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Self-Healing Gels based on Constitutional Dynamic Chemistry and Their Potential Applications

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Self-healing gels based on constitutional dynamic chemistry and their potential applications

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As representative soft materials with widespread applications, gels with various functions have been developed. However, traditional gels are vulnerable to stress-induced formation of cracks. The propagation of these cracks may affect the integrity of network structures of gels, resulting in the loss of functionality and limiting the service life of the gels. To address this challenge, self-healing gels that can restore their functionalities and structures after damage have been developed as "smart" soft materials. In this paper, we present an overview of the current strategies for synthesizing self-healing gels based on the concept of constitutional dynamic chemistry, which involves molecular structures capable of establishing dynamic networks based upon physical interactions or chemical reactions. The characterization methods of self-healing gels and the key factors that affect self-healing properties are analyzed. We also illustrate the emerging applications of self-healing gels, with emphasis on their usages in industry (coatings, sealants) and biomedicine (tissue adhesives, agents for drug or cell delivery). We conclude with a perspective of challenges facing the field, along with prospects for future development.

1. Introduction

The colloidal condition of gels – as D.J. Lloyd wrote in 1927 – "is one which is easier to recognize than to define".[1] This statement is still valid today. As yet, no definition has been worked out that satisfies all scientific needs. Fundamentally, a gel is characterized by the presence of at least two components which together comprise a three-dimensional (3D) solid scaffold immobilizing a much larger liquid volume. The 3D networks can be formed from small molecules or large macromolecules. The networks are interpenetrated by a large amount of fluid component in such a manner that no apparent boundary exists between the networks and the fluid. Due to the presence of a continuous solid structure with macroscopic dimensions, the gels exhibit mechanical properties of solids and maintain their form under the stress of their own weight. There are several subclasses of gels. For example, hydrogels are a particular class of gels where the swelling agent is water,[2-6] while gels with hydrophobic polymer networks swollen by organic solution are denoted as organogels.[7-10]

Significant progress has been achieved in the development of smart gels with capability to respond to external stimuli, such as temperature,[11-13] electrical field,[14-17] magnetic field[18-21] and light.[22-24] Furthermore, hydrogels with outstanding mechanical performance have also been developed.[25-30] These unique and tunable properties have led to their diverse applications in various fields, such as sensors, actuators, cell/drug delivery systems, tissue engineering and regenerative medicine.[31-40]

In spite of the superior performances of polymer gels, their desirable properties often deteriorate or even lose when damaged by cracks at macro- or microscale. Further propagation of these cracks may affect the integrity of network structures and mechanical properties of bulk gels, limiting their lifetime. To address these limitations, novel smart gels have been developed with self-healing or self-repairing properties that can restore their functionalities and structures after damage. For example, a hydrogel that can self-heal at low pH through hydrogen bonds has been employed as a sealant for vessels filled with corrosive acids.[41] This ability of the self-healing hydrogel is also capable of sealing stomach perforations and avoiding leakage of gastric acids, which holds great potential as a tissue adhesive.

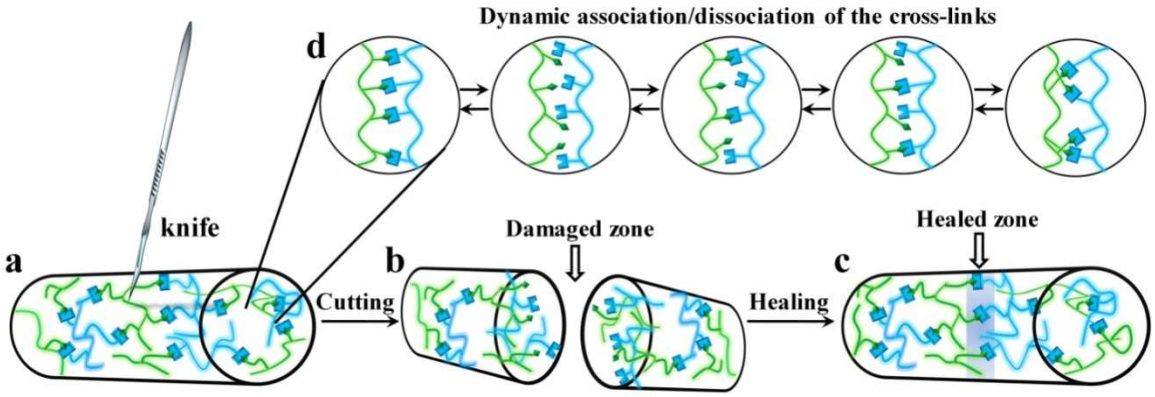

Fig. 1 Schematic illustration of self-healing mechanisms of self-healing gels based on CDC. (a) A cylindrical self-healing gel is cut by a knife; (b) The gel is cut into two pieces and the functional groups stay dissociated across the damaged zone; (c) The crack is healed by the reformed dynamic bonds after the fractured surface contacting each other; (d) The dynamic association and dissociation of the reversible cross-links based on CDC.

Due to their great potential, various approaches have been developed for preparing self-healing gels, many of which are based on the concept of constitutional dynamic chemistry (CDC).[42-45] CDC comprises both dynamic covalent chemistry and non-covalent chemistry.[46-49] The key features of CDC are "dynamic" and "reversible", where dynamic bonds contribute to the preparation of dynamic polymer networks. A common feature of dynamic polymer networks is their self-healing nature, due to their ability to undergo dynamic/reversible bonds breaking-reformation reactions. Consequently, self-healing gels can fuse into their original shape after damage and further restore their original properties (Fig. 1). Since the healing process is reversible, self-healing gels based on the CDC concept can experience multiple healing cycles.

In the past decade, there has been a growing interest in the broad field of self-healing/self-repairing materials, as reflected by the growth in the number of publications (Fig. 2). Nevertheless, the researches on self-healing gels are still in its infancy, with only ~100 publications in 2013. Several reviews have been recently published on the topic of self-healing materials,[55-62] including polymers, ceramics and metals, but none on self-healing gels. In this review, we mainly aim to introduce novel ideas and show attractive examples of self-healing gels based on CDC. Section 2 introduces general features of the dynamic mechanisms of CDC-based self-healing gels, and summarizes the methods for characterization of self-healing gels. Section 3 analyzes the physical and chemical strategies for designing self-healing gels (Table 1), and the key factors that affect self-healing properties. Section 4 describes some emerging applications of self-healing gels. The review concludes with a discussion of current challenges and future perspectives for self-healing gels.

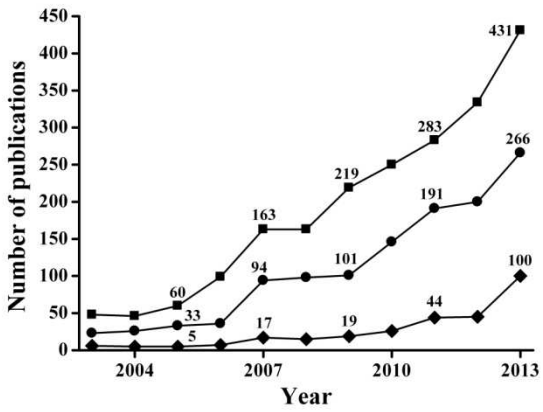

Fig. 2 The number of publications in last ten years with the keywords of "self-healing/self-repairing material"(■), "self-healing/self-repairing polymer"(●) and "self-healing/self-repairing gel"(♦). The exact numbers of publications are provided annually from 2003 to 2013 (Source: SciFinder Scholar).

Table 1 Examples of various self-healing gels and their self-healing properties.

Classification	Self-healing mechanisms	Substances	Healing conditions	Mechanical recovery test	Rheology recovery	Healing efficiency	Ref.
Physical self-healing gels	Hydrophobic interactions	Micelle-based	RT, 10~130min	Yes	—	98%~100%	[77] [a] [81]
		Liposome	RT	—	Yes	—	[78] [a]
	Host-Guest interactions	PAA-6βCD	RT, 24h	Yes	Yes	84%	[73] [a]
		PMMA-DB24C 8-benzyl	RT, 30s	—	Yes	95%	[82] [b]
		PMMA-DB24C 8-cyclohexyl	RT, 10s	—	Yes	100%	[82] [b]
	Hydrogen bonds	PA6ACA	RT, pH≤3, 24h	Yes	—	66±7%	[41] [a]
		PDMAEMA/SC MHBMA	20°C, pH=7~8, 2min	—	—	—	[83] [a]
	Crystallizations	Peptide	RT	—	Yes	80~90%	[88] [a]
		F-actin	RT	—	Yes	—	[89] [a]
		PVA	RT	Yes	—	72%	[87] [a]
	Polymer-nanocomposite interactions	SDM	RT	—	Yes	—	[84] [a]
		D-NC	37~80°C, 20min~100h	Yes	—	27%~100%	[85] [a]
		GO	4~30°C, 24h	Yes	—	88%	[86] [a]
	Multiple interactions	Chol-NBD	RT	—	Yes	—	[92] [b]
		SOE	RT	—	Yes	—	[90] [a]
Chemical self-healing gels	Phenylboronate ester complexations	PBA-SHA	RT, pH=4.2	—	Yes	—	[118] [a]
		cPEG-BDBA	RT, pH=9.0	—	Yes	—	[119] [a]
	Disulfide Bonds	Star branched disulfide	RT, >20min	—	—	—	[65] [b]
	Imine Bonds	Chitosan-PEG	RT, 2h	—	Yes	—	[64] [a]
	Acylhydrazone Bonds	PEO-aldehyde	RT, 7h	—	—	—	[63] [b]
		HG1G2	RT, pH=6~9, 24~48h	Yes	—	>50%	[125] [a]
	Reversible Radical Reactions	PBA-TTC	RT, UV, 4h, acetonitrile, nitrogen	Yes	—	94%	[127] [b]
		Polyurethane-TDS	RT, visible light, 12h, nitrogen	Yes	—	~100%	[127] [b]
		PPG-DABBF	RT, air, DMF wetting, 24h	Yes	—	98%	[129] [b]
	Diels-Alder Reactions	PFMA-BM	120°C, 4h	—	—	—	[133] [b]
		Dex-l-PEG[a]	37°C, 7h	—	Yes	98.7%	[69] [a]

[a] hydrogel; [b] organogel; RT: room temperature

2. General considerations

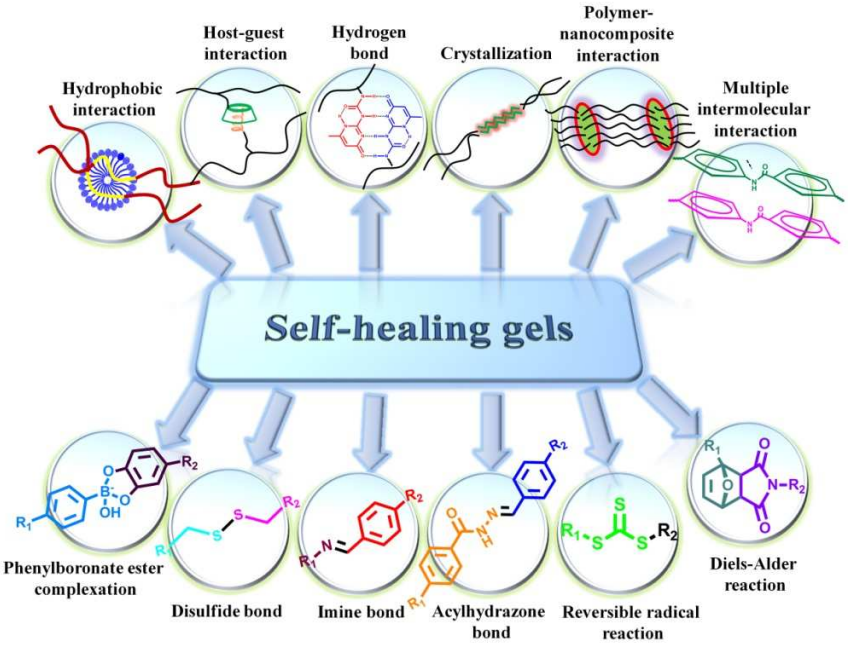

Fig. 3 Various strategies used to synthesize physical and chemical self-healing gels based on CDC. Physical gels (upper) achieve their self-healing behavior through various physical interactions, including hydrophobic interaction, host-guest interaction, hydrogen bond, crystallization, polymer-nanocomposite interaction, and the multiple intermolecular interactions. Chemical gels (down) achieve their self-healing through various chemical bonds, including phenylboronate complexation, disulfide bond, imine bond, acylhydrazone bond, reversible radical reaction and Diels-Alder reaction.

Based on the healing mechanisms, self-healing gels can be divided into physical and chemical self-healing gels (Fig. 3). Physical self-healing gels re-establish networks through dynamic formation of attractive non-covalent interactions between molecules, oligomers or polymer chains, including hydrophobic interactions, host-guest interactions, hydrogen bonds, crystallization, polymer-nanocomposite interactions and multiple intermolecular interactions. Chemical self-healing gels re-establish networks through the dynamic formation of covalent bonds, including boron-oxygen bond (phenylboronate ester), sulfur-sulfur bond (disulfide), carbon-nitrogen bond (imine, acylhydrazone), carbon-carbon/carbon-sulfur bond (reversible radical reaction) and cyclohexenes (reversible Diels-Alder cycloaddition). For both physical and chemical self-healing gels, the dynamic equilibrium of the gel networks is achieved via dissociation and recombination of physical interactions or chemical bonds. This means that the functional groups of polymer chains must exist in the gel networks in a form that permits physical interactions or chemical reactions in damaged regions of gels, initiating the self-healing process.

Similar to other self-healing polymer materials, two important features are existed in self-healing gel systems. First, they can generate "mobile phase" in or around crack areas after damage, which will fill and bridge the damaged zone to heal themselves.[59] This requires the excellent flowability of the gels to generate the "mobile phase". Gels have their unique advantages over polymers in achieving self-healing performance, because the solvent contained in hydrogel networks facilitate formation of "mobile phase" formation around cracks. Second, self-healing gels can be non-automatically or automatically self-healable depending on whether or not they need additional external energy, intervention or trigger (e.g., heat, light, pH or catalyst) to recover their original structures and properties.

Assessment of the healing ability of damaged gels focuses on restoration of gel morphology and mechanical properties. A variety of available techniques, which were developed originally for characterization of gel morphology, have been extended to track the self-healing process of scratched gels.[62] Digital monitoring (*e.g.*, using a digital camera) is a conventional method to keep an eye on the rejoin and fusion of two pieces of knife-cut gels at macroscopic level, and has been intensively used to quantify self-healing time and

efficiency.[63,64] The spatial resolution can be significantly improved by using optical microscopy and scanning electron microscopy (SEM) to meticulously track the closure of notches on the gel surface.[133] Atomic force microscopy (AFM) can also monitor the self-healing process by offering continuous images of scratch on gel surface.[65,66] The details of depth and width of cuts or cracks on the gel surface can be tracked throughout the healing process. Scanning electrochemical microscopy (SECM),[67,68] based on recording the electrochemical current measured by a microelectrode above the sample surface, has recently been applied to qualitatively and quantitatively monitor the hydrogel healing process.[69] SECM can be applied to *in situ* tracking healing process and provide 3D topography data and images by detecting spatially- and temporally-resolved electrochemical signals.

Besides morphology, the healing ability has also been monitored through detection of mechanical properties including tensile strength, compressive strength, and rheology. Healing efficiency (*HE*) can be defined as the ratio of the stress or modulus of the healed (M_h) and pristine gels (M_p), i.e., $HE = (M_h/M_p)$.[57] Wedged-shape strain compression, which determines the adhesion strength on the joint surface created by a wedge-shaped plunger, is suitable for characterizing soft and fragile samples.[70-73] Rheological assessment of the internal 3D structures of gels, which allows quantitative assessment of the extent of damage or self-healing, can also be used to probe the variation of storage modulus (G') and loss modulus (G").[74-76]

3. Strategies used to synthesize self-healing gels

3.1 Physical self-healing gels

This section focuses on the strategies for preparation of physical self-healing gels based upon dynamic networks of non-covalent interactions, including hydrophobic interactions,[77-81] host-guest interactions,[72,73,82] hydrogen bonds,[41,83] crystallizations,[87-89] nanocomposite interactions[84-86] and the multiple intermolecular interactions.[66,90-92]

3.1.1 Hydrophobic interactions

Hydrophobic interaction plays a dominant role in the formation of self-healing hydrogels. The polymer chains containing hydrophobic monomer units lead to the associations of hydrophobic interchains, yielding a network with transient cross-links.

Recently, micellar polymerization has been nicely expanded for the construction of self-healing hydrogels which are cross-linked through hydrophobic interactions among surfactant micelles.[77,80,81] In this system, the reversible dissociation and association of the hydrophobic cross-links in networks endow self-healing property to the hydrogels. For example, micelle-based hydrogel could be obtained by copolymerizing of hydrophobic monomer stearyl methacrylate (C18) with hydrophilic monomer acrylamide (AAm) (PAAm-*co*-C18) in a micellar solution of sodium dodecyl sulfate (SDS) in the presence of NaCl (Fig. 4a).

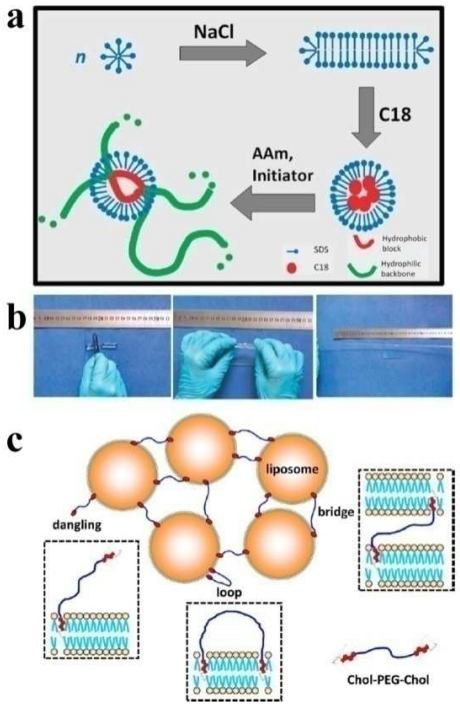

Fig. 4 Hydrophobic interaction-based micellar and liposome self-healing hydrogels. (a) Schematic illustration shows the formation of micelle-based hydrogel through hydrophobic monomer C18 copolymerized with hydrophilic AAm in SDS-NaCl micellar solution; (b) Photographs of a micelle-based hydrogel cut into two pieces (left) merge into a whole one after pressing the fractured surfaces together for 10 min (middle), and the self-healed hydrogel shows a large stretching ability (right); (Reprinted with permission from ref. 77. Copyright 2012, American Chemical Society.) (c) The liposome hydrogel networks contain three possible binding modes, including "bridge", "loop" and "dangling". (Reprinted with permission from ref. 78. Copyright 2011, Elsevier Ltd.)

Two pieces of ruptured micelle-based hydrogel samples could merge into a single piece by simply pressing them for a few seconds. The

healing efficiency was nearly 100% and the self-healed hydrogels could withstand similar applied strain as original one, with the maximum tensile strain of 3600% (Fig. 4b). The surfactant micelles were confirmed to be important for self-healing and mechanical properties of the micelle-based hydrogels. The self-healing behavior lost after extraction of the micelles from hydrogel networks,[79] because the hydrophobic interactions between pure C18 chains (without micelles) are too strong to exhibit reversibility. Furthermore, self-healing hydrogels with improved mechanical strength can be obtained by replacing SDS micelles with mixed cetyltrimethylammonium bromide (CTAB)-SDS micelles. The CTAB-SDS micelle-based hydrogels exhibit the maximum tensile strain of 5000% due to high solubility and hydrophobicity of the mixed micelles compared to SDS micelles. The stretchable micelle-based self-healing system provides an ideal candidate for designing tough self-healable hydrogels for tissue engineering, such as artifical muscles.

In addition, a novel liposome based self-healing hydrogel has been developed.[78] The gelation derives from hydrophobic interactions between liposome and polymer chains of cholesterol (Chol)-end capped polyethylene glycol (PEG) (Chol-PEG-Chol). The liposome hydrogel contains three possible binding manners of Chol-PEG-Chol to liposome: (i) "bridge", two cholesterol end groups of Chol-PEG-Chol insert into the bilayers of two different liposome particles, (ii)"loop", two cholesterol end groups of Chol-PEG-Chol insert into the bilayers of a single liposome particle or (iii) "dangling", only one cholesterol end group of Chol-PEG-Chol insert into the bilayers of liposome particle while the other end group exposes to the aqueous solution (Fig. 4c). Since the cholesterol groups of Chol-PEG-Chol may dynamically pull out and insert into the bilayers of liposomes, the liposome hydrogel could recover quickly to gel state after being broken into sol state under the strain of 100% or even 1000% as reflected by rheological recovery test.

3.1.2 Host-guest interactions

Host-guest interaction is another important physical bond that has been widely used in designing self-healing gels, due to the combination of multiple dynamic interactions between two corresponding compounds, including hydrophobic interactions, hydrogen bonding, π-π stacking, etc.

Cyclodextrin (CD) has been widely used to prepare host-guest gels since its hydrophobic internal cavity accomodates hydrophobic binding sites for guest molecules. The hydrophobic cavity can envelope a variety of appropriate guest molecules. For instance, Nakahata et al. reported a redox-responsive self-healing hydrogel with 6-amino-β-cyclodextrin (6β-CD) as main host molecules and ferrocene (Fc) as guest groups.[73] The transparent hydrogel was quickly formed by mixing poly (acrylic acid) (PAA)-6β-CD and PAA-Fc (Fig. 5a). Redox-responsive Fc derivative mediated a reversible sol-gel phase transition by redox stimulus, because Fc with a high affinity for β-CD led to gel, while Fc^+ with a low affinity for β-CD resulted in sol. As a typical demonstration, two half pieces of PAA-6β-CD/PAA-Fc hydrogels cut by a razor could fuse and sufficiently integrate as a whole after self-healing for 24 h. The rheological recovery test showed that, the G' of the hydrogel networks destroyed by 200% strain could recover to 90% of its original value within 20 s when the strain was reduced to 0.1%. Furthermore, the mechanical recovery test of wedge-shaped strain compression on the joint surface recovered 84% breaking stress. In addition, the healing efficiency can be further improved to ~99% by polymerization of inclusion complexes (pre-organized by host acrylamide modified β-CD monomers and guest monomers, N-adamantane-1-yl-acrylamide) via host-guest interaction (Fig. 5b).[72]

Crown ether can also serve as host groups.[93-94] A pair of crown ether-based host-guest self-healing organogels has been developed. The pendent dibenzo (24) crown-8 (DB24C8) modified poly(methyl methacrylate) (PMMA) (PMMA-DB24C8) could be cross-linked by two kinds of cross-linkers, i.e., bisammonium having phenyl and cyclohexyl terminal groups, respectively, obtaining PMMA-DB24C8-benzyl and PMMA-DB24C8-cyclohexyl gels (Fig. 5c).[82] Interestingly, the PMMA-DB24C8-benzyl gel recovered 95% of its initial G' and G'' values in ~30 s. While the PMMA-DB24C8-cyclohexyl gel could be fully recovered in ~10 s, due to the combined contribution of host-guest interactions, electrostatic interaction and hydrogen bonds in the gel.

In addition, Huang et al. developed a series of self-healing supramolecular gels assembled from low-molecular-weight monomers through crown ether-based recognition. Those gels exhibited excellent self-healing property due to the reversible host-guest interaction as well as the high mobility of the low-molecular-weight gelators.[95]

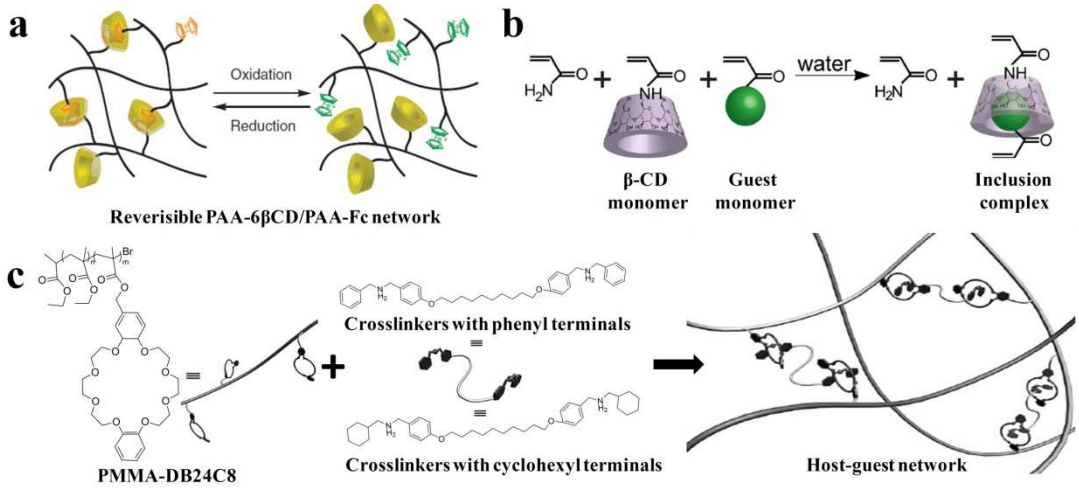

Fig. 5 Host-guest interaction-based self-healing hydrogels. (a) The reversible PAA-6β-CD/PAA-Fc polymer networks induced through redox reaction between 6β-CD and Fc; (Reprinted with permission from ref. 73. Copyright 2011, Nature publishing group.) (b) Pre-organized inclusion complex by host acrylamide modified β-CD monomers and guest N-adamantane-1-yl-acrylamide; (Reprinted with permission from ref. 72. Copyright 2013, Wiley-VCH.) (c) The host-guest networks of PMMA-DB24C8-benzyl/cyclohexyl gels cross-linked by PMMA-DB24C8 with bisammonium having phenyl and cyclohexyl terminals. (Reprinted with permission from ref. 82. Copyright 2012, Wiley-VCH.)

3.1.3 Hydrogen bonds

Hydrogen bond is one of the most well-known and commonly used physical interactions in the preparation of physical self-healing gels. For instance, a loosely cross-linked hydrogel could perform self-healing behavior by hydrogen bonds between terminal carboxyl groups and amide groups of aminocaproic acids which are side chains of poly (acryloyl-6-aminocaproic acid) (PA6ACA).[41] The long and flexible aminocaproic acid side chains could across the interface of two pieces of contacted hydrogels and connected to each other by hydrogen bonds.

The healing property of PA6ACA hydrogel is pH-dependent. Two separated PA6ACA hydrogel pieces could self-heal rapidly within 2 s when pH ≤ 3. The healed hydrogel was strong enough to sustain repeated stretch. This is because the terminal carboxyl groups are protonated at low pH, allowing them to generating hydrogen bonds with other terminal carboxyl or amide groups between the interfaces. The healed hydrogel pieces were separated again when exposed to high pH (pH > 9) solution, because the deprotonation of terminal carboxyl groups under alkaline environment induced electrostatic repulsion, preventing the formation of hydrogen bonds (Fig. 6a).

This approach was extended by other researchers to design a self-healing gels based on molecular structure of PA6ACA. Jiang *et al.* recently developed a zwitterionic self-healing hydrogel by changing the side chains of PA6ACA to poly(carboxybetaine acrylamide) (PAAZ), which could achieve self-healing performance under physiological pH (7.4).[96] Because the PAAZ has both positively and negatively charged groups, the different charged groups could easily cross the interface between two broken hydrogels by electrostatic attraction, and then formed zwitterionic pairs under physiological conditions, resulting in a self-healed hydrogel.

Hydrogen bond-based self-healing hydrogel has also been developed by copolymerizing of 2-(dimethylamino) ethyl methacrylate (DMAEMA) and 2-(3-(6-methyl-4-oxo-1, 4-dihydropyrimidin-2-yl) ureido) ethyl methacrylate (SCMHBMA).[83] The reversible and dynamic multivalent hydrogen bonds dimerized by 2-ureido-4-pyrimidone (UPy) units (from SCMHBMA) conferred the self-healing ability to this poly (DMAEMA-co-SCMHBMA) hydrogel (Fig. 6b).

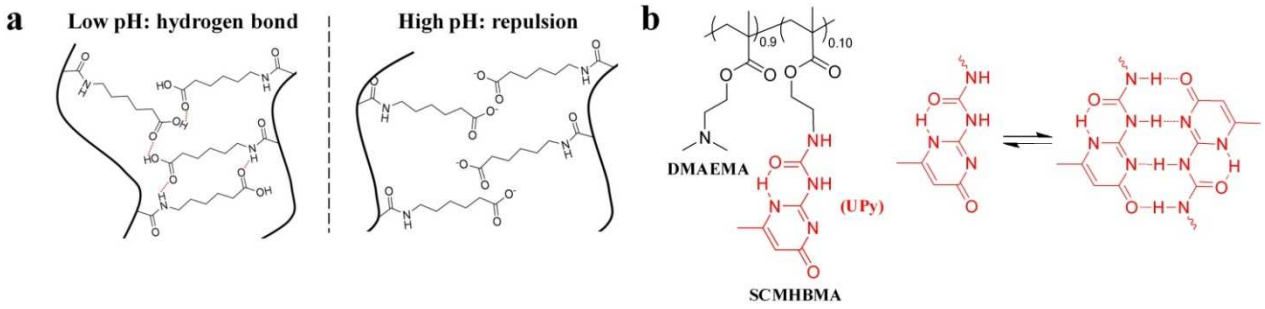

Fig. 6 Hydrogen bond-based PA6ACA and poly (DMAEMA-*co*-SCMHBMA) self-healing hydrogels. (a) Self-healing mechanism of PA6ACA hydrogels: at low pH, the pendant side chains in hydrogen bond lead to self-healing, whereas at high pH, the deprotonated carboxyl groups prevent the healing process due to electrostatic repulsion between the side chains; (Reprinted from ref. 41. Copyright 2012, National Academy of Sciences.) (b) Chemical structure of the poly (DMAEMA-co-SCMHBMA) and the dynamic multivalent hydrogen bonds dimerized by UPy. (Adapted from ref. 83.)

The poly (DMAEMA-*co*-SCMHBMA) was soluble in acid condition, and the gelation of the solution is induced when the pH increased to alkaline (pH > 8) due to the dimerization of the UPy units. Furthermore, similar self-healing system could be obtained by using different monomers copolymerized with SCMHBMA, such as 2-hydroxyethyl methacrylate (HEMA), 2-(2-methoxyethoxy) ethyl methacrylate (MEO2MA) or N-isopropylacrylamide (NIPAAm). This indicates that the dynamic ability of UPy units can be applied to prepare self-healing materials with different functions and properties.

3.1.4 Crystallization

Crystallization results in forming a relatively stable non-covalent bond formed among polymer chains with specific conformations, such as L-polylactide (L-PLA) acid,[97] peptide chain of α-helices or β-sheets,[98,99] and poly (vinyl alcohol) (PVA),[100,101] *etc*. The diblock copolypeptides can form self-healing hydrogels in aqueous solution via the crystallization of polypeptide chains. For instance, self-healing peptide-based hydrogels could be fabricated through self-assembly of diblock copolypeptide amphiphiles with two domains of different hydrophobicity, i.e., charged hydrophilic segment and hydrophobic segment with regular structures in dilute solutions (2~8 wt%).[88] In this case, highly charged polyelectrolytes, poly (L-lysine·HBr) or poly (L-glutamate sodium salt), served as hydrophilic domains, and poly (L-leucine) with rod-like α-helices or poly (L-valine) with crystalline β-sheets served as hydrophobic domains.

Formation of the peptide-based self-healing hydrogels not only depends on the amphiphilic feature of the polypeptides but also the crystallization among regular conformations of α-helices or β-sheets. Unlike other protein gels that generally dissolved at certain temperatures higher than 60°C,[102] these peptide-based self-healing hydrogel networks showed no visible collapse at temperatures as high as 90°C. The high thermal stability derived from the relatively stable crystallization in this peptide-based hydrogel. Furthermore, the peptide-based self-healing hydrogels could recover 80~90% of G' after breaking down by large amplitude oscillation, mainly due to the high mobility of relatively low molecular weight of copolypeptides.

Filamentous actin (F-actin) self-healing hydrogel consisting of globular actin (G-actin) as repeating units has also been developed.[89] The G-actin subunit is a globular protein built up by 375 amino acid units, which can self-assemble into the F-actin with double helical filamentous structure. The F-actin hydrogel was covalently cross-linked by bismaleimide-PEG linkers (Fig. 7a). The dynamic sol-gel transition of F-actin hydrogel could be induced by changing the electrolyte concentration or by the rheological recovery test. G' of the hydrogel could recover immediately to its original value after removing the breaking strain (20~1000%) (Fig. 7b). Prolonged recovery time was needed if a longer duration of breaking strain was enforced. (Fig. 7c).

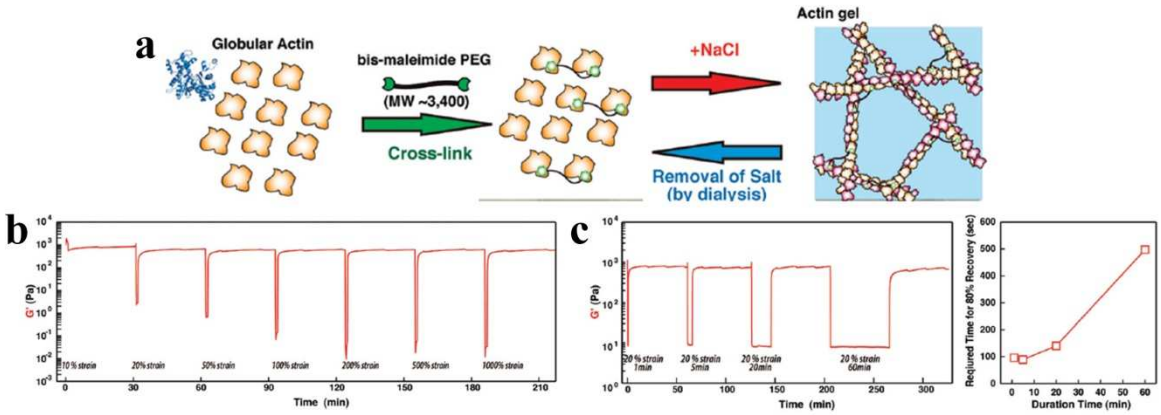

Fig. 7 F-actin self-healing hydrogel. (a) Schematic illustration of the preparation of bis-maleimide PEG cross-linked F-actin hydrogel consisting of G-actin as repeating units. (b) The rheological recovery test of F-actin hydrogel under the varied oscillatory shear strain (10~1000%). (c) The rheological recovery of G' changes as a function of time under 20% breaking strain (left) and the required healing time of 80% recovery of G' as a function of duration time (right). (Reprinted with permission from ref. 89. Copyright 2011, American Chemical Society.)

Traditional physical hydrogels with crystallized polymer networks can also show self-healing performance through hydrogen bonds. For instance, the PVA hydrogels can be cross-linked by the crystallization of hydrogen bonds via freezing-thawing method. By adjusting the amount of free hydroxyl groups and crystallized hydrogen bonds, the self-healing behavior of PVA hydrogel may be attained. Zhao et al. obtained the self-healing PVA hydrogel by increasing the PVA concentrations to 35 wt%, in which the proper balance between sufficient number of free hydroxyl groups and mobility of PVA chains could be obtained.[87] The self-healing behavior derived from the diffusion of PVA chains passed through the cut interface and reformation of the hydrogen bonds. The self-healing PVA hydrogels may have a great impact on wide range of applications, owing to its low cost, ease of synthesis, and generally recognized biocompatibility.[100,101,103]

3.1.5 Polymer-nanocomposite interactions

Hybrid nanocomposite (NC) hydrogels constituted by the network structure of polymer/inorganic nanoparticles (clay and graphene oxide) can also exhibit self-healing capability.[104-107] For example, a self-healing dendritic macromolecule (SDM) hydrogel has been developed by simply mixing dendritic macromolecules (G_3-binder; 3, generation number) (Fig. 8a), clay nanosheets and polyacrylate (ASAP) into aqueous solution.[84] The SDM hydrogel could be prepared as follows (Fig. 8b): firstly, the exfoliated clay nanosheets were homogeneously dispersed into ASAP aqueous solution, in which the positively charged edge parts of clay nanosheets were wrapped by anionic ASAP; then G_3-binders were added into the aqueous solution to form SDM hydrogel. The salt-bridge can be formed by the multiple guanidinium ion pendants at termini of G_3-binder with the oxyanionic groups of clay nanosheets through electrostatic interaction, which contributed to gelation and self-healing of the SDM hydrogel.

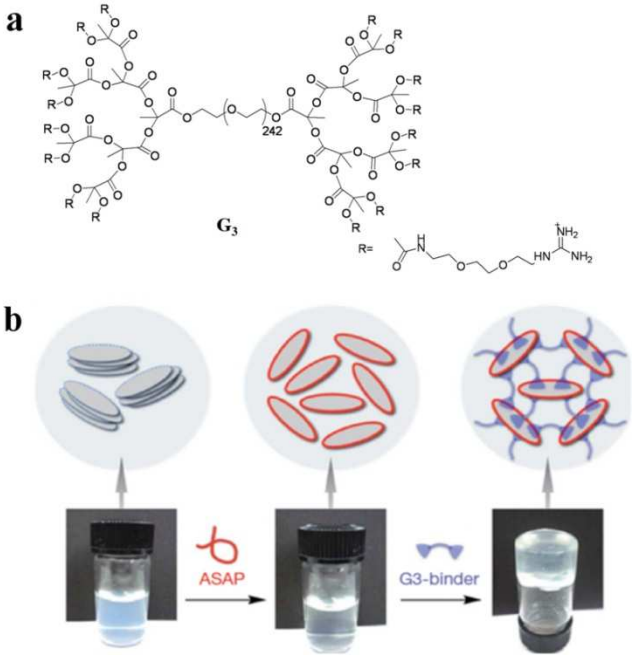

Fig. 8 Polymer-nanocomposite interaction-based dendritic self-healing hydrogel. (a) Schematic structures of dendritic macromolecules (G_3-binder); (b) The illustration and optical images for the fabrication procedures of SDM hydrogel. (Reprinted with permission from ref. 84. Copyright 2010, Nature publishing group.)

Similar to SDM hydrogel, nanocomposite hydrogels constituted by entangled long polymer chains, i.e., poly (N, N-dimethylacrylamide) (PDMAAm), poly (N-isopropylacrylamide) (PNIPAAm)), were polymerized on the surface of clay nanosheets also demonstrated excellent self-healing properties.[85] Self-healing D-NC or N-NC hydrogels could be prepared via free-radical polymerization of DMAAm or NIPAAm in the aqueous solution of clay nanosheets. The self-healing capability of the hydrogels is mainly attributed to non-covalent interactions in networks, i.e., the hydrogen bonds between clay surface and polymer chains, as well as between polymer chains. It is note worthy that the NC hydrogels still exhibited self-healing ability, even the cut surfaces were deposed for a long time (*e.g.*, 120 h), which was much longer than that of SDM hydrogel (~1 min).

D-NC hydrogel with several fresh knife cuts could autonomously heal by contacting the cut surfaces for 48 h at 37°C (Fig. 9a). Self-healing performance of D-NC hydrogel declined with increasing clay content, because the reduced polymer chain length between adjacent clay nanosheets led to decreased entangled interactions of the polymer chains. Furthermore, although similar self-healing behaviors of N-NC hydrogels have been observed after mechanical damages, they can not self-heal at high temperatures (50 or 80°C). This is because PNIPAAm chains in N-NC hydrogels turn into hydrophobic and contracted state (coil-globule transition) above lower-critical-solution temperature (LCST) (32°C). Interestingly, D-NC and N-NC hydrogels could be alternately jointed together to form an integral N-NC/D-NC hydrogel, by combining several different kinds of cuts of D-NC and N-NC hydrogels for 48 h at 25°C (Fig. 9b). The tightly joined N-NC/D-NC hydrogel performed some interesting behaviors due to constituting of hydrogel sections with different properties. For example, when N-NC/D-NC hydrogel was immersed in water with temperature (50°C) higher than the LCST of PNIPAAm polymer, the N-NC sections became opaque and shrunk, while the D-NC sections remained transparent and swollen. The N-NC/D-NC hydrogels could maintain their integrity even after repeated temperature changes (Fig. 9c,d).

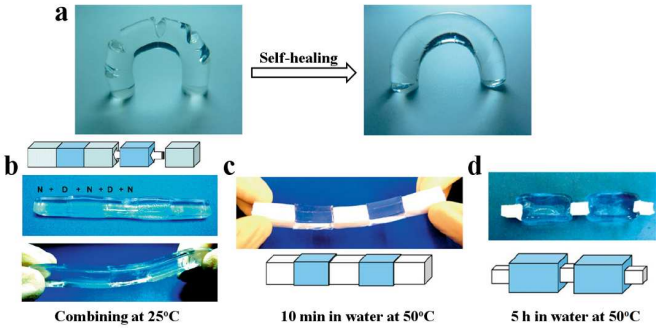

Fig. 9 Polymer-nanocomposite interaction-based PDMAAm and PNIPAAm self-healing hydrogels. (a) Self-healing of D-NC hydrogel with several knife cuts; (b) Self-healing of combined N-NC and D-NC hydrogels at 25°C for 48 h; (c) Changes of combined N-NC/D-NC hydrogels by immersing in 50°C water for 10 min and (d) 5 h, the N-NC sections are opaque and shrinking yet the D-NC sections are swelling. (Reprinted with permission from ref. 85. Copyright 2011, Wiley-VCH.)

In addition to nanoclay, other nanosheets, such as graphene oxide (GO), have also been used to develop self-healing nanocomposite hydrogels. Wang *et al.* fabricated a tough self-healing GO nanocomposite hydrogels by using graphene peroxide both as polyfunctional initiating and cross-linking centers.[86] The strong covalent bonds were formed between the PAAm polymer chains and the GO sheets through *in situ* grafting polymerization on the surface of graphene peroxide. Meanwhile, since GO sheets possess many functional groups like hydroxyl, epoxy, carbonyl and carboxyl groups, a plenty of PAAm polymer chains would physically adsorb onto GO sheets and form hydrogen bonds which conferred the self-healing property to the hydrogels. The GO nanocomposite hydrogel showed 0.35 MPa tensile strength and 4900% elongation, as well as achieved 88% healing efficiency at ambient temperature. Moreover, recently, a similar GO composite hydrogels with enhanced mechanical property using PA6ACA as polymer chains has also been developed.[112]

3.1.6 Multiple intermolecular interactions

Supramolecular gels are self-assembled from low molecular weight gelators in solvent by reversible non-covalent interactions.[108-111,113] The physical nature of multiple interactions acts as combined driving forces for the formation of supramolecular networks, including hydrogen bonds, π-π stacking and hydrophobic interactions, etc. For some supramolecular gels, the destroyed non-covalent bonds in the

network structure can be re-established upon healing.[114] Consequently, there are many kinds of self-healing gels formed through supramolecular self-assembly of small molecular/oligomeric gelators. In addition, lower-molecular-weight gelators may improve the fluidity of the gel networks,[59] which helps to generate the "mobile phase" from contact damaged interfaces, enhancing healing ability.

Fang and co-workers designed lower-molecular-weight gelators, cholesteryl (Chol) derivatives containing nitrobenzoxadiazole (NBD),[115,116] which could form a self-healing organogel (Chol-NBD gel) in the mixture solution of pyridine-methanol (Fig. 10a).[92] Hydrogen bonding and π-π stacking were the main driving forces to promote self-assembly of the gelators. Chol has a rigid and flat skeleton structure that shows a strong tendency to form aggregates with a defined specific orientation. As a consequence, the Chol-NBD gel exhibited remarkable self-healing property, and the three segments of the gel sliced by a razor could fuse into a continuous gel immediately.

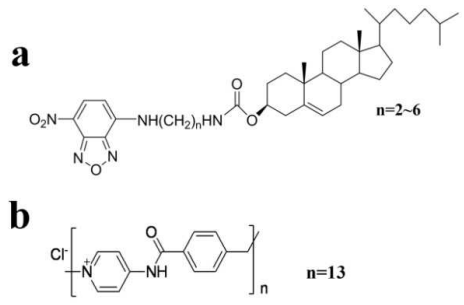

Fig. 10 The gelator chemical structures of (a) cholesteryl (Chol) derivatives containing nitrobenzoxadiazole (NBD); (Adapted from ref. 92.) (b) The molecular structure of oligomeric electrolyte.

Moreover, Yoshida *et al.* created an oligomeric electrolyte as a multifunctional gelator to prepare self-healing oligomeric electrolyte hydrogels (Fig. 10b).[90] The gelation mechanism between oligomeric electrolytes has been explained by multiple physical interactions containing hydrogen bond, cation-π interaction and π-π interaction, *etc*. As expected, the oligomeric electrolyte hydrogel exhibited a recovery of mechanical strength after a large amplitude oscillatory breakdown.

3.2 Chemical self-healing gels

The networks cross-linked by covalent bonds in traditional chemical gels are irreversible and too stable to turn out exchange reaction for self-healing. Dynamic covalent chemistry provides an appealing strategy to prepare chemical self-healing gels. In this approach, the chemical self-healing gels contain reversible dynamic covalent linkages, which can reform new covalent bonds around the damaged zone with or without specific stimuli (heat, light or pH). Various self-healing gels have been synthesized by dynamic covalent interactions, including phenylboronate complexations,[117-120] disulfide bonds,[65,121,122] imine bonds,[64,123,124] acylhydrazone bonds,[63,125,126] reversible radical reactions[127-130] and Diels-Alder (DA) reactions.[131-133]

3.2.1 Phenylboronate ester complexations

Complexation of diols and boronic acid can form a reversible boronate ester in aqueous solution, the stability of which depends on pH value.[134-138] Kiser and co-workers designed a dynamically restructuring self-healing hydrogel based on reversible boronate ester complexation of polymer-bounded phenylboronic acid (PBA) and salicylhydroxamic acid (SHA) (PBA-SHA) (Fig. 11a).[118] Neutral poly(2-hydroxypropylmethacrylamide) (PHPMA) and negatively charged poly(acrylic acid) (PAA) were chosen as backbones to modify PBA and SHA moieties, obtaining PHPMA-based PBA-SHA hydrogel and PAA-based PBA-SHA hydrogel, respectively (Fig. 11b). The reversible PBA-SHA complex in both kinds of hydrogel networks allowed cross-linking of the hydrogel networks to dynamically restructure and self-heal under acidic environment.

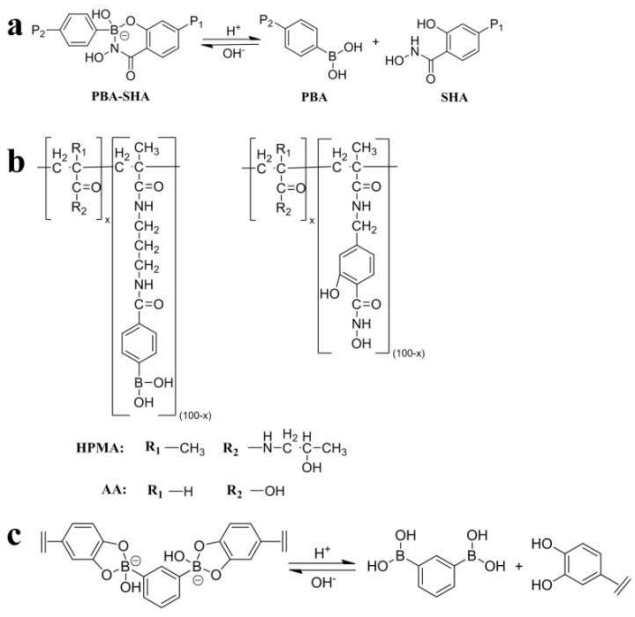

Fig. 11 Schematic illustration of (a) the dynamic pH-responsive PBA-SHA bonds and (b) linear PHPMA or PAA polymers containing either PBA or SHA moieties; (Reprinted with permission from ref. 118. Copyright 2007, Wiley-VCH.) (c) The pH-dependent bonds of catechol and 1,3-benzenediboronic acid in aqueous solution at 20°C. (Adapted from ref. 119.)

Afterwards, Messersmith's group exploited self-healing hydrogels through complexation of a catechol derived tetra-arm PEG (cPEG) with 1, 3-benzenediboronic acid (BDBA) in phosphate buffer saline (PBS) at 20°C under alkaline pH.[119] The presence of free BDBA (confirmed by ^{11}B NMR) proved that there was a dynamic equilibrium between free BDBA and borate ester complex in the hydrogel. Therefore, the dynamic complexation between boronic acid and catechol conferred the self-healing ability to the hydrogel at pH = 9.0. The hydrogel could almost fully recover its G' in 100 seconds when subjected to a large amplitude deformation (1000% strain). In addition, the hydrogel transformed from a gel to sol state when pH value was decreased from alkaline (pH = 9.0) to neutral (pH = 7.0) or acidic (pH = 3.0) (Fig. 11c). The above examples demonstrate that the self-healing ability of the hydrogels based on phenylboronate ester complexations strongly depends on pH changes.

3.2.2 Disulfide bonds

The disulfide bonds are dynamic covalent bonds based on thiol/disulfide dynamic exchange reactions, which are sensitive to pH or redox potential.[139-143] So far, a number of disulfide dynamic polymers have been constructed, and a self-healing rubber from epoxy resins containing disulfide links has been developed by Klumperman *et al.*[121] The self-healing rubber exhibited obvious advantages, such as full recovery of appearance and mechanical properties at moderate temperatures. However, only a few disulfide bond-based gels have been developed.

In 2012, Matyjaszewski and co-workers presented an approach to construct a self-healing organogel film based on thiol/disulfide redox reversible exchange reaction.[65] In this system, the multi-arm star polymers which has better flowability, were selected as the gelator due to low intrinsic viscosity. Thiol/disulfide groups were modified on the end of the branched polymers to ensure their accessibility for exchange reaction and thus undergo a rapid self-healing process.

Thin reversible organogel films cross-linked through S-S bonds were formed by depositing the solution of SH-functionalized star polymer (multi-arm star polymer chains with thiol (-SH) groups at arm periphery) on silicon wafers in the presence of an oxidation catalyst (I_2 or $FeCl_3$) (Fig. 12a). AFM test showed that the cut gel film with thickness of 1.5 μm and width of < 2.5 μm could heal within 20 min. However, healing efficiency was strongly dependent on the width of damage area. The gel film with cut width of 5 μm and 10 μm only partially healed within 2 h (Fig. 12b).

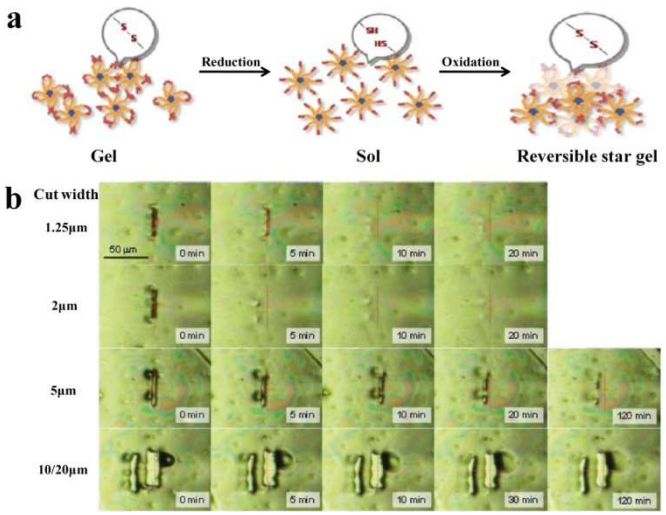

Fig. 12 Disulfide bond-based thiol/disulfide redox self-healing organogels. (a) Schematic illustration of the reversible gel film oxidized from the reductive SH-functionalized star polymers; (b) The optical microscope images of the self-healing process with initial cut width of 1.25, 2, 5, 10 and 20 μm, respectively. (Reprinted with permission from ref. 65. Copyright 2011, American Chemical Society.)

3.2.3 Imine bonds (Schiff base)

Imine bonds, commonly called Schiff base, are recently used as dynamic cross-linkers for creating self-healing hydrogels. Wei *et al.* obtained a self-healing dynamic chitosan-PEG hydrogel using aromatic Schiff base linkages.[64,123,124] The amine groups of main chitosan polymer chains were cross-linked by the benzaldehyde modified telechelic PEG to form the hydrogel (Fig. 13a).[64] Aromatic Schiff base is preferred in this case since it is relatively more stable than aliphatic Schiff base, which can not only maintain the dynamic nature but also improve the mechanical property of the hydrogel.[144,145] The uncoupling and recoupling of imine bonds dynamically occurred in the hydrogel networks, imparting self-

healing capability to the hydrogel. In self-healing test, the boundary between two different colored semicircle hydrogels (one was stained by rhodamine B) obscured and even the hole punch in the middle of the hydrogel disappeared completely after 2 h (Fig. 13b). In addition, the recovery of the mechanical properties of the hydrogel was confirmed by rheology recovery test, i.e., the G' recovered to original value after decreasing the amplitude to 20%.

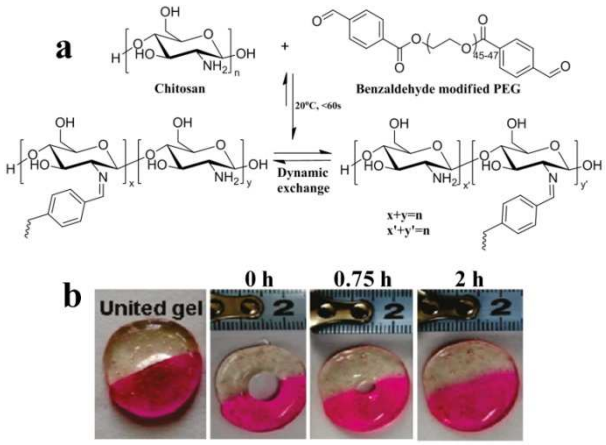

Fig. 13 Imine bond-based self-healing hydrogels. (a) chitosan-PEG hydrogel prepared by cross-linking of chitosan with benzaldehyde modified telechelic PEG; (b) The appearance of self-healing process between two different color semicircle hydrogels (the red one is stained by rhodamine B) and the hole punched in the middle of the united gel. (Reprinted with permission from ref. 64. Copyright 2011, American Chemical Society.)

Amazingly, the self-healing chitosan-PEG hydrogels were also sensitive to many chemical or biological stimuli including pH, amino acids (with amino groups) and vitamin B6 derivatives (with aldehyde groups), which can trigger the dynamic association/dissociation of the imine bonds, even leading to the final decomposition of the hydrogels. In fact, beside chitosan, a lot of biomacromolecules (e.g. gelatin, proteins and peptides) contain amine group. It is expected that more self-healing hydrogels based on imine bonds would be potentially developed by using these biomedical polymers.

3.2.4 Acylhydrazone bonds

Acylhydrazone bond is one of the imine bonds generated from the reaction of aldehyde and hydrazine, which has been used to prepare dynamic covalent polymers with different functions,[146-148] such as mechanically or fluorescent tunable dynamic polymers.[149-151] Recently, self-healing gels based on acylhydrazone bond have been reported. For instance, self-healing organogels cross-linked by acylhydrazone bonds through condensation of acylhydrazines at the two ends of a poly (ethylene oxide) (PEO) with aldehyde groups in tris[(4-formylphenoxy) methyl] ethane have been developed (Fig. 14a).[63] Breaking and regeneration of acylhydrazone bonds were reversible in polymer networks with glacial acetic acid as catalysis, leading to the fusion of cracked gel plates by keeping them in touch for 7 h.

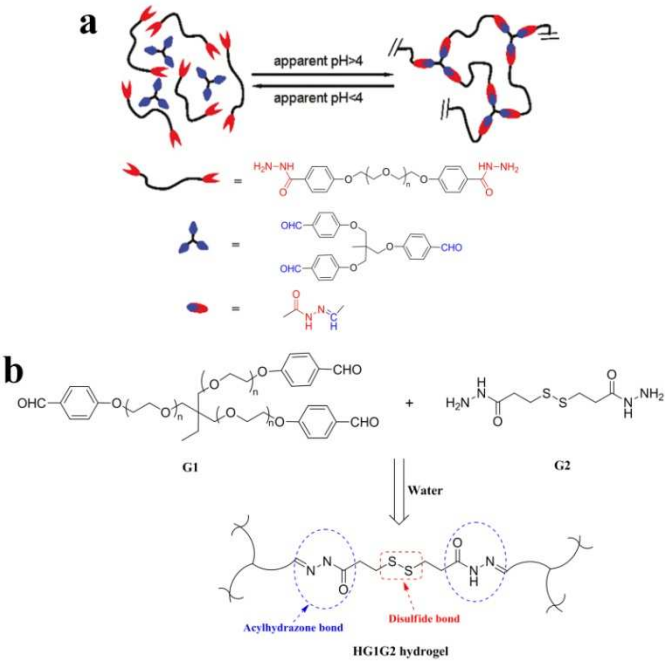

Fig. 14 Acylhydrazone bond-based self-healing gels. (a) The reversible polymer networks cross-linked by acylhydrazone bonds through condensation of acylhydrazines at the two ends of PEO with aldehyde groups; (Reprinted with permission from ref. 63. Copyright 2010, American Chemical Society.) (b) HG1G2 hydrogel contains both acylhydrazone and disulfide bonds. (Reprinted with permission from ref. 125. Copyright 2012, American Chemical Society.)

The same research group also created self-healing hydrogel named HG1G2 containing both acylhydrazone and disulfide bonds as multi-dynamic bonds, which was prepared by simply mixing aldehyde-terminated tris-armed PEO (G1) and dithiodipropionic acid dihydrazide (G2) in pure water at room temperature (Fig. 14b).[125] Three cut gel pieces could completely merge into an integrate HG1G2 hydrogel plate for 48 h under acidic conditions (pH = 6) or under basic conditions (pH = 9), due to the acylhydrazone exchange reaction and disulfide exchange reaction, respectively. However, the

self-healing behavior failed under neutral condition (pH = 7) since both dynamic acylhydrazone and disulfide bonds are kinetically "locked".

However, it should be pointed out that acylhydrazone exchange reaction would be "unlocked" in neutral condition by adding aniline as catalyst.[152] As a result, three pieces of HG1G2 hydrogel plates contained catalytic aniline self-healed into integration in 48 h with >50% self-healing efficiency according to tensile test. Furthermore, the self-healing performance of HG1G2 hydrogel was repeatable. This provided us an expanded idea to develop novel self-healing hydrogels by incorporating multi-dynamic bonds into one system. Inspired by this work, it would be interesting to broaden self-healing conditions by combining two dynamic chemical bonds, or even the physical and chemical interactions into the same gel system.

3.2.5 Reversible radical reactions

The gels based on reversible radical reactions exhibit self-healing behavior under photo illumination. Matyjaszewski and co-workers developed a self-healing system via dynamic covalent reshuffling of trithiocarbonate (TTC) units, which could undergo repeatable self-healing under UV irradiation.[127] The self-healing organogel with TTC units was synthesized by using n-butyl acrylate (BA) as monomer and TTC played the roles both as chain transfer agent and cross-linker in anisole, via reversible addition-fragmentation chain transfer polymerization (RAFT) (Fig. 15a). The self-healing mechanism of the organogel could be explained as follows. Under UV irradiation, the TTC units generated carbon radicals at the reactive chain ends by bond homolysis in nitrogen atmosphere. The diffusion of carbon radicals through the cross-linked networks allowed chain rearrangement and new backbone formation based on reshufflling reaction.

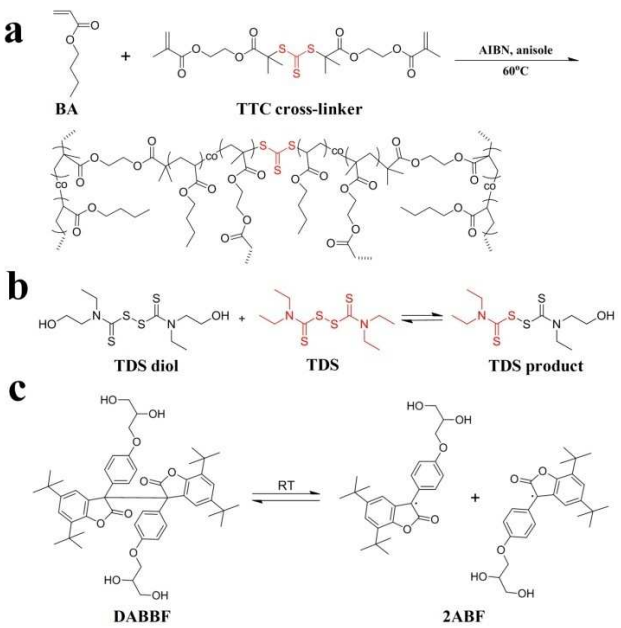

Fig. 15 Reversible radical reaction-based self-healing organogels. (a) The gel prepared by n-butyl acrylate monomer, cross-linking with TTC in anisole through RAFT copolymerization; (Reprinted with permission from ref. 127. Copyright 2011, Wiley-VCH.) (b) Model reshuffling reaction of TDS units under visible light; (Reprinted with permission from ref. 130. Copyright 2012, Wiley-VCH.) (c) The thermodynamic equilibrium of DABBF and ABF. (Reprinted with permission from ref. 129. Copyright 2012, Wiley-VCH.)

In further study, the gels based on reshuffling of thiuramdisulfide (TDS) units could self-heal only under visible light instead of UV irradiation,[130] because TDS can degeneratively exchange under visible light (Fig. 15b). The TDS cross-linked polyurethane organogel could be obtained by polyaddition of TDS diol, tetra (ethylene glycol), triethanolamine, and hexamethylene diisocyanate, in N, N-dimethylformamide with dibutyltin dilaurate as initiator at room temperature. The two pieces of organogel merged into integrity after 12 h under a commercial tabletop lamp, and the mechanical tensile strength remained nearly the same as that of the original.

Otsuka et al. has developed a dynamic organogel with ability to autonomously self-heal in air at room temperature without any light stimulus, using diarylbibenzofuranone (DABBF) as a novel dynamic covalent bond unit.[129] The self-healing organogel was prepared by polyaddition of DABBF and a toluene-2, 4-diisocyanate-terminated poly (propylene glycol) (PPG, Mn=2400) in 1, 4-dioxane, containing the DABBF unit as a reversible cross-linking point (Fig. 15c).

DABBF was a dimer of arylbenzofuranone (ABF, known as antioxidant), and the two oxygen-insensitive radicals ABF combined to form a C-C bond which only need air to reach a state of thermo-dynamic equilibrium.[153-156] The freshly cut surfaces of the two pieces of organogels wetted with a small amount of DMF (preventing urethane units of PPG forming hydrogen bond) almost disappeared at room temperature under air after 24 h, and the healing gels could withstand manual stretching. The gels performed self-healing even after being separated for 5 days, demonstrating that healing properties slightly depend on the freshness of damaged surfaces. Moreover, the tensile tests showed that longer healing times result in higher healing efficiency.

3.2.6 Diels-Alder reactions

DA reaction as one of "click chemistry" has played an essential role in preparation of various functional gels because of their high selectivity and yields without any side reactions and byproducts.[157-162] Moreover, the thermo-reversibility of the DA reaction is an interesting feature, and the DA linkages formed by diene and dienophile can be cleaved on heating and reach a new equilibrium.[163-167] Due to the above advantages, DA reaction has been developed as one of the most well-known chemical reactions for synthesizing self-healing gels.

Kavitha and Singha obtained a thermoreversible self-healing organogel film by using poly (furfuryl methacrylate) (PFMA) as dienes which was cross-linked with the dienophiles of bismaleimide (BM) in dichloromethane (Fig. 16a).[133] SEM images confirmed that a notch on the surface of PFMA-BM film slowly recovered at 120°C (Fig. 16b), and finally, the notch was completely repaired by thermal treatment for 4 h, due to new DA bonds formation via the cycloaddition reaction. In addition, high temperature enhanced the mobility of the cleavage and achieved a new equilibrium.

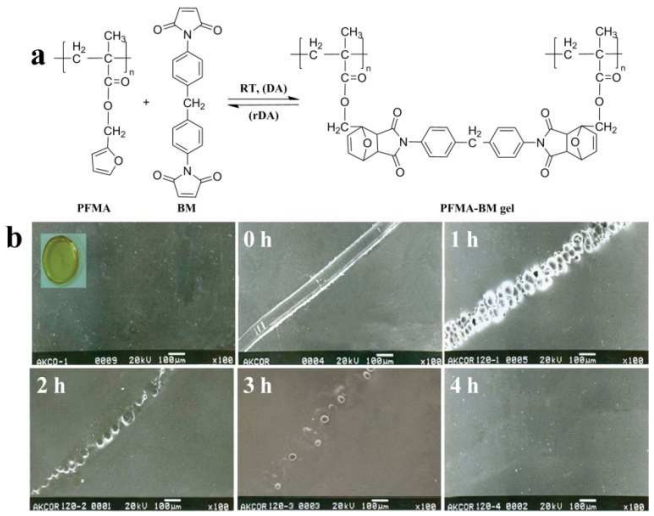

Fig. 16 DA reaction-based PFMA-BM organogel film. (a) Preparation of thermally reversible PFMA-BM gel through DA reaction; (b) SEM images of the PFMA-BM gel with a knife-cut healed for 1, 2, 3, and 4 h at 120°C, respectively. (Reprinted with permission from ref. 133. Copyright 2009, American Chemical Society.)

Moreover, Wei and Chen have recently developed a dextran-PEG based (Dex-l-PEG) self-healing hydrogel formed by reversible DA reaction.[69] Cytocompatible dextran modified by fulvene as dienes and PEG modified by dichloromaleic acid as dienophile were used to fabricated Dex-l-PEG self-healing hydrogel (Fig. 17a). These chemistries made it possible to prepare hydrogel that could self-healable under physiological conditions (pH 7.4, 37°C). The SECM was firstly used to *in situ* track the self-healing process of the hydrogels, providing detailed information of the self-healing process. The sequence of SECM images of the scratched hydrogel during the healing process could be produced in 2D and 3D, which showed that the longitudinal depth of scratch on hydrogel surface almost self-healed at 37°C after 7 h (Fig. 17b).

Currently, only limited dynamic covalent bonds were used to synthesize chemical self-healing gels. Many other reversible reactions belonged to dynamic covalent chemistry, such as ester exchange and amide exchange reactions,[48,49] potentially contribute to synthesize self-healing gels. It is envisioned that more new types of chemical self-healing gels should be developed by using the other reversible reactions.

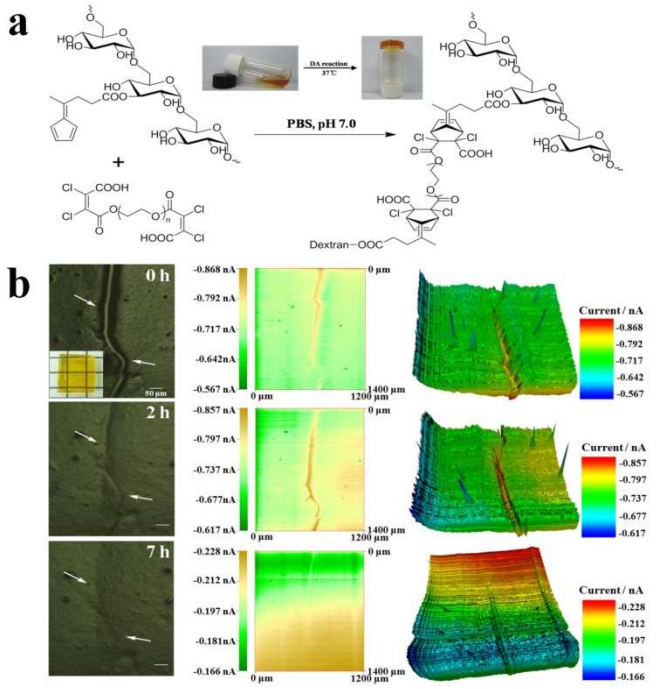

Fig. 17 DA reaction-based Dex-l-PEG hydrogel. (a) Chemical structures and photographs of the hydrogel cross-linked by reversible DA reaction through the fulvene groups and the two dichloromaleic acid groups at the end of cross-linkers; (b) 2D and 3D SECM images and corresponding optical microscope images (scale bar: 50 μm) of the self-healing process of a piece of the hydrogel with a scratch on its surface for 0, 2 and 7 h. (Reprinted with permission from ref. 69. Copyright 2013, Wiley-VCH.)

The progress of self-healing gels has been achieved by introducing the concept of dynamic and reversible CDC to meet the goal of designing a series of physical and chemical self-healing gels. It is worth noting that physical self-healing gels offer some advantages compared with chemical self-healing gels. The mechanical properties of some physical self-healing gels are superior to chemical self-healing gels, although the bond energy of covalent bonds is commonly higher than that of physical interactions. For example, the self-healing GO nanocomposite hydrogels, PVA hydrogels and micelle-based hydrogels exhibit a high mechanical strength and large tensile strain.[81,86,87] The phenomena indicate that although bonding energy of a single physical interaction is much lower than that of chemical bond, the cooperative action of numerous physical interaction may lead to the self-healing gels with enhanced mechanical performance.

Moreover, most physical self-healing gels have ability to autonomously repair themselves without external stimuli. However, the chemical self-healing gels usually require external stimuli to trigger their reversible reactions. For examples, the exchange reactions of phenylboronate ester are triggered by acid, the reversible DA reactions acquire heating, and the reshuffling of radical reactions need light stimulus, etc. The autonomously repair of physical self-healing gels provides a convenient way of restoring gel structure and functions.

In addition, self-healing gels based on reversible metal ions-ligand coordination have also been developed.[50-54] Nie et al. developed a self-healing gel through ferric ions coordinated with the PAA chains via metal ions-ligand interactions.[53] The free ferric ions and the reversible ionic bonds existed in the hydrogel networks conferred the self-healing ability to the hydrogel. Interestingly, Banerjee's group synthesized a series of supramolecular metallo-hydrogels based on the amphiphilic tyrosine interacting with the Ni^{2+}.[54] The self-healing property and stiffness of the metallo-hydrogel could be tuned by changing the chain length of the amphiphile. These examples provide the novel routes to further design and prepare the self-healing gels.

4. Emerging applications of self-healing gels

Self-healing gels have attracted increasing interests in industrial and biomedical fields. Thanks to the enthusiastic efforts of scientists working in CDC, various self-healing gels have been developed, and some potential applications have been proposed. For instance, the biocompatible liposome-based hydrogels,[78] peptide-based hydrogels[88] and injectable chitosan-PEG hydrogels[64,123,124] possess promising applications in cell culture, tissue engineering and drug delivery. More interestingly, the hydrogels can also be used to develop complex soft structures that can be finally applied as soft actuators and robotic devices.[41] However, compared with design of self-healing gels that have covered a broad domain in synthetic strategies, investigations on the application of self-healing gels remain sparse. Herein, some applications of self-healing gels in industrial field including coatings, sealants as well as in biomedical field including tissue adhesives, drug delivery and cell therapy are introduced.

4.1 Coatings/sealants

The PA6ACA hydrogels with self-healing capability at low pH based on hydrogen bonds aforementioned in section 3.1.3 have been exploited for a series of industrial applications.[41] For coating purpose, a 300 μm wide crack of PA6ACA hydrogel coating could self-heal within seconds when exposed to low-pH buffers (Fig. 18a,b). Therefore, people could repair the hydrogel coatings by succinctly spraying the cracks with a low pH buffer. As PA6ACA hydrogels were able to stick to various plastics due to hydrophobic interactions, they could also be used as sealant (Fig. 18c). For example, the hydrogel instantly sealed the hole of a polypropylene container filled with HCl and prevented any leakage of the acid. (Fig. 18d).

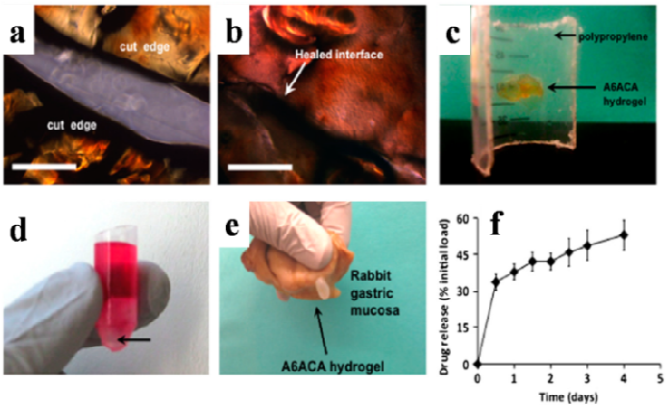

Fig. 18 Applications of self-healing PA6ACA hydrogels. (a) A cut in the PA6ACA coating on a polystyrene surface (scale bar: 500 μm); (b) The cut is healed after exposure to low-pH buffer. (c) The PA6ACA hydrogel adheres to a polypropylene surface; (d) The arrow indicate the hole on the polypropylene container of HCl, which is sealed with PA6ACA hydrogel; (e) The PA6ACA hydrogel adhere to a rabbit gastric mucosa. (f) Cumulative tetracycline release from PA6ACA hydrogel as a function of time. (Reprinted from ref. 41. Copyright 2012, National Academy of Sciences.)

4.2 Tissue adhesives

Self-healing hydrogels can be used as tissue adhesives. For instance, PA6ACA hydrogels were capable of adhesion well to the gastric mucosa of a rabbit, and the adhesion was strong enough to support its own weight (Fig. 18e). Therefore, the PA6ACA hydrogel was expected to be used as mucoadhesive for stomach perforations. In addition, it could also store and release drugs like tetracycline and thereby achieve therapeutic goals as well (Fig. 18f). All these findings demonstrate that the PA6ACA hydrogels could be used widely in the surroundings containing corrosive acids, promoting rapid pH-dependent self-healing.

4.3 Drug/cell delivery

Injectable hydrogels are promising for controlled-release of encapsulated therapeutics (cell therapy and drug delivery) by being injected as a liquid and gelated *in situ* to accommodate irregular defects of desired position.[168-170] However, traditional injectable hydrogels with slow gelation may lead to cargo loss (cell/drug) and diffusion from the target site, while the extremely rapid gelation would result in undesired premature solidification.[171-173] These practical problems can be solved by using self-healing hydrogels.

After developing the biocompatible chitosan-PEG self-healing hydrogels as new injectable biomaterials with self-repairing and drug delivery capability,[124] Wei et al. further developed a series of functional self-healing chitosan-PEG hydrogels with expanded applications, such as glycol chitosan (GCS)-based hydrogels for cell therapy carrier, and magnetic self-healing hydrogels for remotely controllable drug delivery system.[178-179] The synthesis strategy of self-healing GCS-based hydrogels was the similar to that of chitosan-PEG hydrogels described above in section 3.2.3, beside substituting chitosan of GCS with better solubility under physiological pH. As expected, self-healing GCS-based hydrogels could homogeneously encapsulate the cells *in vitro*. After injection from a needle, the broken hydrogel pieces can form an integral gel at the target site (Fig. 19a). The strategy can reduce the risk of early solidification to clog catheter during the injection and also prevent cargo loss due to slow gelation.

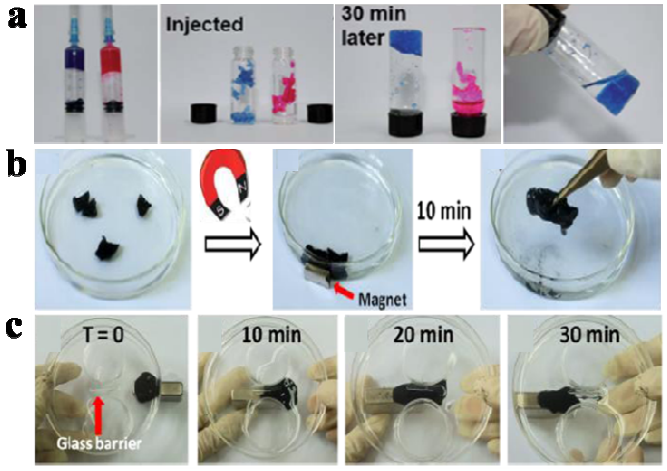

Fig. 19 Applications of self-healing chitosan-PEG hydrogels. (a) Injection and self-healing process of the GCS-based hydrogel (blue) as well as the contrast gelatin hydrogel (red); (Reprinted from ref. 124.) (b) Self-healing process of the scattered broken magnetic chitosan-PEG hydrogels which move together under an external magnetic field and fuse into an integrated gel after 10 minutes; (c) The magnetic chitosan-PEG hydrogel is manipulated by a magnet to pass through a narrow channel with an obstacle in the middle by shape transformation within 30 minutes. (Reprinted from ref. 123.)

Moreover, to improve remote controllability of drug delivery system, magnetic self-healing hydrogels have attracted particular attention. The fragments of self-healing hydrogels with magnetism can be easily guided and automatically merge together under magnetic field, rendering self-healing and magnetic remote control. Wei's group embedded carboxy modified Fe_3O_4 nanoparticles into chitosan-PEG self-healing hydrogels, affording dual functionalities, i.e., self-healing and magnetism, to the hydrogel.[123] The scattered broken magnetic self-healing hydrogel fragments moved together under an external magnetic field and then fused into an integrated gel after several minutes (Fig. 19b).

The hydrogel could also be remotely manipulated by a magnet to pass a narrow channel with an obstacle in the middle in 30 minutes (Fig. 19c). After the process, the hydrogel still maintained an integral shape because of the excellent synergistic effect of magnetic and self-healing features. These studies show that the self-healing gels offer a possible solution to a wide range of industrial and clinical pragmatic applications in the near future.

5. Conclusions and outlook

Studying on self-healing gels is one of the cutting-edge topics in polymer materials. The potential extensive applications of self-healing gels require us to address some open issues including (i) designing of self-healing gels with biocompatibility, toughness, and multi-functionalities; (ii) promoting theoretical study on self-healing mechanism; (iii) exploring the applications of self-healing gels; (iv) developing assessment systems for quantitatively evaluating self-healing performance.

Thanks for the development of molecule design and synthetic technology, a variety of self-healing gels have been developed. Particular attention will be paid to automatically self-healable gels, which do not need any external stimuli for recovery their original structures and functions. Triggering a self-healing process by external stimuli (heat, light, pH or catalyst) not only consumes energy, but also complicates the realization of self-healing performance. This would definitely limit their applications, particularly in biomedical field. For examples, temperature change or catalyst addition may irreversibly damage cells or biological tissues; light is impracticable for opaque samples or implanted samples that are impossible for irradiation. Furthermore, in order to meet the need of biomedical field, biocompatibility, non-toxicity and biodegradability are critical parameters for automatically self-healing gels.

So far, most self-healing gels have not yet fund practical applications, mainly due to their poor mechanical properties. Developing tough self-healing hydrogel is desperately needed. Several efforts have been devoted to address this challenge.[81,86,87] Compared with reported high strength gels (*e.g.*, double network hydrogel,[25-27] nanocomposite hydrogel,[104-106] topological hydrogel[174-177] or tough and stretchable hydrogel[29,30]), nevertheless, there is still a big gap between self-healing gels and tough gels which can sustain stress in MPa level and exhibit fracture energy in an order of 1,000 Jm^{-2}.

It is increasingly needed to develop self-healing gels with multifunctional systems. A promising class of self-healing gels in the future is multifunctional smart gels, which integrate self-healing ability and other functions, such as electrical conductivity, magnetism and luminescence, into a single gel system. The self-healing gels with multifunctionality and toughness would be potentially used in artifical electronic skin[180], soft actuator, and artifical muscle.

Understanding the mechanism of self-healing is crucial for synthesis and optimization of self-healing gels. Multi-scale numerical simulation, from atomic-scale, molecular-scale, to macroscopic continuum scale, is needed to fill the gap between theory and experiment. Unfortunately, the related study on this aspect is very sparse and it is far from fully understand the mechanism of self-healing. Note that Long et al. presented a 3D constitutive model to model the dynamic self-healing of gels.[181] Research towards this trend should be encouraged and expected.

Although some approaches have been developed for evaluating self-healing gels on macroscopic and microscopic level, most of them are still based on qualitative information. The development of assessment systems for quantitative evaluating self-healing

performance via *in situ* and non-destructive testing are urgently needed.

The aforementioned challenges require interdisciplinary collaborative researches. People from chemistry, biology, physics, and engineering, should work together to boom this field. Efforts should focus on molecular designing, biological evaluation, theoretical simulation and characterization. The contribution from multifaceted researchers will promote the progress in self-healing gels in near future.

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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