acidic (pH = 6) Gly solution. (b) Schematic illustration of the topological change in polymeric network during the shape memory cycle. (Reproduced from Ref. [37] with permission from the Royal Society of Chemistry.)

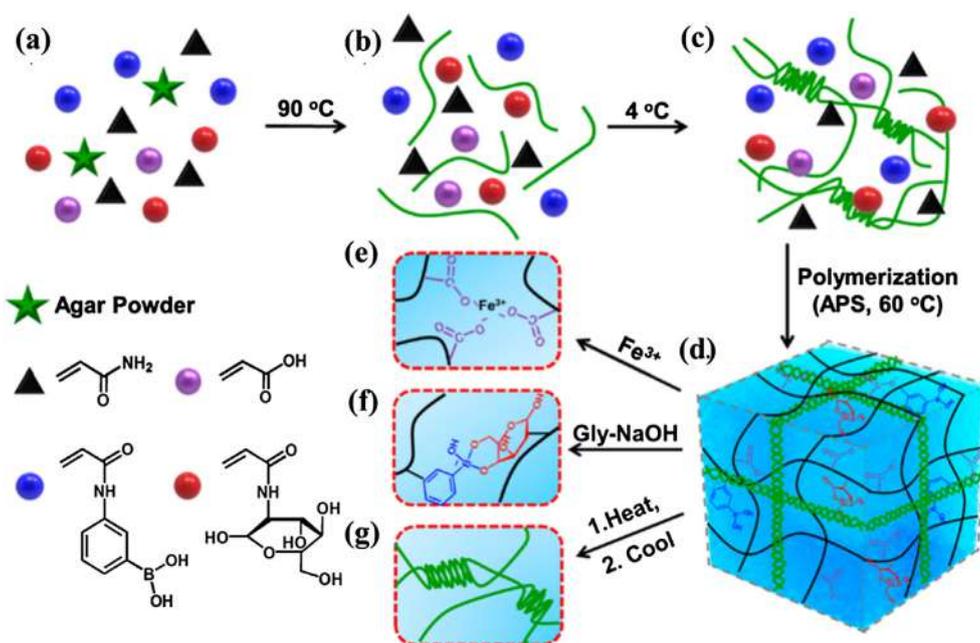


Fig. 12. (a–d) Schematic illustration of hydrogel fabrication and the network formation; (e–g) The triple-SME realization by coordination interactions between Fe^{3+} and carboxyl groups, dynamic covalent bonds formed by PBA and glucosamine and helix-coil transition of agar as physical cross-links, respectively. (Reproduced from Ref. [13] with permission from the American Chemical Society.)

Cyclodextrins (CDs), which consist of different number of glucose units from 6 to 8 (α -, β -, γ -), are a class of cyclic compounds with hydrophobic cavities [71]. CDs can selectively form host-guest inclusion complexes with a range of molecules or polymer chains. The formation of inclusion complexes, which are mainly driven by the hydrophobic interactions or hydrogen bonds between the CDs and guest molecules, can be used as temporary cross-linking net-points to fix the temporary shapes. As reported, some host-guest interactions between CDs and cationic polymeric guests are sensitive to pH [72,73]. Han et al. [74] discovered pH-sensitive complexation behavior between β -CD and short chain aliphatic amines, diethylenetriamine (DETA), and applied it to the molecular structure design of SMH. The inclusion complexes

between β -CD and DETA associated under an alkaline environment (pH = 11.5), whereas dissociated at neutral pH. The reversible inclusion complexes served as physical cross-links to realize the SME with an R_f of about 94.8% and a recovery ratio (R_r) of about 95.7%.

DNA hydrogel, where polymeric network is formed based on interlocking of assembled DNA secondary structures, is a candidate material for application in biomaterials [75,76]. The base sequence in nucleic acids endows the DNA hydrogel with the ability of carrying information and undergoing reversible transitions of the nucleic acids between two states in response to certain stimuli [68,77].

Recently, a series of shape memory DNA hydrogels based on pH-sensitive i-motifs and triplex DNA units were reported by Willner et al.

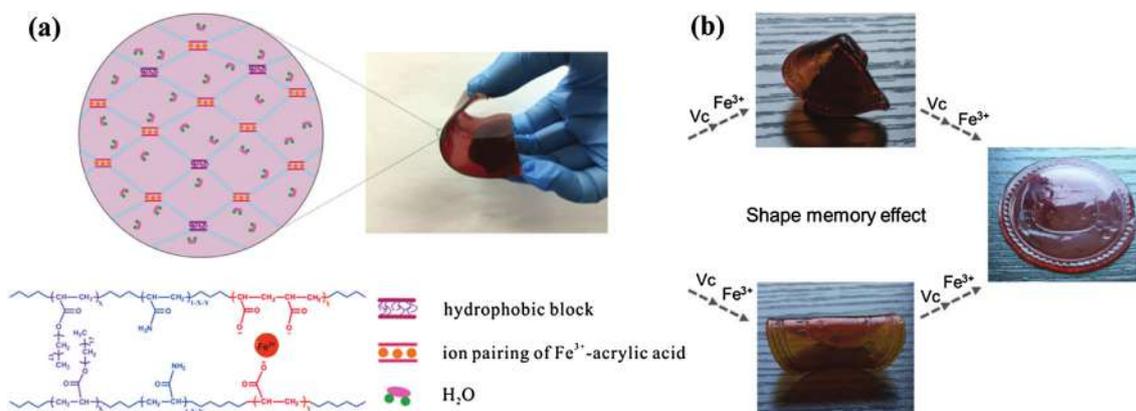


Fig. 13. (a) The chemical structure of the SMH based on Fe^{3+} -carboxyl coordination; (b) the SME in response to Vc. (Reproduced from Ref. [35] with permission from the Royal Society of Chemistry.)

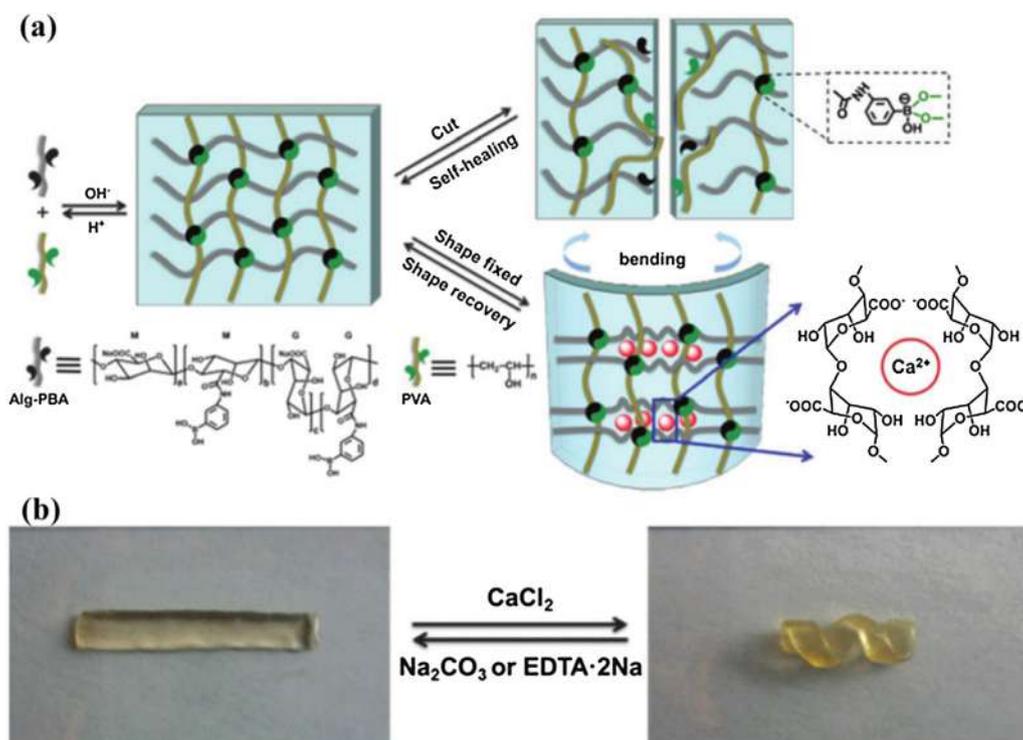


Fig. 14. (a) Schematic illustration of the hydrogel network. (b) The shape memory cycle by alternative treatment of CaCl_2 aqueous solution and $\text{Na}_2\text{CO}_3/\text{EDTA}\cdot 2\text{Na}$ solutions. (Reproduced from Ref. [85] with permission from the Royal Society of Chemistry.)

[15,69,78]. A DNA hydrogel network consisting of polyacrylamide backbone and two different pH-responsive oligonucleotide crosslinking units were fabricated as shown in Fig. 10a [69]. The cooperative crosslinking of the two crosslinking units by hydrogen bonds could stabilize the hydrogel at a triangle-shaped gel state under the pH of 7, while subsequent adjustment of the pH up to 10 caused the dissociation of one of the thymine-adenine-thymine (T-A-T) DNA bridging units, resulting the hydrogel in a quasi-liquid state. As shown in Fig. 10b, retreatment of the hydrogel in neutral environment led to the recovery of the triangle-shaped gel state in the presence of another DNA bridging as an initial shape memory provider. Similarly, another DNA bridging unit was sensitive to the acidic condition (pH = 5) and transformed into a protonated cytosine-guanine-cytosine (C-G-C⁺) triplex by separating one of the crosslinking units, leading to the shapeless quasi-liquid state. As expected, the hydrogel recovered to its initial triangle-shaped gel state again when it was retreated to neutral environment [69]. Such pH-triggered SME showed promising applications in sensor systems, drug

delivery matrices and selective cell adhesion matrices [15].

In spite of pH-sensitive supramolecular interactions, some dynamic covalent bonds like PBA-diol ester bonds and Schiff base linkages, which are capable of reversible cleavage-reformation in response to pH change, are also widely used in the design of pH-responsive SMHs. Chen et al. [13,37,38] introduced PBA-diol ester bonds formed by PBA covalently bonding with hydroxyl-rich PVA polymer chains (Fig. 11) and glucosamine (Fig. 12), respectively, into the SMHs network as pH-triggered switching segment. The hydrogels can fix their temporary shape after removing the external force under the basic environment (Gly-NaOH, pH = 10.6) due to the formation of PBA-diol ester bonds, while shape recovery was observed after treatment of the deformed hydrogel in acidic condition (pH = 6).

3.3. Chemo-responsive SMHs

Because of the three-dimensional network structure of hydrogel, the

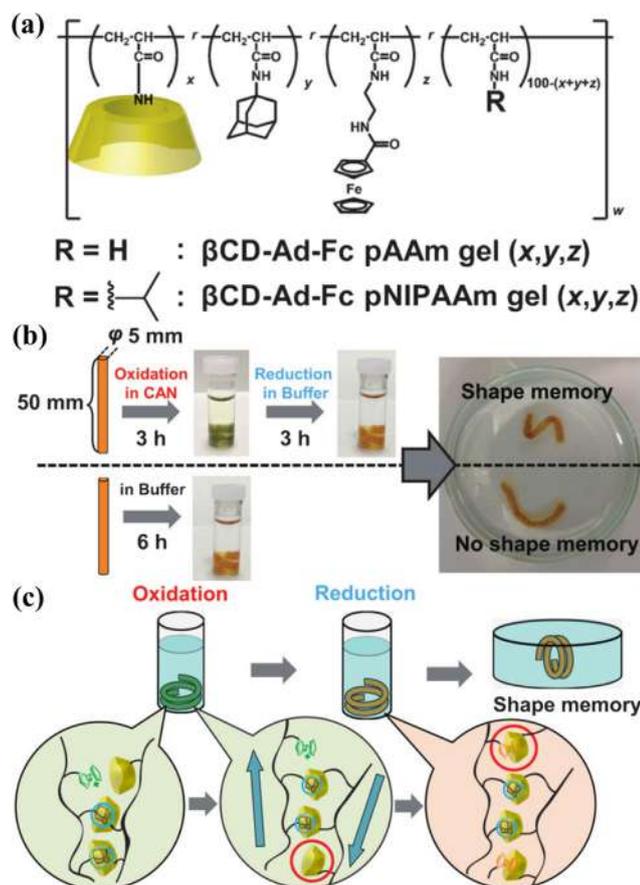


Fig. 15. (a) The molecular structure and properties of the hydrogel with two sets of host-guest interactions; (b) the SME of the hydrogel in response to redox stimuli. (c) Schematic illustration of the shape memory mechanism. (Reproduced from Ref. [79] with permission of John Wiley and Sons.)

SME of SMHs can be achieved by the diffusion of molecules and ions. Thus, a series of reversible chemical reactions that are activated by molecules or ions can be employed as physical cross-links in polymeric network [17], which is also advantageous in the case of SMHs as compared to dried SMPs. Typically, metal ion-ligand interactions and their redox reactions associated with association-dissociation process have been investigated widely [13,38,79].

Metal ions including Cu^{2+} , Fe^{3+} , Ca^{2+} , Zn^{2+} , etc., can coordinate to the corresponding ligands to develop metal ion-ligand interactions which can associate and dissociate reversibly under certain conditions, typically, redox stimuli [80–83]. The reversible nature of the metal ion-ligand interactions in response to external stimuli has been widely applied in the design of SMHs using as switching segments. As a common organic ligand, carboxyl groups ($-\text{COOH}$) can selectively coordinate with metal ions like Fe^{3+} or Ca^{2+} to serve as stable non-covalent cross-links in polymeric network [84]. Thus, removal of these metal ions by competitive ligands or reduction reaction with a reductant can change the cross-linking topology of network, leading to the recovery of the permanent shape. By incorporating Fe^{3+} -carboxyl complex into the hydrogel network in the presence of hydrophobic interactions of C18 (n-octadecyl acrylate) as permanent cross-links (Fig. 13a), Peng et al. [35] prepared a SMH in a very facile way. The deformation of the hydrogel was well stabilized by the coordination of Fe^{3+} with carboxyl group as compared to the Fe^{2+} . Thereby, reduction treatment of the hydrogel by immersing into ascorbic acid (Vc) aqueous solution could recover the permanent shape (Fig. 13b). During the whole shape memory cycle, both the R_f and R_r values were above 95%.

Polysaccharides like alginate [85], chitosan [38] and carrageenan [86] are anionic biopolymers derived from plants and animals. These

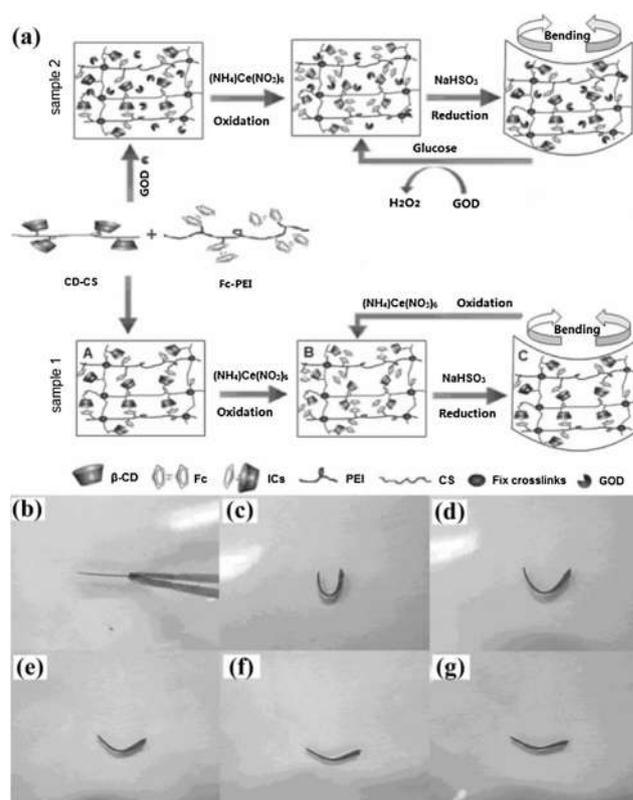


Fig. 16. (a) The polymeric network structure of the β -CD/Fc inclusion complex of the SMH and its SME in response to the redox stimuli and glucose; (b) original shape of a prepared hydrogel; (c) fixed temporary shape of the hydrogel by successive treatment with $(\text{NH}_4)\text{Ce}(\text{NO}_3)_6$ and NaHSO_3 aqueous solution; (d-g) shape recovery after retreating the film with $(\text{NH}_4)\text{Ce}(\text{NO}_3)_6$ solution again. (Reproduced from Ref. [89] with permission of John Wiley and Sons.)

polysaccharides have an ability to chelate corresponding metal ions. Taking advantage of this feature, Meng et al. [85] designed an alginate-based hydrogel network in which polymeric chains were dual-cross-linked by dynamic PBA-diol ester bond and the coordination of Ca^{2+} to carboxylate and hydroxyl groups of four G monomers presented on two adjacent chains of alginate (Fig. 14a). The SME of the hydrogel could be realized by cyclic treatments with CaCl_2 and $\text{Na}_2\text{CO}_3/\text{EDTA}\cdot 2\text{Na}$ aqueous solutions (Fig. 14b).

Despite metal-ligand coordination, host-guest interactions are also an ideal candidate to be employed in the polymeric network as switching segment owing to their sensitivity to chemo-stimuli like competitive host/guest molecules and redox agents [17,87]. A typical example is the host-guest interaction between β -CD and ferrocene which has been investigated in depth in recent years to design SMHs. Ferrocene (Fc) is an organometallic compound with sandwich structure composed of one ferrous ion center and two cyclopentadiene rings [88]. The β -CD cavity can include the Fc (reduce state) group at a mole ratio of 1:1 owing to the hydrophobic nature, while the inclusion complex dissociates immediately upon oxidation of the Fc to the oxidized ferrocenium cation (Fc^+) state because of the dramatic increase in hydrophilicity. Based on this redox-sensitivity, Miyamae et al. [79] fabricated a SMH with self-healing ability using the β -CD/Fc complex as a switching segment in the present of β -CD/adamantane (Ad) as hard segment (Fig. 15a). Oxidation in an aqueous solution of ammonium cerium nitrate (CAN) dissociated the β -CD/Fc complex, making the hydrogel soft and easy to be deformed. The subsequent reduction of the gel reassociated the complex at the deformed helical shape of hydrogel. Because of the formation of physical crosslinking by reassociation of the β -CD/Fc complex, the temporary helical shape was fixed (Fig. 15b, c). However, the control experiment showed that the helical shape could

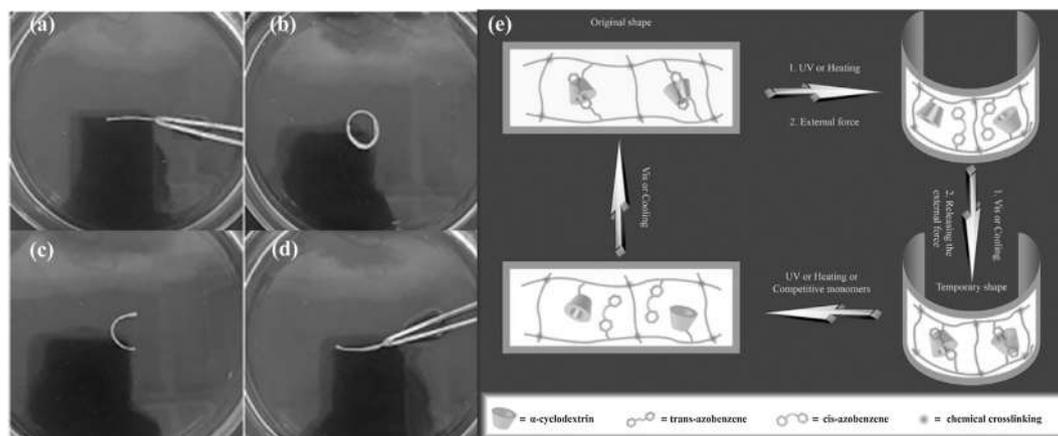


Fig. 17. Illustration and photographs of the photo-responsive SMH based on the reversible Azo/ α -CD inclusion complex. (a–d) The shape fixing and shape recovery process; (e) the topological change in polymeric network during the shape memory cycle and the SME of the SMH. (Reproduced from Ref. [40] with permission from John Wiley and Sons.)

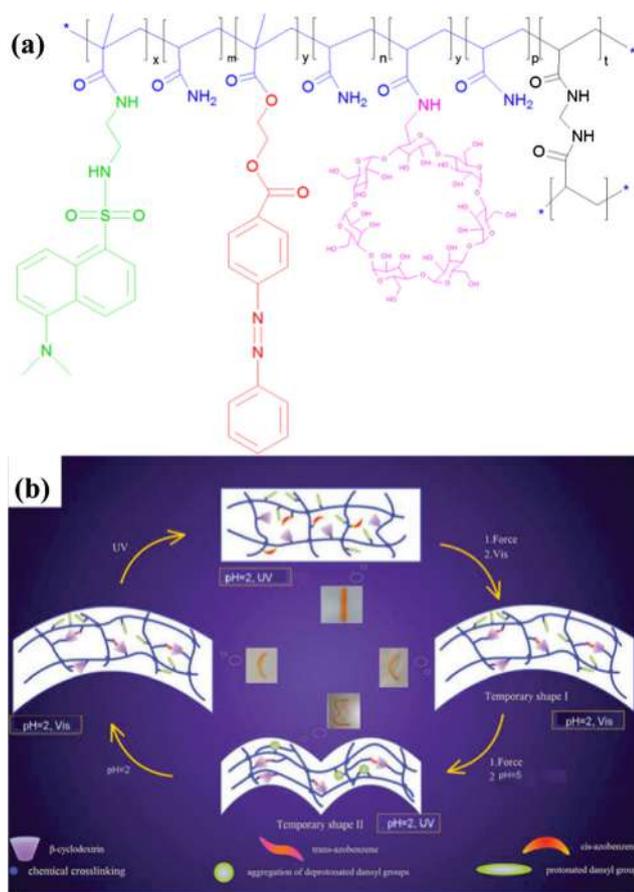


Fig. 18. (a) The chemical structure of the dual physical cross-linked hydrogel; (b) Demonstration of triple-SME in response to pH and light. (Reproduced from Ref. [41] with permission from the Royal Society of Chemistry.)

not be fixed as a temporary shape without the sequential oxidation-reduction treatment.

Similarly, Dong et al. [89] incorporated the β -CD/Fc complex into a hydrogel through a facile route. They simply mixed the β -CD modified chitosan (β -CD-CS) solution and ferrocene modified branched ethylene imine polymer (Fc-FEI) solution together to form a film. The polymeric network was chemically bonded with ease by glutaraldehyde (GA) due to the abundant amino groups in both sets of the polymer chains. Therefore, the hard segment was generated for permanent shape. As

shown in Fig. 16a, the host-guest interactions between β -CD and Fc can be dissociated and reassociated by cyclic oxidation and reduction treatments using $(\text{NH}_4)\text{Ce}(\text{NO}_3)_6$ and NaHSO_3 solutions, respectively, leading to a redox-responsive SME (Fig. 16b–g). Moreover, encapsulation of glucose oxidase (GOD) endowed the film with the shape memory ability in response to glucose.

3.4. Photo-responsive SMHs

The use of light as an external stimulus for responsive systems is of particular interest because of its non-polluting nature, and it can be manipulated remotely, precisely in space and time [90,91]. The functions and properties of hydrogels in response to photo irradiation can be modulated with temporal and spatial resolution [92,93]. Photo-responsive SMHs are emerging smart materials with the potential applications in information carrier, soft robot and actuators [12,94]. According to the previous works, photo-responsive SMHs are mainly fabricated by two routes [40,48], i.e., introducing additives or fillers with photo-thermal effect into the thermal-responsive SMHs to convert photo energy into heat, and introducing light-sensitive bonds or interactions into the polymeric network as switching segment. It is worth pointing out that SMHs which is triggered by photothermal stimuli have been classified as thermal-responsive SMHs because of their intrinsic thermal sensitive property, i.e., photo-irradiation is an indirect stimulus. Thus, we focused on the SMHs that directly respond to light irradiation in this section.

Azobenzene (Azo) is a well-known molecule with the ability of isomerization between the *cis*- and *trans*-isomer in response to ultra-violet (UV)/visible light (Vis) or heat [95,96]. Besides, *trans*-Azo can form a stable inclusion complex with β -CD or α -CD with a considerable inclusion constant of 770 M^{-1} and 2000 M^{-1} , respectively, while the *cis*-isomer cannot do so due to the low inclusion constants [97]. Because of the reversible conclusion nature in response to light, the Azo/CDs inclusion complexes have proven to be feasible elements to serve as switching segments in the design of SMHs.

Pan et al. [40] employed Azo and α -CD into the polymeric network by grafting on the alginate and PAA chains, respectively. The inherent sensitivity to UV/Vis light and heat endowed the hydrogel with SME in response to corresponding stimuli (Fig. 17a–d). Irradiation with UV dissociated the *trans*-Azo/ α -CD complexes due to the *trans* to *cis*-isomerization of Azo groups, leading to the breakage of the physical crosslinks. The following irradiation with Vis light would fix the hydrogel at a stable temporary blended shape without external force because of the reformation of the *trans*-Azo/ α -CD complexes as physical crosslinking. Finally, re-irradiation with UV recovered the hydrogel to

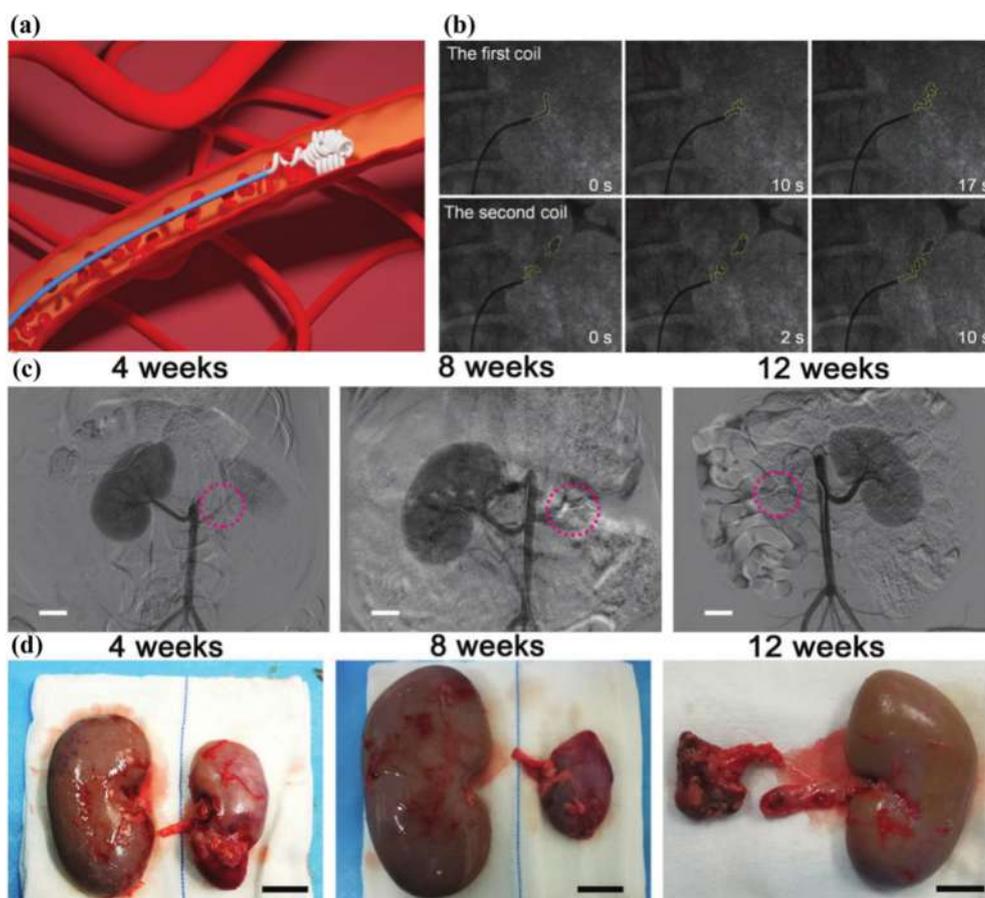


Fig. 19. The SME of radiopaque hydrogel coils *in vivo* and their embolisation assessment. (a) Schematic illustration of the TAE process. (b) Angiograms of the delivery of radiopaque hydrogel coils. (c) Angiographic images obtained at different time intervals after embolization. (d) Gross examination of the embolized and normal kidneys at 4, 8, and 12 weeks after surgery (Scale bar = 2 cm). (Reproduce from Ref. [55] with permission from John Wiley and Sons.)

the original shape because of the dissociation of *trans*-Azo/ α -CD complexes (Fig. 17e).

Similarly, Xiao et al. [41] integrated the pH-sensitive dansyl group and the light-responsive Azo/ β -CD inclusion complex into the hydrogel network to fabricate a dual physical cross-linked hydrogel (Fig. 18a). Due to the pH-dependent hydrophobic association of dansyl groups and the switchable association/dissociation of Azo/ β -CD inclusion complex in response to UV/Vis light or heat, the hydrogel exhibited a triple SME (Fig. 18b).

4. Potential applications in biomedical field

Technological improvements in SMHs have extremely enriched the family of SMHs, and the application fields have been extended due to their versatile stimuli-responsive ability [5,21]. In comparison with rigid hydrophobic polymers, hydrogels as a class of soft and hydrated substrates is more suitable for application in the field involving physiology, especially biomedical materials. Interventional therapy for tumor or aneurysm is a typical example. Transcatheter arterial embolization (TAE) is widely used in the treatment of hepatic tumors and aneurysm because of its low risk, high efficiency, rapid procedure, low cost, and minimal invasive administration [98–100]. The surgery involves delivery of selected embolization materials to the target blood vessel to block the blood supply, thereby controlling the local tumor growth or preventing the aneurysm from rupturing [101].

Generally, metal microcoils (such as platinum coils) or gelatin sponge sheet are usually used to treat large vessel or aneurysms. However, metal microcoils are notoriously prone to recanalization arising from the low filling ratio due to their extreme rigidity. Additionally, the gelatin sponge can be absorbed by the body gradually, making embolization unpredictable [102,103]. To solve this problem, Zhang et al. [55] fabricated a highly stiff body-temperature-responsive

SMH. The Young's modulus of the hydrogel is up to 16 MPa at low temperature ($\sim 20^\circ\text{C}$), which makes the SMH conducive to pass through the transcatheter. However, the hydrogel becomes soft upon raising the temperature to 37°C due to the dissociation of physical cross-links. The hydrogels were firstly fabricated with a permanent coiled shape and then coated with BaSO_4 for radiopacity. The fabricated coils were applied to the embolization of pig's renal arteries for *in vivo* evaluation as seen in Fig. 19a. The embolization could be monitored by X-ray, and the shape recovery was triggered rapidly within 17 s by body temperature, leading to a successful embolization (Fig. 19b). The embolized kidney shrunk gradually with the passage of time and became much smaller than the contralateral normal kidney (Fig. 19c–d).

Similarly, Wong et al. [104] fabricated a water-responsive shape memory embolization plug by coating crosslinked poly(ethylene glycol) diacrylate (PEGDA) hydrogel onto a poly(DL-lactide-co-glycolide) (PLGA) blend containing radiopaque filler. The plug had a permanent coiled shape, and a strip temporary shape could be fixed after drying and deforming at 70°C followed by quenching. After immersing in water at 37°C , the dried composite recovered to its coiled permanent shape which contributed to the dissolving of PEG crystalline phase by absorbed water. *In vitro* embolization experiment shows that complete occlusion can be achieved within 120 s, as a result, fluid flow could be restricted progressively after the embolization.

Moreover, SMHs are promising in the application of hemorrhage control. Compared to the current hemostatic agent like cyanoacrylates [105], widely used zeolite-based QuickClot [106] and fibrin bandages [107] etc., hemostatic agents having SME show great advantages in stopping the hemorrhage caused by irregularly shaped, non-compressible or deep wounds [108,109]. Recently, Zhao et al. [110] developed a cryogel based on carbon nanotube (CNT) and glycidyl methacrylate functionalized quaternized chitosan. CNT was applied to provide the cryogel with hydrophobic drug encapsulation ability, near-

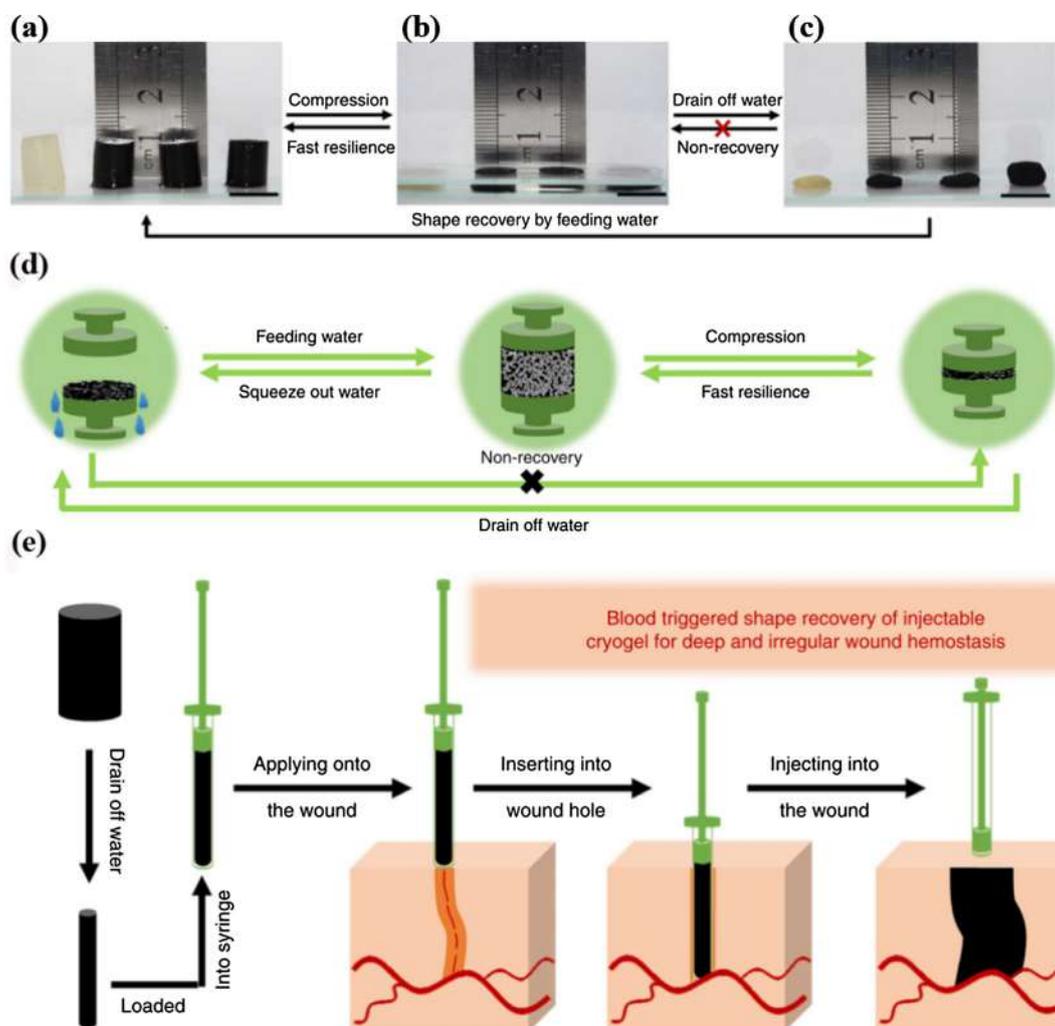


Fig. 20. Water-responsive SME of the cryogel and its application in hemorrhage control. (a–c) Photographs that demonstrate the SME of the four cryogels with different CNT concentration. (d) Schematic illustration of the SME of the cryogel. (e) Schematic representation of the hemostatic application of injectable shape memory cryogel hemostatic in a deep and irregularly shaped wound model. (Reproduced from Ref. [110] with permission from John Wiley and Sons.)

infrared (NIR) light stimuli-responsivity and good mechanical strength. Polymerization was carried out at -20°C to form the cryogel with interconnected and macroporous structure which endowed the cryogel with rapid water-triggered shape memory property and high water absorption ability. Fig. 20a–c shows the water-responsive SME of four cryogels with different CNT concentration. Simple compressing of the cryogels induces the extrusion of water and thereafter temporary shapes could be stably fixed at a contraction state. However, shape recovery of the cryogels could be completed within 1 s after reabsorbing water. The shape memory capability originated from the interconnected and macroporous structure within the cryogel matrix. The sponge-like structure allowed the drain of water easily by compressing, and the collapsed pores could maintain the matrix at the contraction state and store the deformation energy without absorbing water. After placing the contracted matrix in an aqueous environment, shape recovery could be completed immediately due to the rapid absorption of water (Fig. 20d). A cylinder cryogel matrix could be loaded into a syringe after squeezing and injected into the narrow, deep and irregular wound hole. Shape recovery happens immediately after uptaking blood, and thereby enabling the hemostatic process (Fig. 20e).

5. Summary and outlook

We have emphasized the outcomes of SMHs in response to the

temperature, pH, chemicals and light in this review due to the extensive research work related in the area of SMHs. As an arsenal of smart polymer materials, SMHs have gained much attention in the recent decades. SMHs in response to various stimuli including temperature, pH, chemicals, light, water and even ultrasound have been designed and fabricated with bright future. For designing a hydrogel network with SME, at least one switching segment constructed by reversible netpoints from dynamic covalent bonds or supramolecular interactions is essential.

Although the scientific research in SMHs area is developing day by day still there are a number of challenges and new avenues to be explored. Firstly, good mechanical properties like high strength and good resilience should be indispensable for SMHs involving load-bearing applications, however, most of the reported SMHs are weak (less than 1 MPa in tensile stress or Young's modulus) [37,38,51]. Technologies including introducing effective energy-dissipation mechanisms [80] and homogeneous network construction [111] are promising candidate to bestow SMHs with considerable mechanical properties, making SMHs more attractive and applicable. Secondly, the previous research works is mainly devoted to the design and fabrication of their hydrogel network with irreversible SME, i.e., one way SME [20]. However, for a typical one way SME cycle, shape recovery can only occur from the deformed and fixed temporary shape(s) to the permanent shape, which cannot meet human requirement for reuse without reprogramming,

thereby limiting their applications. Thus, achieving a two way SME, in which SMHs can switch between two different shapes (i.e., shape recovery from temporary shape(s) to permanent shape, vice versa.) under stimuli can be a promising research task. Thirdly, as a promising smart material, programmable nature is necessary for not only the temporary shape(s) but also the permanent shape in practice. However, existing works mainly revolves around the versatility in temporary shape fixing, while the innovations involving permanent shape are scarce. To deal with this challenge, introducing physical/dynamic covalent bonds instead of covalent netpoints to memorize the permanent shape may be a feasible strategy [85,112]. For instance, a double network system that consists of two non-interfering molecular switches could simultaneously impart SME and permanent shape reconfiguration ability to a hydrogel. In this system, the permanent shape(s) can be defined by one set of molecular switches and the temporary shape(s) can be fixed by another. The reversible capability of molecular switches makes the reprogramming of permanent shape(s) possible. Fourthly, the water rich 3D network endows a hydrogel with the SME ability that can be triggered by diffusion of chemicals, which is an advantage compared to dried polymers. However, the response rate is strongly dependent on the diffusion of chemicals and is relatively low in contrast to the thermal-triggered mode, thereby, efforts to increase the response rate can provide a new pathway in this field. Finally, compared to the great development of SMHs on design concept and fabrication technology, more efforts need to be made to explore their potential applications. The soft and wet characters provide a great advantage in application areas such as soft-robots, soft-actuators, scaffolds and biomedicines. The in-depth evaluation of the above applications is necessary and conducive to the future prospects of SMHs. Various of SMHs have been designed and fabricated, and the relative researches on SMHs are booming in recent years. With more efforts made by researchers in this field, SMHs will be more versatile, more robust and more widely used in the coming future.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eurpolymj.2019.03.004>.

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