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Designing self-healing hydrogels for biomedical applications

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Self-healing hydrogels have emerged as the most promising alternatives to conventional brittle hydrogels used in the biomedical field due to the features of long-term stability and durability. However, the incompatibility between the fast self-healing property and enough mechanical strength of hydrogels remains a challenge. Therefore, hydrogels that possess not only mechanical toughness but also autonomous self-healing capacity are sought after. This review presents a comprehensive summary of the latest self-healing mechanisms. Specifically, we review various systems based on dynamic bonds, ranging from dynamic covalent bonds to non-covalent bonds. Additionally, this review presents different characterization methods for self-healing hydrogels, and also highlights their potential applications in the biomedical field, such as tissue engineering, drug delivery, cell therapy, and wound dressing. Furthermore, this review aims to provide valuable guidance for constructing diverse self-healing hydrogels with tailored functions.

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Wider impact

Over the past few years, hydrogels have gained increasing attention in both basic and translational biomedical studies due to their unique physicochemical and mechanical properties. Although the chemically crosslinked hydrogels with static networks have been extensively explored, a growing body of research has revealed that the dynamic self-healing hydrogels can more closely simulate the soft tissues. However, choosing suitable dynamic crosslinking chemistries for specific biomedical applications remains a challenging endeavor. In this review, we aim to provide a comprehensive summary of the recently reported self-healing mechanisms, ranging from dynamic covalent bonds to non-covalent interactions, and detail their respective reaction conditions, hydrogel properties, as well as performances in diverse biomedical fields. Additionally, various characterization methods used to assess self-healing efficiencies are briefed. Furthermore, we shed light on the potential applications of these self-healing hydrogels in different biomedical fields such as tissue engineering, drug delivery, cell therapy, and wound dressing. Lastly, we conclude this review by discussing the challenges and emerging trends to guide the future developments and applications of self-healing hydrogels, with the vision of constructing more advanced self-healing hydrogels for clinical translational studies.

1. Introduction

Hydrogels are crosslinked hydrophilic polymer networks with high water content that mimic the extracellular matrix.[1–3] They have attracted considerable attention in the biomedical field owing to their unique physicochemical properties.[4–7] In particular, the *in situ* gelation of hydrogels allows the filling of irregular defects without the requirement of a pre-fabrication process.[8] Additionally, the biomimetic network structure of hydrogels makes them promising candidates for use as scaffolds in tissue engineering.[9,10] The porous morphology of hydrogels also enables them to be utilized as carriers for loading bioactive compounds and controlling their release for various biomedical applications.[11,12] To date, a wide range of polymers, both chemically synthesized and derived from natural sources, have been employed for constructing versatile hydrogels through physical interactions or covalent bonds.[13–15] Furthermore, recent trends indicate that hydrogels generated from biological molecules or by incorporating biologically active moieties, such as growth factors, exhibit distinct biofunctionality.[16–18]

The mechanical strength of hydrogels is also a crucial property for their long-term use in the biomedical field. For example, cellular behavior can be modulated when the

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cell-embedded hydrogels have tunable stiffness and bioactive groups.[19–21] Additionally, when employed *in vivo*, the implanted hydrogels always suffer from continuous mechanical force owing to the frequent body movement, which may result in hydrogels losing their integrity.[22,23] This is particularly of concern as the broken hydrogels can significantly increase the risk of infection due to the external bacterial intrusion. Thus, hydrogels for *in vivo* applications require excellent mechanical durability. Generally, there are several decisive factors, including the hydrogel concentrations, crosslinking densities, and the type of chemical bonds,[24–26] that can be tuned to change the mechanical properties of hydrogels. Although the improvement in mechanical strength may lead to the long-term durability of hydrogel's integrity, other desirable properties may be compromised. For instance, with increasing crosslinking density, the pore size in hydrogels can be significantly decreased,[27,28] which can greatly restrict the diffusion of nutrients and have an adverse effect on cell growth when cells are cultured in hydrogels. In contrast, the degradation rate of hydrogels can be distinctly slowed down, causing the hydrogel degradation rate hardly match tissue generation and ultimately limiting new tissue regeneration. Therefore, when designing hydrogels for diverse biomedical applications, the mechanical properties must be considered.

In spite of the attractive performance of hydrogel materials, the integrity, mechanical strength, as well as the lifespan of the hydrogel networks may deteriorate or even be lost due to the accumulation of cracks, which significantly restricts hydrogel applications. In order to resolve this issue, hydrogels are highly anticipated to intrinsically and automatically recover their original morphology, mechanical properties, and functions after repeated damage. Based on blueprints derived from nature, the self-healing mechanism has been greatly developed in recent years.[29,30] For instance, skin can autonomously restore its initial functions after contusion or scrapes. Another instance is the secretion of mussels, which has inspired us to design pH-responsive self-healing hydrogels.[31,32] Classically, one effective method to construct self-healing hydrogels is by integrating different fillers or adhesives into the hydrogels. This allows for the self-healing behavior to be achieved by releasing healing agents to the damaged regions.[33,34] However, there are several limitations that still exist, including the irreversible healing process, limited healing efficiency, and interference of healing agents, which inevitably have an adverse effect on hydrogel applications. To achieve more efficient autonomous self-healing behavior, to date, two main strategies including the non-covalent interactions (*e.g.*, host–guest, hydrogen bonds, hydrophobic interactions, and metal–ligand coordination) and dynamic covalent bonds (*e.g.*, acylhydrazone bonds, Schiff base bonds, boronate ester bonds, disulfide bonds) have been employed to construct self-healing hydrogels.[35–37] For both hydrogel systems, the constant breaking–reformation reactions contribute to the self-healing performance.

Herein, we thoroughly scrutinize the recent advancements in self-healing hydrogels, and mainly concentrate on the proposed self-healing mechanisms and the diverse characterization stratagems used to test the self-healing efficiency. Particularly, the utilization of self-healing hydrogels in the biomedical field, such as drug delivery, tissue engineering, cell therapy as well as wound healing, is illustrated in detail as well. Furthermore, the future development prospects are also presented.

2. Characterization of self-healing hydrogels

The properties of hydrogels have been thoroughly characterized by various methods. However, for the self-healing hydrogels that could repair themselves without the need for external stimuli, it is typically important to evaluate the self-healing behavior by macroscopically monitoring the repairing process as well as by quantifying their healing performance. So far, multiple strategies based on either qualitative or quantitative evaluation have been employed to estimate the self-healing performance of dynamic hydrogels.[38] For example, when analyzing the reversible interactions within hydrogels,

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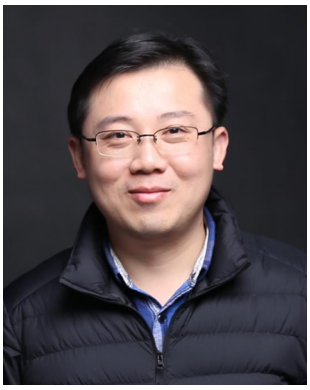

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spectroscopic methods, such as Fourier transformation infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR), and Raman spectroscopy, can be applied to present the dynamic nature of dynamic covalent bonds by demonstrating the transition between the bond states. Morphology characterization, primarily through macroscopy, optical microscopy, atomic force microscopy (AFM), and scanning electron microscopy (SEM), is also a major and simple way to estimate the self-healing properties.[39,40] The commonly used methods to quantify the healing efficiency include tensile/compressive and rheological experiments, by comparing the mechanical properties of the repaired and initial hydrogels. To define the healing efficiency, the ratio of mechanical strength of the repaired hydrogel and its initial hydrogel is utilized.

Through observation one can simply analyse the morphology of hydrogels. Specifically, the hydrogel is bisected and rejoined. After a certain period of time, the healed interface is examined (Fig. 1a).[41] If there is no obvious macroscopic crack observed and also the two pieces of the hydrogel can be stretched without breaking, it can be predicted that the hydrogel has healed well. Before observations, the pieces are often stained with different dyes, such as rhodamine B (red), methyl orange (orange), calcein (yellow), and so on, for easy visual identification. Furthermore, with the assistance of SEM and AFM, it is evident to observe the nanoscale morphology in healing interfaces for the dynamic hydrogels. Although the healing process can be monitored at different times through observation, the healing efficiency can hardly be observed solely through macroscopic methods. This is because the healing effect is closely related to other factors, such as polymer mobility, crosslink reformation, temperature, healing time, pH, *etc.*[42–44]

Mechanical measurements that can reflect the crosslinking density within hydrogels can be conducted to evaluate the healing efficiency. The uniaxial elongation test was the most frequently used way to assess the self-healing efficiency. Hydrogel samples with cylindrical and rectangle/dumbbell shapes were cut into halves and then rejoined for a predetermined time. The stress–strain results of hydrogels could be obtained, in which the fracture stress as well as the elongation at break (elongation ratio, λ) were recorded as vital parameters to estimate the self-healing behavior (Fig. 1b). When the fracture stress was applied to evaluate the self-healing capacity, the corresponding healing efficiency can be quantified using the ratio of the strength of the repaired hydrogel at the point of fracture to that of the original hydrogel (Fig. 1c). Similarly, the healing efficiency can also be estimated *via* elongation ratio of the pristine hydrogel and the healed hydrogel. This method is mainly suitable for tough and stretchable hydrogels. However, for soft and flexible hydrogels, it is not appropriate to employ the tensile test because these hydrogels are too soft to bear clamping. Instead, the strain compressive test using a wedge-shaped jig is a viable alternative for assessing the strength of the healed interface in soft hydrogels. Additionally, the rheological test is another commonly adopted strategy for evaluating the self-healing performance.[45] In general, the continuous step-strain sweep tests are usually conducted to monitor the self-healing properties (Fig. 1d and e). Upon undergoing a high strain (*e.g.*, 500%), the storage modulus (G') of the hydrogel is reduced and it falls below the loss modulus (G''), manifesting the destruction of the hydrogel network. However, once the strain is subsequently changed to a relatively small value (*e.g.*, 1%), both G' and G'' can quickly recover to their pristine state. Such a breaking–healing process is fully reversible and repeatable, thereby demonstrating the remarkable self-healing capacity of dynamic hydrogels. Actually, when evaluating the self-healing performance of dynamic hydrogels, the test method can be chosen based on the hydrogel's unique properties. For example, hydrogels with high viscosity can be evaluated using the linear viscosity measurements at alternating low and high shear rates.[46] Additionally, for conductive dynamic hydrogels, not only can the above presented testing methods be used to evaluate the self-healing performance, but also the recovery of electrical signals such as resistance and conductivity can be employed as a useful tool to assess the hydrogel's self-healing capability.[47,48]

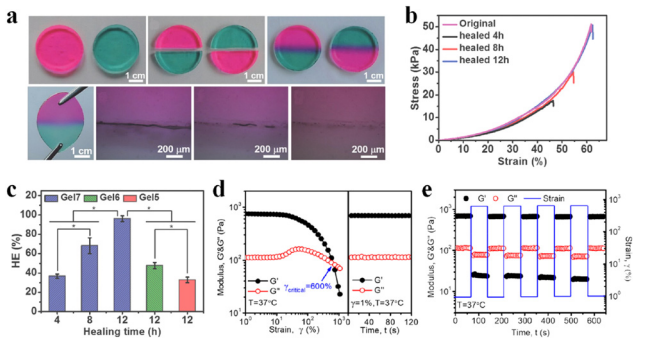

Fig. 1 Different strategies to test the self-healing performance of dynamic hydrogels. (a) Photographs showing the self-healing property. Both of these hydrogels were separately stained with rhodamine B and methylene blue, and then broken into two sections. Two semicircular hydrogels could be fused into a complete hydrogel after 6 hours, and meanwhile the crack nearly disappeared as revealed by microscopic observation. (b) Stress–strain curves of the hydrogel healed at different times. (c) Quantitative healing efficiencies for the hydrogel concluded from panel (b). Reproduced with permission.[41] Copyright 2017, Wiley-VCH. (d) Strain sweep measurement followed by a time sweep test (1% strain) for a hydrogel obtained in acidic PBS solution (pH 3) indicating the rapid recovery from destruction. (e) The step-strain test for the dynamic hydrogel. Reproduced with permission.[45] Copyright 2021, American Chemical Society.

3. Mechanisms of self-healing hydrogels

The self-healing mechanisms of dynamic hydrogels are primarily derived from dynamic covalent bonds and noncovalent interactions. Dynamic covalent bonds, which are distinct from the traditional covalent bonds, not only have the stability similar to covalent bonds but also the reversibility to

noncovalent interactions. The typical dynamic covalent bonds include boronate ester bonds, acylhydrazone bonds, disulfide bonds, imine bonds, *etc.* Besides, the noncovalent bonds includes hydrogen bonds, ionic interactions, hydrophobic interactions, metal–ligand coordination, *etc.* (Fig. 2). The self-healing capacity is achieved on account of the continuous dissociation and reformation of dynamic cross-linkers.

3.1 Dynamic covalent bonds

3.1.1 Imine bonds. Imine bonds, constantly referred to as "Schiff base bonds", are reversible covalent bonds that can be generated through a nucleophilic attack of a primary amine on an aldehyde or carbonyl group with the production of a water molecule. This reaction almost proceeds under mild conditions, such as neutral and acidic pH. Generally, aromatic Schiff base bonds are more widely used than the aliphatic Schiff base bonds owing to their much higher stability.[49] Although the generated imine bond is strong (150 kcal mol^{-1}), a dynamic equilibrium can occur through the uncoupling and recoupling of imine bonds if water molecules are present. Thus, the imine bond is always utilized as the dynamic crosslinker to fabricate dynamic self-healing hydrogels.[50,51] Given this, a study by Zhang *et al.* applied the Schiff-base linkage between telechelic-difunctional poly(ethylene glycol) (DF-PEG) and chitosan to construct a dynamic hydrogel (Fig. 3a).[52] Both the polymers could form an entire hydrogel within 60 s at 20 °C with a storage modulus of about 3500 Pa. Particularly, in a self-healing test, the punched hole in the hydrogel disappeared after 2 hours and further the G' of the hydrogel being broken at a high strain (200%) recovered to its original value when a low strain (1%) was applied. Apart from the superior self-healing ability, an attractive property for Schiff base bonds is their multiple responsiveness to different kinds of external stimuli, such as pH, temperature, amino acids (*e.g.*, L-lysine), as well as pyridoxal, which can not only induce the reversibility of the Schiff base bonds, but also lead to the decomposition of such bonds and the subsequent degradation of hydrogels.

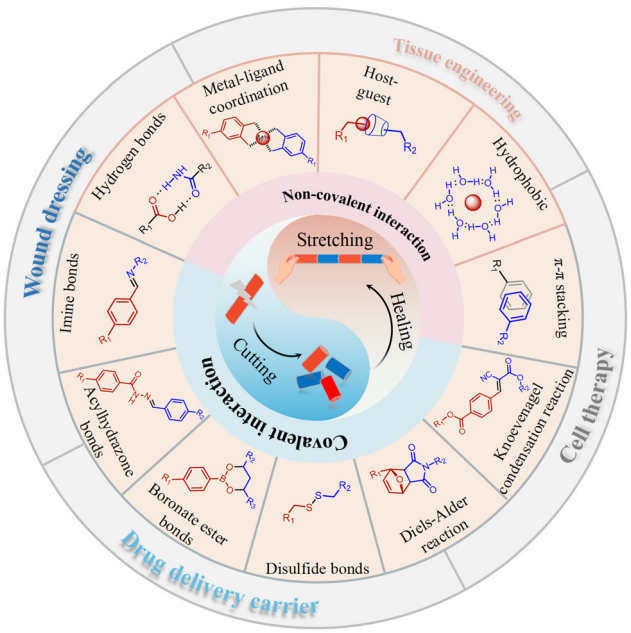

Fig. 2 The various strategies to design self-healing hydrogels and their biomedical applications.

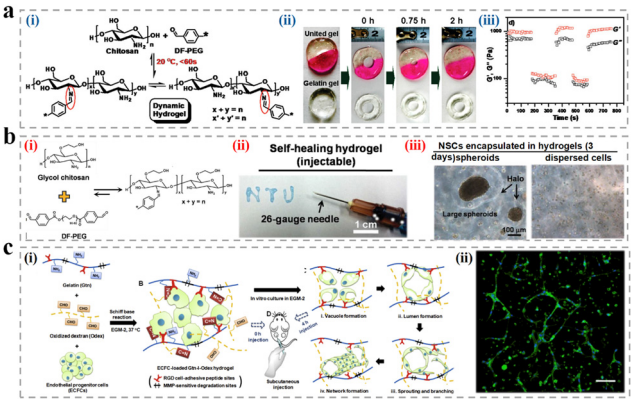

Fig. 3 Hydrogels crosslinked with imine bonds. (a) (i) Preparation of DF-PEG and its crosslinking with chitosan for developing dynamic hydrogels. (ii) Macroscopic self-repairing process of hydrogels over time. (iii) The step-strain measurement for the self-healing hydrogel. Reproduced with permission.[52] Copyright 2011, American Chemical Society. (b) (i) Benzaldehyde-functionalized PEG crosslinking with glycol chitosan for constructing self-healing hydrogels. (ii) Such a hydrogel can be injected *via* the syringe needle (26 G) without any clogging. (iii) The morphology of NSC spheroids incorporated within the self-healing hydrogel. Reproduced with permission.[53] Copyright 2015, Wiley-VCH. (c) (i) Fabrication of a self-healing hydrogel from gelatin and oxidized dextran, and its application for use as an injectable carrier. (ii) The formed microvascular networks in the hydrogel after 48 h. Reproduced with permission.[54] Copyright 2018, Elsevier.

Although the use of chitosan in fabricating self-healing hydrogels crosslinked with imine bonds is increasing, its limited solubility under physiological conditions hinders its use in biomedicine. To address this challenge, Tseng *et al.* utilized glycol-functionalized chitosan and combined it with DF-PEG to prepare a hydrogel with self-healing properties (Fig. 3b).[53] It exhibited not only superb injectability but also the self-healing behavior. Even after breaking, the G' of the hydrogel was capable of quickly recovering to its initial level. Most remarkably, murine neural stem cells (NSCs) integrated within this hydrogel displayed a faster proliferation and differentiation rate, indicating the valuable potential of this hydrogel for restoring the diseased nervous system (Fig. 3c).[54] Apart from chitosan, other polymers with amino groups, such as gelatin[55] and polyetherimide,[56] could also be chosen for the preparation of dynamic hydrogels through the formation of imine bonds with the aldehyde-functionalized polymers, demonstrating the good universality of imine bonds in practical applications.

Based on the synthetic versatility, material availability, ease of use, and mild reaction conditions, dynamic hydrogels crosslinked with imine bonds have been extensively applied in various biological fields. Particularly, several protein hydrogels that are formed through the available amine groups of proteins and aldehyde linkers (*e.g.*, glutaraldehyde or formaldehyde)

have been exploited for clinical applications.[57,58] Currently, there are several commercial hydrogel products based on imine bonds that have been developed, such as the collagen-based hydrogels for wound dressings and tendon wraps, as well as albumin-based hydrogels for vascular sealants. However, one notable shortcoming may be the toxicity of the unreacted glutaraldehyde molecules.

3.1.2 Acylhydrazone bonds. Acylhydrazone bonds, which have similar characteristics to imine bonds, are formed through a condensation reaction between aldehyde and hydrazine groups. Acylhydrazone bonds can also be formed under physiological conditions, similar to imine bonds. The formative acylhydrazone bonds are more stable than imine bonds owing to the mesomeric effect. Also, this reaction demonstrated a highly efficient and chemospecific feature. The dissociation of acylhydrazone bonds can be triggered only under acidic conditions (pH 4–7) or at high temperatures.[59] Therefore, such bonds are promising to prepare self-healing hydrogels. As an illustration, Deng *et al.* developed a hydrogel by mixing aldehyde-modified tris[(4-formylphenoxy)methyl]ethane and acylhydrazine-modified polyethylene oxide (PEO) (Fig. 4a).[60] This hydrogel displayed excellent self-healing performance on account of the reversible acylhydrazone bond cross-linkages. Once broken, the acylhydrazone bonds at the interface decomposed into acylhydrazine and aldehyde groups. The hydrogel network was repaired when the separated pieces were reconnected and the acylhydrazone bonds reformed under acidic conditions (pH $>$ 4), and such sol–gel transition could be reversibly carried out multiple times by adjusting the acidity of the hydrogel, indicating promising potential for smart soft materials.

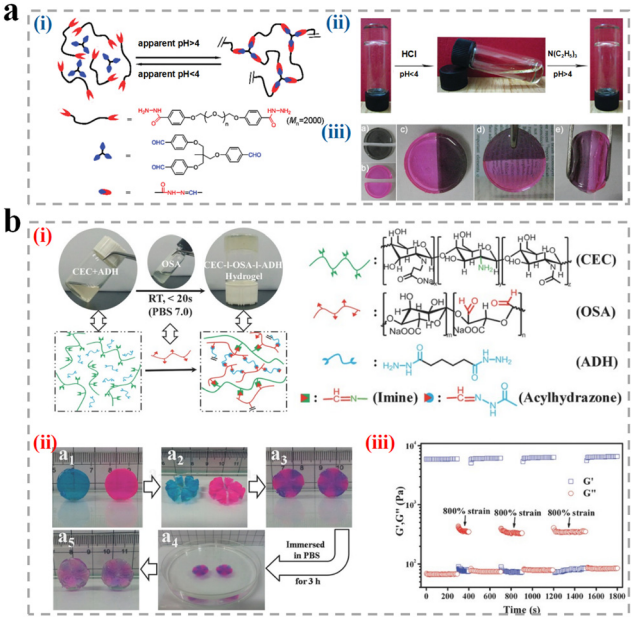

Fig. 4 Hydrogels crosslinked with acylhydrazone bonds. (a) (i) Fabrication of hydrogels from the acylhydrazone bonds. (ii) The gelation process of polymer solutions with the altered acidity. (iii) The photos showing the self-healing process for the hydrogel. Reproduced with permission.[60] Copyright 2010, American Chemical Society. (b) (i) Scheme of the polysaccharide-based self-healing hydrogels. (ii) Two disk-shaped hydrogels that were broken into 8 pieces could reform the complete hydrogels and stand for 6 h without collapse. And the hydrogels immersed into PBS solution for 3 h still retained their original shape. (iii) Cyclic G' and G'' for hydrogels that underwent the alternated strain of 1% and 800%. Reproduced with permission.[61] Copyright 2015, Wiley-VCH.

High stability is a fascinating feature for the hydrogels based on acylhydrazone bonds. However, acylhydrazone bonds are more stable in acidic environments, which is not beneficial for the application of these hydrogels in biomedical fields. In order to solve such challenge, a strategy that combined diverse kinds of dynamic bonds into a system has been provided. Zhao *et al.* fabricated a polysaccharide-based self-healing hydrogel *via* adipic acid dihydrazide (ADH) and *N*-carboxyethyl chitosan (CEC) with oxidized sodium alginate (OSA), which was constructed through the formation of Schiff base bonds as well as acylhydrazone bonds (Fig. 4b).[61] The self-healing characterization showed that the self-healing performance at neutral pH was primarily derived from the Schiff base bonds, the healing efficiency of which reached up to 95%. Meanwhile, the self-healing efficiency could be improved by increasing the healing time and raising the temperature. The step strain measurements further illustrated the self-repairing ability of this hydrogel. Furthermore, we anticipated that such a hydrogel with outstanding self-healing ability would be suitable for use as a cell and drug carrier.

Despite the higher stability of acylhydrazone bonds under acidic conditions, the efficiency of this reaction significantly decreased at pH values beyond this range. For example, the reversible acylhydrazone bonds would be more stable in a neutral environment. As a result, the self-healing performance of hydrogels prepared from acylhydrazone bonds is greatly compromised. It has been demonstrated that the application of catalysts was effective in facilitating the exchange dynamics of acylhydrazone bonds under neutral conditions. Several catalyst systems have been developed so far, including aniline,[62] 2-(aminomethyl) benzimidazole,[63] 2-aminophenols,[64] as well as 4-amino-DL-phenylalanine (4a-Phe).[41] Consequently, hydrogels prepared using benzaldehyde-terminated poly(ethylene glycol) and hydrazide-functionalized cellulose, which contained a higher concentration of catalytic 4a-Phe, fully merged into a perfect hydrogel after 36 h at room temperature, with a repairing efficiency of 96.1 $\pm$ 3.0%. On the other hand, hydrogels with relatively few 4a-Phe hardly healed completely after several days. This situation provided an idea that hydrogels crosslinked with acylhydrazone bonds would have extensive applications in the biomedical field by incorporation of a biocompatible catalyst. To date, significant progress has been made in the biomedical applications of acylhydrazone bond-based hydrogels. As an illustration, Purcell and colleagues designed a hydrazone bond-based hyaluronic acid hydrogel loaded with heparin binding recombinant TIMP-3 for treating heart failure.[65] Owing to the existence of protease-sensitive units, the hydrogel can be gradually degraded, releasing the loaded cargo to the intended target. However, due to the complicated technology, undefined toxicity, and relatively low

mechanical strength of these hydrogels, there is still a long way to go in terms of clinical translation.

3.1.3 Boronate ester bonds. Reversible boronate ester bonds can be generated through the complexation of boronic acid with *cis*-1,2 or *cis*-1,3 diol compounds in an aqueous solution. Generally, when the pH is not lower than the pK_a of boronic acid, the reaction between diol and boronic acid can readily occur.[66,67] Considering the reversibility of boronate ester bonds, Chen *et al.* constructed a reversible hydrogel formed by benzoxaborole and catechol-functionalized methacryloyloxyethyl phosphorylcholine (MPC) (Fig. 5a).[68] On account of the lower pK_a of benzoxaborole (pK_a ~ 7.2), the hydrogel could be easily produced after mixing the two polymer solutions under physiological conditions. When four hydrogel pieces were put together for 1 min, they could be fused together within 20 s because of the refabrication between the residual boronic acid bonds and catechol groups. Rheological tests further demonstrated that the G' of this hydrogel could restore to its initial value when 5% strain was applied after being broken at a 550% strain. In addition, the boronate ester bonds showed pH/sugar-responsiveness, and thus, when this hydrogel prepared from boronate ester bonds was exposed to acidic or competitive diol-containing molecules, the hydrogel network may collapse.

Although boronate ester bonds have been widely employed to construct dynamic hydrogels, most boronic acids have a pK_a value of $\geq$8, which greatly limits the application of these materials under physiological conditions. To this end, Yesilyurt and co-workers designed a variety of hydrogels *via* mixing four-arm poly(ethylene glycol) (4-arm PEG)-dio and different phenylboronic acid-functionalized 4-arm PEG polymers (PEG–FPBA, PEG–PBA, as well as PEG–APBA) (Fig. 5b).[69] It has been reported that the pK_a values of the three phenylboronic acid molecules followed the order PBA (7.8) > FPBA (7.2) > FPBA (6.5–6.7).[70,71] Thus, two hydrogels could be rapidly formed within 30 s in the buffer solution at pH ranging from 6 to 8 when PEG–FPBA and PEG–APBA acted as the hydrogel building blocks. However, for the PEG–PBA, the hydrogel can hardly be constructed at pH 6 due to a higher pK_a of PEG–PBA compared to the other phenylboronic acid polymers. These hydrogels displayed obvious shear-thinning as well as self-healing capacities and were capable of serving as a glucose-responsive drug carrier for the controlled release of drug molecules. Cell encapsulation within the hydrogel demonstrated up to 80% cell viability after 72 h, indicating the outstanding potential for 3D cell culture.

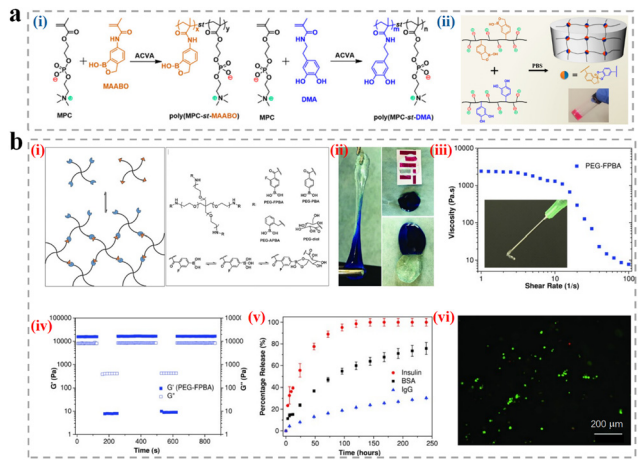

Fig. 5 Boronate ester bond-based self-healing hydrogels. (a) (i) and (ii) Synthesis route for poly(MPC-*st*-MAABO) and poly(MPC-*st*-DMA) and preparation of dynamic hydrogels. Reproduced with permission.[68] Copyright 2018, American Chemical Society. (b) (i) Chemical structures of PEG–phenylboronic acid and PEG-diol, and construction of PEG–FPBA hydrogels from boronate ester bonds. (ii) The macroscopic self-healing characterization for the PEG–FPBA hydrogel. (iii) Shear-thinning capacity of the hydrogel. (iv) Dynamic strain amplitude test of the PEG–FPBA hydrogel at pH 7. (v) Release curves of different proteins from the PEG–FPBA hydrogel. (vi) Fluorescent images of cells loaded in this hydrogel after incubation for 3 days. Reproduced with permission.[69] Copyright 2016, Wiley-VCH.

Apart from pH/sugar responsiveness, alteration of the internal structures is a feasible strategy for controlling the degradation of these hydrogels. Ding *et al.* selected 2-formylphenylboronic acid (2-FPBA) as a crosslinker and designed an injectable hydrogel based on C=C double bonds and boronate ester bonds between cyanoacetate-modified 4-arm PEG and poly(vinyl alcohol).[72] This hydrogel could be constructed within seconds and readily dissolved by introducing cysteine through forming the stable thiazolidino boronate complex between 2-FPBA and cysteine. Its further applications for on-demand dissolution wound dressings were also confirmed by using a full-thickness wound model with promising results. Taken together, these studies indicate that the highly pH-sensitive dynamic hydrogels based on boronate ester bonds can be employed to fabricate self-healing and compatible hydrogels for various biomedical applications.

There are many advantages of boronate ester bonds used for the construction of dynamic hydrogels. For example, the diol groups exist in most natural polysaccharides, which can be easily obtained without the need for a complex synthesis process. Moreover, the multi-responsiveness of boronate ester bonds also makes these hydrogels much smarter for use as drug/cell carriers in the biomedical field. However, despite many advances in these kinds of hydrogels, they are still far from clinical applications due to the complex technology and harsh reaction conditions between the boracic acid and diol groups.

3.1.4 Disulfide bonds. Disulfide bonds are commonly used reversible covalent bonds that are formed through the thiol–disulfide exchange reaction, and they can be created by oxidizing thiol groups under neutral or alkaline conditions as well. Besides, the disulfide bonds are highly sensitive to different stimuli, including pH,[73] reducing agents[74] (*e.g.*, dithiothreitol (DTT)[75]), UV light,[76] and so on. So far, numerous dynamic self-healing hydrogels from disulfide bonds have been designed. For instance, Song *et al.* developed a F127-LA hydrogel that was crosslinked with α-lipoic acid (LA)-functionalized Pluronic F127.[77] The hydrogel exhibited self-healing performance after UV irradiation because of the rapid exchange between thiol and disulfide bonds. When two separated hydrogels were brought

together, the free thiol groups at the fracture surface rapidly exchanged with the other disulfide bonds under UV irradiation, causing the interface to disappear. The self-healing efficiency could reach up to 82.5% after 30 min from stress–strain results. However, it should be noted that the thiol groups are susceptible to oxidation in air, resulting in hydrogels based on disulfide bonds lose their self-healing ability. In addition, hydrogels based on disulfide bonds may not be stable under physiological conditions. They can be broken down by physiologically relevant reduction because of the existence of reducing molecules, such as glutathione and cysteine. To address these issues, Pablo Casuso and colleagues reported a dynamic hydrogel that was crosslinked by Au–S and disulfide bonds *via* mixing 4-arm thiol-functionalized polyethylene glycol and $HAuCl_4$, in which the Au(I) capping could prevent thiolates from being oxidized by air and had no effect on the thiolate/disulfide exchange.[78] The results of rheological studies demonstrated that the two pieces of the hydrogel could be completely healed within 1 min. In addition, it was shown through cytotoxicity studies that this hydrogel was not cytotoxic to human dermal fibroblasts, demonstrating the potential of this hydrogel for application in drug/cell carriers and wound healing. Furthermore, hydrogels based on disulfide bonds can respond to multiple external stimuli by combining different interactions into one hydrogel system. To this end, a multi-sensitive and multifunctional hydrogel based on the reversible boronic ester and disulfide linkages was developed (Fig. 6a),[79] which exhibited pH, glucose, and redox tri-responsive features.

Despite the great advances in hydrogels based on disulfide bonds, their poor mechanical properties resulting from the low density of disulfide bonds and inefficient energy dissipation mechanisms can be problematic for their use in the biomedical field. To address these shortcomings, Van Tron Tran and co-workers constructed a multifunctional hydrogel *via* mixing *meso*-2,3-dimercaptosuccinic acid and 2,3-dimercapto-1-propanol. The hydrogel displayed rapid self-healing performance in both water and air, prominent extensibility, as well as biocompatibility (Fig. 6b).[80] This strategy provides an innovative route for exploiting disulfide bond-based dynamic hydrogels for biomedical and engineering applications. Taken together, disulfide bonds have shown great promise for the construction of self-healing hydrogels owing to the mild gelation conditions. However, it should be particularly noted that the delivery of protein drugs using these hydrogels can be challenging owing to the possible reaction between the cysteine residues of proteins and thiol groups in the hydrogel polymers, which may not only affect the loading efficiency of the proteins, but also pose a risk of restricting protein activity.

3.1.5 Knoevenagel condensation reaction. The Knoevenagel condensation (KC) reaction has been reported as a representative nucleophilic reaction between aldehyde or ketone groups and active methylene. Some studies have reported that this reaction proceeds smoothly in water at room temperature,[81] and at a faster rate under alkaline conditions than under acidic conditions. Besides, the generated C=C double bond could respond to multiple stimuli such as pH,[82]

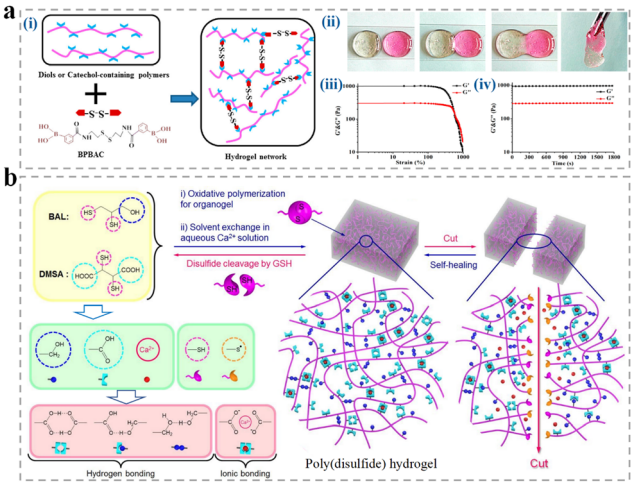

Fig. 6 Disulfide bond-based self-healing hydrogels. (a) (i) Schematics of hydrogels crosslinked through bis(phenylboronic acid carbamoyl) cystamine (BPBAC). (ii–iv) Evaluation of the self-repairing ability of the hydrogel prepared from disulfide bonds. Reproduced with permission.[79] Copyright 2017, American Chemical Society. (b) Schematic structure of the self-repairing hydrogel prepared from 2,3-dimercapto-1-propanol and *meso*-2,3-dimercaptosuccinic acid, as well as the self-healing mechanism of this hydrogel. Reproduced with permission.[80] Copyright 2020, Elsevier.

temperature,[83] and other small molecules.[84,85] Based on these properties, hydrogels prepared from the dynamic C=C double bonds displayed excellent self-healing, injectable, and thermoplastic properties. In recent studies, the KC reaction has been proven to produce various biomedical dynamic hydrogels. As an illustration, Ding *et al.* prepared a hydrogel by using tandem dynamic covalent bonds including reversible C=C double bonds as well as boronate ester bonds in a physiological environment (Fig. 7a).[72] In this system, 2-formylphenylboronic acid (2-FPBA) served as a bifunctional crosslinker and reacted with polyvinyl alcohol (PVA) and cyanoacetate-functionalized 4-arm PEG (4-arm-PEG-CA). Such a hydrogel exhibited obvious injectable as well as self-healing capacity and further the tandem dynamic covalent bonds could be dissociated by cysteine (Cys) on account of the generation of thiazolidino boronate. In addition, the dissolution time was dependent on the concentration of cysteine, and an increase in cysteine content can lead to a decrease in dissolution time. When applied to manage wounds, the hydrogel can not only achieve the immediate wound closure within a few seconds, but also on-demand removal by spraying the cysteine solution.

The KC reaction can be obviously facilitated under alkaline conditions, while it could be significantly hampered in an acidic environment. Inspired by this phenomenon, Ding *et al.* developed a multifunctional graphene oxide (GO) hydrogel scaffold, which could be formed by injecting GO hybrid benzaldehyde and cyanoacetate group-modified dextran solution into histidine solution (Fig. 7b).[86] Such a scaffold revealed excellent biocompatibility and adjustable mechanical properties. Therefore, scaffolds loaded with vascular endothelial growth factors (VEGFs) can serve as hydrogel dressings for accelerating infected wound healing. Overall, this reaction is

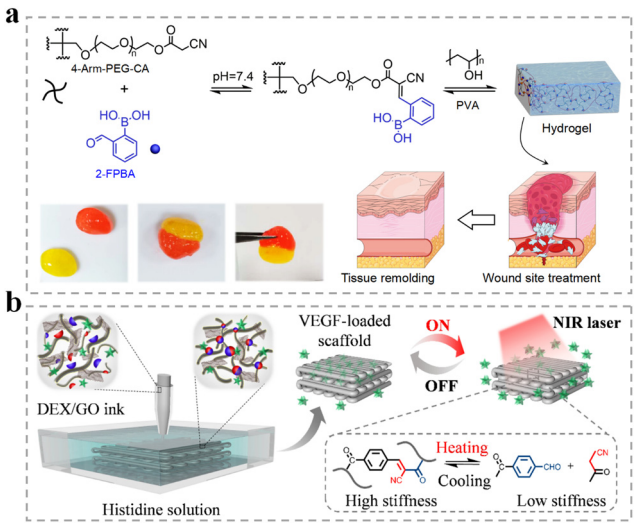

Fig. 7 Knoevenagel condensation reaction-based self-healing hydrogels. (a) A dynamic hydrogel generated through the reaction of 2-FPBA with PVA and 4-arm PEG-CA, and its application for wound dressings. Reproduced with permission.[72] Copyright 2021, Wiley-VCH. (b) The construction of a GO hybrid scaffold and its controllable drug release under NIR irradiation. Reproduced with permission.[86] Copyright 2021, American Association for the Advancement of Science.

highly compatible with cells and tissues, and demonstrates tremendous potential for use in the biomedical field and clinical translation. However, for the hydrogels crosslinked by the KC reaction, the inherent shortcomings, such as poor mechanical properties, low toxicity of cyanoacetate groups, and modest stability, may partially limit their application in biomedical fields. As a result, the control of the dynamics of C=C double bonds remains a critical issue for the future.

In addition to the above mentioned dynamic covalent bonds, thermally reversible Diels–Alder (DA) reactions based on conjugated dienes and dienophiles (*e.g.*, alkene or alkyne) were also employed to generate dynamic hydrogels. Although a lot of studies have demonstrated that self-healing hydrogels prepared from the DA reaction can self-heal under mild conditions,[50,87] most dynamic bonds formed by the DA reaction typically require a high temperature (>100 °C) to trigger the retro-DA reaction,[88] which demonstrated that these kinds of hydrogels may not be suitable for biomedical applications.

3.2 Noncovalent interactions

3.2.1 Hydrogen bonds. The hydrogen bond is a physical interaction that occurs between an atom with strong electronegativity (*e.g.*, N, O, or F) and a hydrogen atom, and is widespread and relatively stable in our biological system. For example, complementary strands of DNA are combined *via* hydrogen bond interactions, and these hydrogen bonds exist in folded proteins as well. Among the reported hydrogen bonds, the bonding strength between H and F is the lowest, while hydrogen bonds that contain hydroxyl and amide groups show the highest strength. Although the bonding energy for hydrogen bonds is lower than that of covalent bonds, hydrogels based on hydrogen bonds still display relatively high strength when a significant amount of hydrogen bonds are present within the hydrogels. The high stability of hydrogen bond-based hydrogels makes them suitable for drug delivery as well as biomedical engineering applications.[89–91] Furthermore, the dissociation and reformation of hydrogen bonds occur within a picosecond, which results in the damaged hydrogels cross-linked with hydrogen bonds heal rapidly. Based on the aforementioned properties, hydrogels based on hydrogen bonds have shown excellent self-healing performance. PVA is a widely used polymer to fabricate hydrogen bond-based hydrogels. PVA hydrogels can be produced through multiple freezing/thawing cycles, during which numerous crystallites induced by hydrogen bonds among hydroxyl groups could be formed.[92,93] However, the pure PVA hydrogels have been proven to be brittle, which greatly restricts their potential applications. To address this challenge, hydrogen bonds and other covalent bonds are generally employed in one system to construct hydrogels that exhibit both self-healing performance and enhanced mechanical strength. For instance, Zhang *et al.* developed a hydrogel with double networks using PVA and poly(acrylamide-*co*-acrylic acid) (PAM-*co*-PAA) through the polymerization reaction as well as freezing/thawing (Fig. 8a).[94] The first network was prepared based on hydrogen bonds between PAM and PAA. After treatment by the cyclic freezing/thawing process, the second network could be formed because of the generation of crystalline domains. The presence of reversible cross-linked networks enhances the self-healing ability and imparts outstanding mechanical strength to the resulting hydrogels. In addition to the commonly used PVA, other polymers, such as polyethyleneimine, hyaluronic acid, and chitosan, have gained extensive attention for fabrication of hydrogen bond-crosslinked self-healing hydrogels as well.

Hydrogen bond-based hydrogels can also be realized by incorporating hydrogen bonds into the backbone or side chain of polymers. Until now, the most commonly used component for cross-linking hydrogen bonds has been 2-ureido-4-pyrimidone (Upy), which possesses a high equilibrium association constant, is easy to be synthesized, and allows for the production of functional macromolecules.[95] After modification with Upy, hydrogels with improved mechanical strength and toughness could be readily generated *via* the generation of Upy dimers. In addition, the multiple and reversible hydrogen bonds between Upy units were able to impart hydrogels with rapid self-healing capacity (Fig. 8b). Apart from the Upy units, many other structures, such as urea moieties and nucleobase pairing, could contribute to the generation of dynamic hydrogels relying on hydrogen bonds as well.[96,97]

Recently reported self-healing hydrogels based on hydrogen bonds tend to exhibit intelligent behavior, particularly in a pH-dependent manner. For example, the hydrogel composed of poly(acryloyl-6-aminocaproic acid) (PA6ACA) can self-heal within 2 s under the condition of pH $\leq$ 3. In an environment with low pH, more carboxyl groups can be protonated and then form hydrogen bonds with other amide groups at the interface, which contributes to the rapid self-healing performance of this

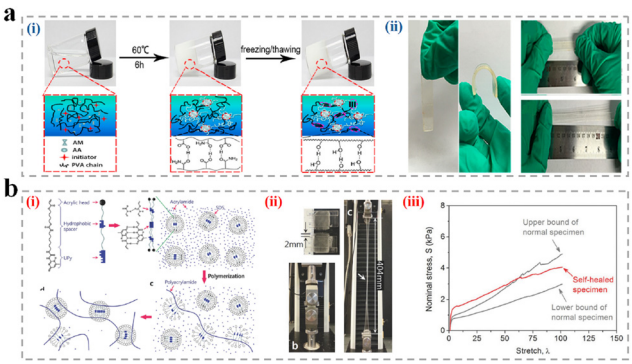

Fig. 8 Hydrogen bond-based hydrogels. (a) (i) Preparation of a fully physically cross-linked self-healing hydrogel. (ii) This healed hydrogel could not only withstand its own weight, but also could be bent/stretched without rupture. Reproduced with permission.[94] Copyright 2016, American Chemical Society. (b) (i) The chemical structure of the UPyHCBA monomer and the formation of the hydrogel by crosslinking UPyHCBA-loaded SDS micelles with acrylamide. (ii) and (iii) Photographs of the tensile process of the hydrogel and the representative stress–stretch curves. Reproduced with permission.[95] Copyright 2016, Wiley-VCH.

PA6ACA hydrogel.[98] However, when this hydrogel was exposed to high pH (pH > 9), the healed hydrogel could be broken again. This is because carboxylic acid groups along the polymer chain could be deprotonated under alkaline conditions, resulting in electrostatic repulsion among the carboxylic groups and thereby preventing the formation of hydrogen bonds. Therefore, we can conclude that hydrogen bond crosslinking is a type of mild interaction without using any potential toxic crosslinkers. Although there are many advantages of hydrogen bonds, few commercial hydrogel-based products that are solely crosslinked with hydrogen bonds have been available until now. However, it should be noted that, owing to the ubiquity of hydrogen bonds, this interaction can universally exist between polymer chains within many hydrogel systems.

3.2.2 Metal–ligand coordination. Studies have shown that the coordination between metal ions and ligands could enable hydrogel formation and confer excellent self-healing capacity. 3,4-Dihydroxyphenylalanine (dopamine), which is the main constituent of mussel foot proteins, has been confirmed as a critical factor for rapid and wet adhesion.[99,100] Additionally, many studies have reported that dopamine, which contains a catechol group, can form a gel with Fe^{3+} through the formation of bis- or tris-complexes at pH > 7. However, when the pH < 7, the hydrogel was hardly formed due to the low solubility of the complexes formed between dopamine and Fe^{3+}.[101] Based on this gelation mechanism, altering the pH value allows for the adjustment of mechanical strength as well as gelation time. Owing to the dynamic metal–ligand interactions, the hydrogels exhibited exceptional self-healing and injectable properties. Thus, once such a hydrogel is damaged, the free catechol in the polymer chains rapidly forms complexes with the cation without the need for any external stimuli. Furthermore, Liang *et al.* prepared an on-demand removable hydrogel wound dressing from the coordination reaction based on Fe^{3+} and catechol groups.[102] The results have revealed that when a medical chelating reagent such as deferoxamine mesylate (DFO) was used, this prepared hydrogel could be rapidly removed owing to the formation of catechol–Fe units between DFO and Fe^{3+}.

Bisphosphonates (BPs), which can coordinate with various metal ions, have also been identified as ideal candidates for preparing dynamic hydrogels from the metal–ligand coordination.[103,104] Typically, BPs are able to be incorporated into hydrogels *via* co-polymerization or conjugation onto polymer main chains. On account of the reversible nature of metal–ligand coordination, these hydrogels demonstrate splendid self-healing and injectable capabilities. Shi *et al.* designed dynamic self-healing hydrogels *via* iron oxide (Fe_3O_4) nanoparticles and bisphosphonate (BP)-functionalized hyaluronic acid (HA-BP) through the interactions between BP groups and iron atoms.[105] Additionally, Bian and colleagues prepared a range of BP crosslinked hydrogels through the self-assembled BP-Mg NPs *in situ*. For example, hydrogels based on the coordination reaction between BP and Mg^{2+} were developed by mixing acrylated bisphosphonate (Ac-BP), methacrylated hyaluronic acid (MeHA), and $MgCl_2$ solutions under UV illumination (Fig. 9a).[106] During this process, BP-Mg nanoparticles (Mg NPs) could be formed *in situ* through the reaction between Ac-BP and Mg^{2+}. Then, Mg NPs were used as a crosslinker and reacted with MeHA to produce hydrogels under UV. Moreover, it has been proven that the mechanical strength and stability of these hydrogels constructed by *in situ* assembly of BP-Mg NPs are much higher than those formed using *ex situ* NPs.

This strategy was also proven to be versatile and applicable for other metal ions, such as the earth metals (Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}) and transition metals (Mn^{3+}, Fe^{3+}, Co^{3+}, and Ni^{3+}) (Fig. 9b).[107] Additionally, these kinds of interactions

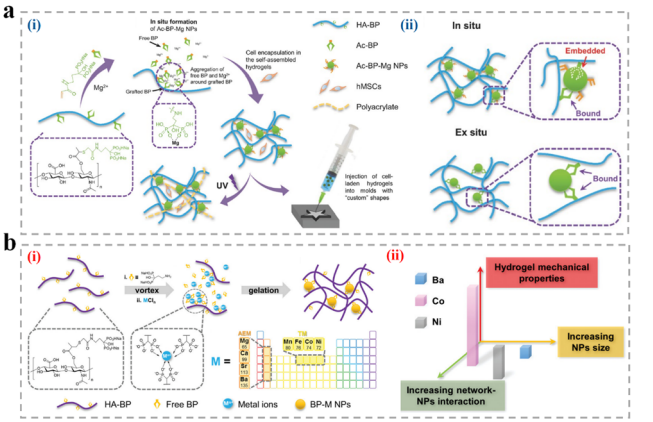

Fig. 9 Metal–ligand coordination-based self-healing hydrogels. (a) (i) Fabrication of a dynamic nanocomposite hydrogel for bone tissue repair. (ii) *In situ* hydrogels indicate that the hydrogel formed through *in situ* formative Ac-BP-Mg NPs, and *ex situ* hydrogels indicate that the hydrogel was generated through *ex situ* formed $MgSiO_3$ nanoparticles. Reproduced with permission.[106] Copyright 2017, Wiley-VCH. (b) (i) Chemical structure of bisphosphonate-modified hyaluronic acid and the chemistry behind the hydrogel preparation process. (ii) The factors that affected the mechanical properties of the nanocomposite hydrogel. Reproduced with permission.[107] Copyright 2019, Wiley-VCH.

demonstrate high stability similar to the covalent bonds and have pH-tunable kinetics. Furthermore, the mechanical properties of the hydrogels constructed through metal–ligand coordination can be tuned by varying the metal ions, the size of BP–metal NPs, as well as interactions between BP–metal NPs and polymer networks. Although these hydrogels can be simply fabricated *via* the direct mixing method, their biocompatibility has to be further evaluated through long-term *in vivo* research. Particularly, high concentrations of metal ions and ligands can be generated along with hydrogel degradation, which may have unknown adverse effects on the tissues. Thus, many problems related to toxicity, biodegradation, clearance, *etc.*, should be further studied before clinical use.

3.2.3 Host–guest interactions. The host–guest interaction is another critical physical interaction, which occurs when the guest moiety is selectively inserted into macrocyclic host molecules to form the inclusion complexation. Because of the existence of various kinds of dynamic interactions between host and guest molecules, for example π–π interactions, hydrogen bonding, hydrophobic interactions, and so on, the complexation of host–guest can be widely employed for the construction of various hydrogels with self-healing properties.[108,109] Cyclodextrins (CDs), which contain a hydrophobic internal cavity to envelope various guest molecules, have been considered as the most used host molecule. For instance, Masaki *et al.* constructed a supramolecular hydrogel by using β-CD together with ferrocene (Fc)-functionalized poly(acrylic acid) (Fig. 10a).[110] This hydrogel displayed self-repairing performance owing to its dynamic complexation of host–guest between β-CD and Fc groups, and its recovery efficiency was about 90% within 20 s from the rheological step-strain test. In addition, as Fc possesses redox-responsiveness, the formed supramolecular hydrogel exhibited reversible sol–gel transition after treatment with a redox agent.

Apart from ferrocene, adamantine (Ad) can be also employed as a guest molecule and generate an inclusion complex with β-CD. A supramolecular hydrogel was developed by Christopher *et al.* from Ad or β-CD modified hyaluronic acid (HA) through the complexation of host–guest between β-CD and Ad (Fig. 10b).[111] This hydrogel could be crosslinked instantly when the two polymer solutions were mixed and further displayed shear-thinning and superior self-repairing performance due to the reversibility of guest–host crosslinking. These features further enabled this hydrogel to be employed as a printing ink for extrusion-based printing. Other small molecules, such as cholic acid,[112] cholesterol,[113] and Pluronic F108,[114] can also exhibit high affinity to β-CD and further form an inclusion complex with β-CD through host–guest interactions. Despite many achievements in designing dynamic hydrogels through host–guest interactions, polymers modified with the host/guest small molecules tend to require a complex synthesis process, which may increase the risk for *in vivo* application. Besides, a major problem may be that hydrogels based on the host–guest interaction generally show relatively low mechanical strength, resulting in their poor usability in the biomedical field. So far, several effective strategies have been applied to improve the strength of these hydrogels, such as increasing the polymer concentrations or combining multiple interactions of host–guest interaction, hydrogen bonds, or covalent bonds into one system. Another concern is that the hydrogels based on the host–guest interactions may have low water-uptake ability owing to the existence of hydrophobic structures. However, this problem can be well solved by adjusting the ratio of hydrophilic and hydrophobic regions within the hydrogel. In view of these challenges, hydrogels based on the host–guest interactions are still in the academic research stage, indicating that there is still a significant journey ahead of us.

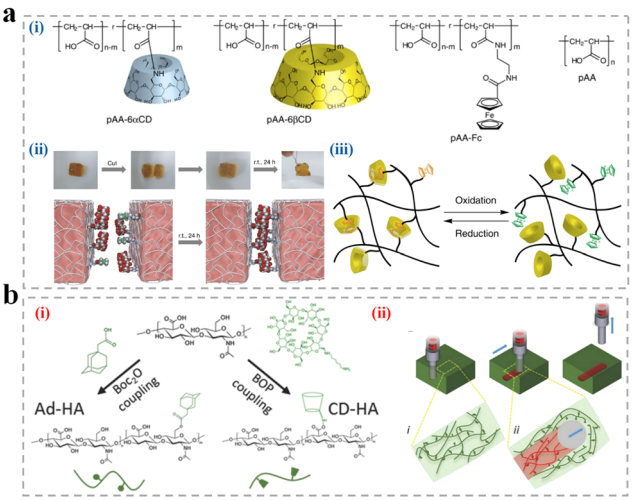

Fig. 10 Host–guest interaction-based self-healing hydrogels. (a) (i) Schematic indicating the structures of host and guest polymers employed for constructing dynamic hydrogels. (ii) Self-healing evaluation to demonstrate that the separated hydrogel samples healed into a complete hydrogel. (iii) Hydrogels generated from the host–guest interaction showed redox-responsive sol–gel transition behavior. Reproduced with permission.[110] Copyright 2011, Springer Nature. (b) (i) Preparation of adamantane and β-cyclodextrin-functionalized hyaluronic acid (HA). (ii) One supramolecular ink (red) was extruded into the other supramolecular support gel (green). Reproduced with permission.[111] Copyright 2015, Wiley-VCH.

3.2.4 Hydrophobic interactions. The hydrophobic interaction, a common noncovalent interaction, occurs when the hydrophobes aggregate in an aqueous solution. Owing to the reversible formation and rupture of hydrophobic interactions, hydrogels based on hydrophobic interactions exhibit self-healing performance. For instance, micellar polymerization is a typical strategy that uses the self-assembly micelles as crosslinkers, and the self-healing behavior of the resulting hydrogel can be attributed to the reversible disruption and reformation of the micelles. Oguz Okay *et al.* developed a hydrogel by polymerizing stearyl methacrylate (C18) with acrylamide (Aam) (PAAm-*co*-C18) in sodium dodecyl sulfate (SDS) solution with NaCl (Fig. 11a).[115] Furthermore, it was demonstrated that two pieces of this hydrogel could be merged into one sample by simply pressing them together for several seconds, and the healing efficiency of this hydrogel could reach up to about 100% after healing for 20 min owing to the dynamic micellar crosslinks. Although some progress has been made, hydrogels

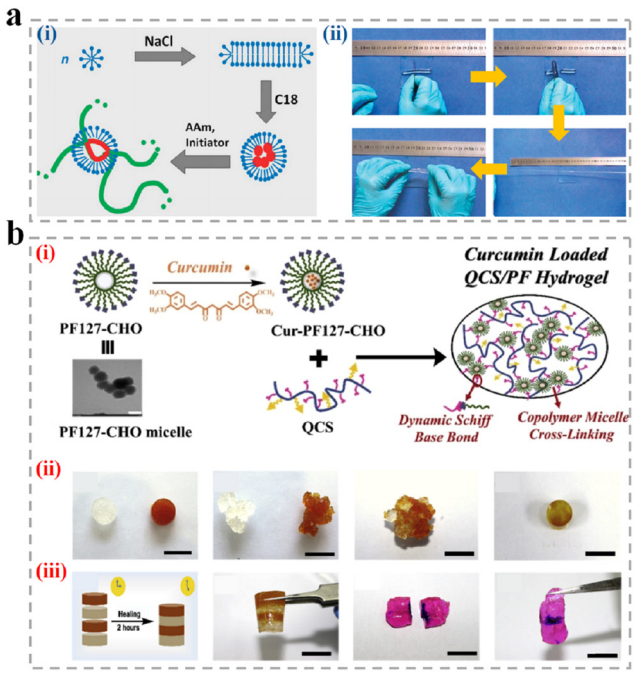

Fig. 11 Hydrogels crosslinked with the hydrophobic interaction. (a) (i) Fabrication of a micelle crosslinked hydrogel through the copolymerization of monomer C18 and AAm in the SDS–NaCl micellar solution. (ii) The formed hydrogel was broken into two pieces, which healed into a complete hydrogel after contact for 10 min, and further this repaired hydrogel could withstand external force without damage. Reproduced with permission.[115] Copyright 2012, American Chemical Society. (b) (i) Schematic diagram of the production process of curcumin-loaded QCS/PF hydrogels crosslinked with micelles and dynamic Schiff base bonds. (ii) Two hydrogels were broken into pieces and then molded to obtain a cylindrical hydrogel. Scale bar: 1 cm. (iii) Four disk-shaped hydrogels were healed into one piece at 25 °C after 2 hours. Also, the cut hydrogel could emerge together within 3 min. Scale bar: 1 cm. Reproduced with permission.[116] Copyright 2018, Elsevier.

based on micelle crosslinking may lose their self-healing ability after swelling in water owing to the limited stability of the micelles. Thus, in order to broaden their use in biomedical fields, more than one interaction including the hydrophobic interaction can be incorporated into one system. In addition, when micelles are employed as the cross-linkages, the mechanical strength of hydrogels can be altered by varying the micelle concentrations. In a typical study, aldehyde-functionalized Pluronic® F127 (PF127) was employed for developing a chitosan-based self-healing hydrogel (Fig. 11b).[116] Specifically, quaternized chitosan (QCS) could react with PF127 through Schiff base bonds and the PF127 micelles served as the cross-linkages. This hydrogel demonstrated excellent malleability, compressibility, and adhesive performance. Besides, upon increasing the number of PF127-CHO micelles, the mechanical strength of this hydrogel was greatly improved. Also, hydrophobic drugs such as curcumin could be loaded into PF127 micelles through hydrophobic interactions and the resulting hydrogel exhibited obvious pH-responsive release behavior. In addition, this hydrogel revealed self-healing performance when damaged, that is to say, it could be completely healed after being incubated at 25 °C for 2 h. In addition, the G' (920 Pa) of the damaged hydrogel at a high strain (γ = 200%) could recover to its initial value (35 000 Pa) when a strain of 1% was applied during the rheological test. The properties mentioned above make this hydrogel suitable for use as wound dressings in joint wound healing.

Generally, hydrophobic interactions are easier to control than hydrogen bonds and they can be tuned *via* altering the shape of hydrophobes and the number of hydrophobic groups. Moreover, no toxic crosslinkers are being used during the hydrogel preparation process. However, there exist many hydrophobic motifs within the hydrogels formed by hydrophobic interactions, which may lead to low water-uptake ability. Although many attempts have already been made to introduce hydrogels based on hydrophobic interactions into the biomedical field, most of them have relatively low mechanical properties and high hydrophobicity, which may limit their applications in clinical settings.

4. Biomedical applications of self-healing hydrogels

Hydrogels are crosslinked 3D network structures of hydrophilic polymers, which have been utilized in diverse applications in particular in biomedical fields such as tissue engineering, drug delivery, cell therapy, as well as wound healing.[117] However, several hydrogels are susceptible to the external stimulus, which would inevitably lead to their mechanical properties and functions being lost under the external forces or physiological conditions. Inspired by the self-healing phenomenon in our living tissues, hydrogels with the capacity to regain their original mechanical structures and functions in response to damage without external stimulus have gained much attention in various biomedical fields. This section mainly focuses on the recent advances in the diversified biomedical applications of different self-healing hydrogels, such as tissue engineering, drug delivery, cell therapy, and wound healing.

4.1 Tissue engineering

Tissue engineering has become a potential therapy for patients with damaged or dysfunctional tissues or organs. Due to the limited source of organs for transplantation and possible foreign body responses, tissue engineering has been extensively studied for tissue repair.[118,119] Self-healing hydrogels, integrated with stem cells, biological factors, and other bioactive molecules, have been considered as the potential alternatives to allografts, particularly for cartilage and bone tissue, neural system, and skin tissue system.[120–123] When injected into the impaired tissue, the hydrogel could recover to its initial mechanical strength and conform to the shape of the defect area and ultimately facilitate tissue repair and regeneration.

In addition to the prerequisite that hydrogels applied *in vivo* should be non-toxic to tissues, they are also required to replicate the unique characteristics of these tissues. For instance, self-healing hydrogels employed for bone and

cartilage tissue engineering should possess mechanical strength and durability. Accordingly, significant efforts have been devoted to developing self-healing hydrogels that could be utilized in load-bearing bone tissues. For example, self-healing hydrogels based on the metal–ligand coordination interactions have been widely applied for bone tissue engineering. Shi *et al.* prepared a dynamic silk fibroin (SF)-based hydrogel from calcium phosphate (CaP) coated silk fibroin (CaP@mSF) and bisphosphonate-modified hyaluronic acid (HA-BP) through metal–ligand coordination (Fig. 12a).[105] Such a hydrogel displayed shear-thinning and self-healing functions, allowing it to effectively cover the irregular tissue defects without the formation of gel fragments because of the reversible metal–ligand coordination. However, the low mechanical strength as well as stability of this dynamic hydrogel resulted in its rapid degradation within 5 h under physiological conditions. To enhance the mechanical properties of this hydrogel, the authors added a second network into the system through *in situ* photo-crosslinking of acrylamide groups in HA-BP. The double network hydrogel (DN hydrogel) exhibited a significant increase in the storage modulus. Furthermore, the DN hydrogel demonstrated promising osteogenic differentiation ability from the *in vitro* test. More importantly, the *in vivo* experiments revealed that the DN hydrogels exhibited a promoted osteogenic capability in rat cranial critical defects, and the bone formation rate was approximately 2 times higher than that of the control group.

When self-healing hydrogels are used for cartilage repair, the case may be different owing to the lack of blood supply in the defective articular cartilage. Thus, hydrogels are required to possess relatively high mechanical properties, good stability, and strong adhesion performance. Hou *et al.* constructed a self-healing hydrogel that was fabricated from ureido-pyrimidinone (UPy)-functionalized dextran through the reversible quadruple hydrogen bonds (Fig. 12b).[124] It was found that the concentration of the grafted UPy has a strong effect on the self-healing and injectable abilities. Moreover, this hydrogel exhibited prochondrogenic ability by promoting the generation of the cartilage-bone tissue complex. The subcutaneous implantation results demonstrated that the tissue complex could transform into the osteochondral graft for tissue engineering fields. Although these systems are providing new opportunities in bone and cartilage tissue regeneration, the applications for dynamic hydrogels are limited owing to their low mechanical strength, poor durability, and stress relaxation behavior. Thus, more efforts are significantly required to improve their durability and *in vivo* performance to facilitate the translation of basic science to the clinical setting.

4.2 Drug delivery

Benefiting from their porous structure, self-healing hydrogels can be utilized as vehicles to release drugs in a sustained manner. In contrast to traditional systemic administration, self-healing hydrogels loaded with drugs may be an efficient way for targeted therapy. The drug-loaded hydrogels could be directly implanted into tissue lesions precisely without any gel

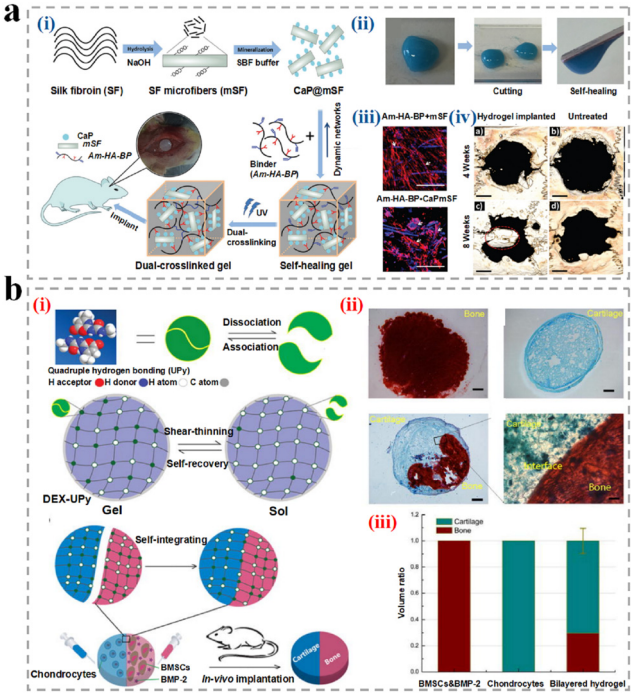

Fig. 12 Illustration of designing self-healing hydrogels for tissue engineering application. (a) (i) Fabrication of a silk hydrogel for repairing bone defects. (ii) Characterization of the healing behavior of the hydrogel. (iii) The hMSCs incorporated into the hydrogel show spreading morphology by staining the cell cytoskeleton (red) as well as nucleus (blue), respectively. Scale bar: 200 μm. (iv) This silk-based hydrogel significantly accelerated bone tissue regeneration in a typical cranial defect model. Scale bar: 2 mm. Reproduced with permission.[105] Copyright 2017, Wiley-VCH. (b) (i) Schematic illustration of the self-healing hydrogels to facilitate tissue complex regeneration, and the chemical mechanism of the self-healing process. (ii) The bone and cartilage were respectively stained with Alizarin red and Alcian blue. Scale bar: 5 mm. (iii) Quantitative analyses of bone and cartilage volumes after being implanted for 8 weeks. Reproduced with permission.[124] Copyright 2015, Wiley-VCH.

fragments. The broken hydrogel could be rapidly self-healed and adjusted to different tissue shapes with defects. Moreover, the self-healing property could help to avoid burst release and meanwhile reduce drug-induced organ toxicity. Liang *et al.* developed a dynamic hydrogel with dual responsiveness to pH and glucose through the reversible Schiff base as well as phenylboronate ester bonds. The hydrogel could be readily prepared by mixing dihydrocaffeic acid, phenylboronic acid, arginine-grafted chitosan (CS-DA-LAG), and benzaldehyde-modified polyethylene glycol-*co*-poly(glycerol sebacic acid) (PEGS–PBA–BA) (Fig. 13a).[125] The presence of double dynamic bonds allows the hydrogels to exhibit excellent self-healing performance, enabling quick repair of wounds and prolonging the lifespan of the hydrogels. Furthermore, owing to the pH responsiveness of the Schiff base, the hydrogel loaded with metformin exhibited a drug release rate of 30.4% at pH 5.5 after 9 days, which was higher than that of 12.7% at pH 7.4. Meanwhile, the final cumulative release of the metformin-loaded hydrogel in the presence of glucose was 23.3%, which was higher than that in the absence of glucose. Furthermore,

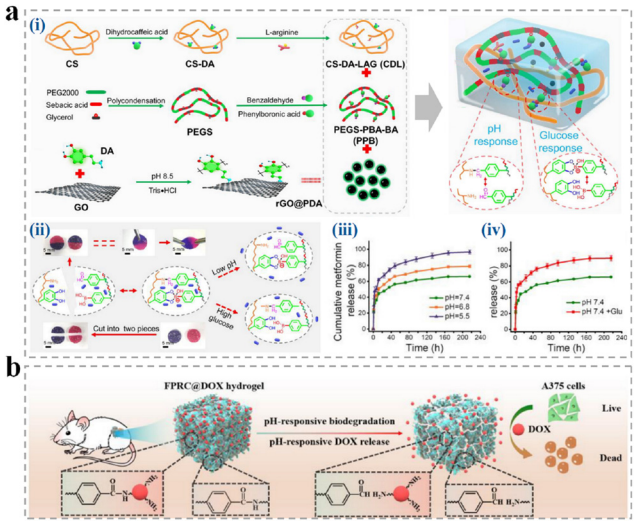

Fig. 13 Self-healing hydrogels for drug delivery application. (a) (i) A reversible dynamic hydrogel formed by imine bonds and phenylboronate ester bonds. (ii) Schematic illustrating the self-healing and dual-responsive drug release performance. (iii–iv) The drug release behavior at different pH and glucose concentrations. Reproduced with permission.[125] Copyright 2022, Wiley-VCH. (b) Schematic representations displaying the generation of a multifunctional hydrogel and its application for the treatment of melanoma. Reproduced with permission.[131] Copyright 2020, Elsevier.

the hydrogel demonstrated outstanding antioxidant ability, enabling it to capture the excessive ROS and reduce oxidative stress. *In vivo* tests showed that the wounds treated with hydrogels incorporated with metformin were essentially closed after 14 days when compared with the control group in diabetic foot wound models, demonstrating the excellent wound healing performance of the hydrogels.

However, due to the macroporous structure of hydrogels, they generally display a relatively rapid release behavior when small molecule drugs are directly encapsulated. To solve this issue, the drugs could be loaded within the nanoparticles or chemically bonded to the hydrogels to delay drug release.[126–128] Dynamic bonds are attractive to be used as stimuli-responsive linkages owing to their ability to respond to various stimuli, including pH, temperature, UV light, and enzymes.[129,130] As a result, the encapsulated drugs can be controllably released into the surrounding environment by cleaving the crosslinking bonds. Given that many clinically approved drugs contain or are facilely modified with amino groups, Schiff base bonds may be a frequently used chemical bond, which can be employed to directly attach drugs onto polymers for targeting purposes. For example, doxorubicin (Dox), a commonly used chemotherapeutic drug, could be conjugated onto the aldehyde-modified Pluronic® F127 (F127) to achieve pH-responsive release behavior under weak acidic conditions (Fig. 13b).[131] Therefore, the prepared self-healing hydrogels have the potential to provide an effective solution to various limitations in the biomedical field in the future.

So far, covalently crosslinked hydrogels have made tremendous achievements in the clinic as drug vehicles and the commercial drug-loaded hydrogel materials such as DEXTENZA (NDA 208742) and VANTAS (NDA 021732) are also available. However, for the dynamic hydrogels, their usage for drug delivery can be primarily limited because of their inherent nature of poor stability and rapid degradation rate, which may not only result in the burst drug release, but also greatly reduce long-term therapeutic efficiency. In addition, the performance of the degradation product inside the body has not been completely elucidated, which may result in unwanted responses *in vivo*. In the future, with the deepening of research on dynamic hydrogels, it is anticipated that the gap between the academic research and the clinic can be tremendously reduced.

4.3 Cell therapy

Cell-based therapy has been a potential approach for treating tissue defects. Cells with specific differentiation abilities, such as stem cells or Schwann cells, have been proven to be effective for tissue repair. Self-healing hydrogels have become a promising platform for 3D cell encapsulation owing to their excellent physicochemical properties.[132] In addition, cell-loaded hydrogels are able to mechanically protect encapsulated cells from death caused by shear forces during the injection process and meanwhile prevent the transplanted cells from loss from the injection site, which is beneficial for cell transplantation.[133,134] For instance, Lou *et al.* designed a dynamic hydrogel *via* hydrazine and aldehyde group-functionalized hyaluronic acid for cell transplantation.[63] With the addition of the 2-(aminomethyl)benzimidazole catalyst, the hydrogel could be rapidly formed and achieved a quicker dynamic exchange of hydrazone bonds, resulting in high cell viability for the cells loaded within hydrogels. In addition, by diffusing the catalyst out of the hydrogel, the hydrogel can show high stability after injection, which can provide a long-term scaffold for cell growth (Fig. 14a).

Although the excellent injectable and self-healing capacity of dynamic hydrogels can contribute to the cell transplantation process, their weak nature and poor stability significantly limit their application in supporting the long-term growth of encapsulated cells. Feng and co-workers constructed a self-healing injectable hydrogel for the treatment of bone defects (Fig. 14b).[135] The hydrogel consisting of double networks was first constructed through the host–guest interactions between acryloyl β-cyclodextrin (Ac-β-CDs) and aromatic groups in gelatin, and then was reinforced by crosslinking Ac-β-CDs under UV irradiation. The hydrogel, loaded with mesenchymal stem cells (MSCs) and drugs, could be injected into the defect. Subsequently, the dynamic nature of the hydrogel supported the infiltration of the incorporated cells into the icaritin-loaded hydrogels, which facilitated the differentiation of MSCs and further promoted *in situ* bone regeneration. Besides, the MSCs seeded on the surface of icaritin-loaded hydrogels not only migrated into the hydrogel but also showed a high viability and adapted a spindle morphology after 14 days of culture. Meanwhile, the upregulated expression of osteogenic markers and adipogenic markers was observed in the groups treated with

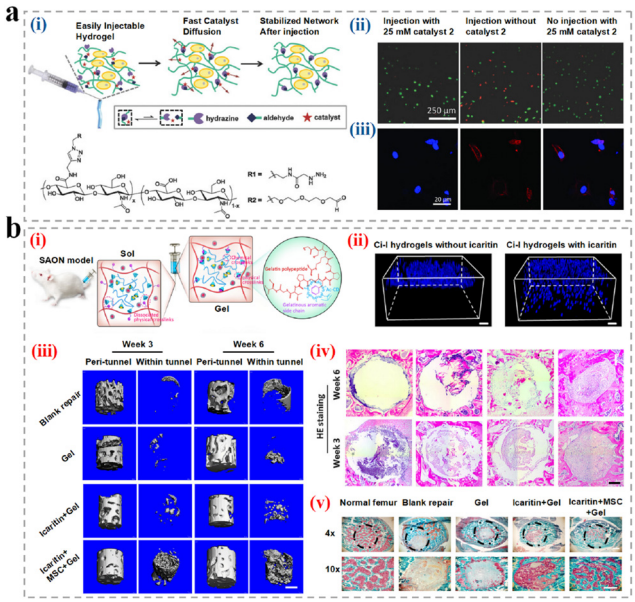

Fig. 14 Self-healing hydrogels for cell therapy application. (a) (i) Schematic diagram of the construction of a reversible hydrogel crosslinked by hydrazone bonds with the catalyst 2-(aminomethyl)benzimidazole. (ii) Live/dead staining test for the encapsulated HUVECs after injection. Scale bar: 100 μm. (iii) HUVECs spreading within hydrogels after injection and incubation for 72 h. Reproduced with permission.[63] Copyright 2017, Wiley-VCH. (b) (i) Fabrication of the injectable gelatin hydrogel used as the therapeutic carrier for treating the bone defects in the rat model. (ii) The confocal images of MSCs within the hydrogels without or with icaritin encapsulation after incubation for 24 h. (iii) Micro-CT images of the newly formed bone in the steroid-associated osteonecrosis model after treatment for 3 and 6 weeks. Scale bar: 500 μm. (iv) and (v) H&E staining as well as Goldner's trichrome staining for the bone after management under different conditions. Scale bar: 100 μm. Reproduced with permission.[135] Copyright 2019, American Chemical Society.

icaritin-loaded hydrogels. Also, icaritin-loaded hydrogels exhibited enhanced new bone formation performance after a 6 week treatment as revealed by Micro-CT images. Therefore, the injectable properties, high mechanical strength and stability, as well as enhanced infiltration and migration abilities provide new insights for designing cell vehicles for cell transplantation.

During the past few years, cell therapy has made significant progress in the biomedical field and some hydrogel commercial products have been increasingly translated to the clinic for living cell therapy. For example, Zhao *et al.* reported a polysaccharide-based hydrogel composed of N-carboxyethyl chitosan and oxidized sodium alginate. Such a hydrogel could serve as a cell carrier to support the proliferation and neuronal differentiation of neural stem cells, and has now been applied in the clinic.[136] Another notable achievement is Apligraf (P950032), which is composed of human allogeneic neonatal keratinocytes and fibroblasts embedded in a bovine Type I collagen matrix, and this hydrogel has been approved by the Food and Drug Administration (FDA). Other hydrogels, such as albumin hydrogels, have also attracted significant attention from researchers for their potential translational applications, but their usage in cell therapy is still in its infancy. Biocompatibility and efficient crosslinking methods for the construction of albumin hydrogels used for the clinic are essential.

4.4 Wound dressing

In terms of skin tissue engineering, the use of hydrogels for physical protection has become a critical way to protect the wounds from bacterial infection. However, traditional hydrogels may be prone to breakage due to accidental external stress, which can not only cause the loss of their properties, but also make them susceptible to the invasion of external bacteria. Therefore, the structural integrity of hydrogels always has a positive influence on the wound healing process. To achieve much better wound healing performance, the adhesion ability of self-healing hydrogels is essential, which allows the hydrogels to seamlessly attach to the wounds and decrease the risk of infection. A bioadhesive hydrogel with self-healing properties was designed by Li *et al.* from catechol-functionalized ε-poly-L-lysine and oxidized dextran through the formation of Schiff base bonds as well as dynamic bonds between catechol groups and Fe^{3+} (Fig. 15a).[137] Such hydrogel demonstrated effective wound closure, repeatable adhesiveness, and on-demand dissolution functions. In addition, with the increasing demands in clinical applications, hydrogels with various performances including antibacterial, antioxidant, anti-inflammatory, or other enhanced biological functions were gradually proposed.[138] Huang *et al.* developed a macroporous hydrogel by mixing carboxymethyl agarose and Ag^{+} through the formation of hydrogen bonding and supramolecular complexation (Fig. 15b).[139] The hydrogel displayed pH/temperature responsiveness, leading to the sustained release of Ag^{+} for a long time. The *in vitro* test showed that bacteria including *S. aureus* and *E. coli* were killed, demonstrating outstanding antibacterial activity. When used to treat infected wounds, the hydrogel possessing excellent antibacterial and anti-inflammatory abilities was proven to significantly promote wound healing. Besides, an antibacterial antioxidant hydrogel composed of benzaldehyde modified poly(ethylene glycol)-*co*-poly(glycerol sebacate) (PEGS-FA) and quaternized chitosan-*g*-polyaniline (QCSP) to facilitate the wound healing process was developed.[140] The blood vessel regeneration is also a critical factor for accelerating wound healing, which is responsible for the transportation of oxygen and nutrients to the wound beds. Indeed, studies have shown that angiogenesis-related cytokines, such as vascular endothelial growth factor (VEGF), CD31, *etc.*, could greatly promote angiogenesis.[141,142] The hydrogels incorporated with oxygen-generating agents (*e.g.*, hemoglobin, microalga, *etc.*) can also promote angiogenesis and further wound healing.[143] Other performances of self-healing hydrogels, such as hemostatic, stimulus-responsive, and conductive performances, demonstrated much benefit for skin healing and regeneration as well.[5,144,145]

So far, there are some dynamic hydrogels based on the imine bond crosslinking that are being employed as wound dressings, such as the commercial products CosmoPlast (P800022 S050) and BioGlue (H990007, P010003). However,

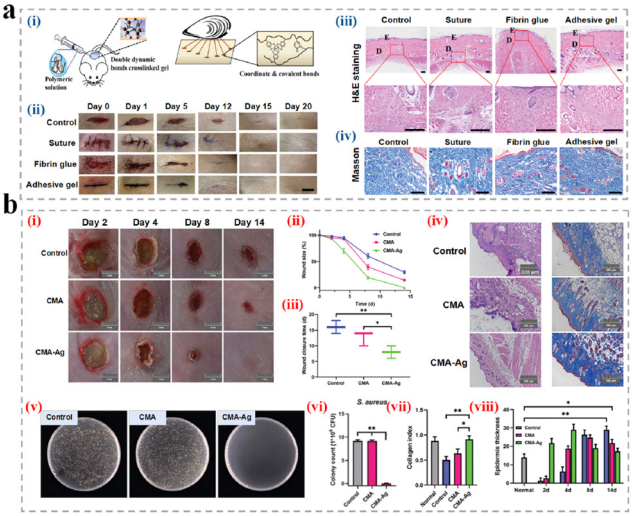

Fig. 15 Self-healing hydrogels for wound healing applications. (a) (i) Schematic illustration of the preparation of the double dynamic bond crosslinked hydrogel for wound closure and promoting wound healing. (ii) Representative images of rat wounds. Scale bar: 1 cm. (iii and iv) H&E and Masson's trichrome staining images for wounds being treated differently. Scale bar: (iii) 200 μm and (iv) 100 μm. Reproduced with permission.[137] Copyright 2020, Wiley-VCH. (b) (i), (ii), and (iii) The wound healing photographs and wound sizes after treatment with different groups on different days. Scale bar: (i) 3 mm and (iv) 300 μm. (iv) Histological images of wounds for different groups on day 14. (v) Photographs of *S. aureus* colonies derived from different wounds. (vi) The quantitative *S. aureus* colonies at the wounds for different groups. (vii) and (viii) The epidermis thickness for different groups after 14 days. Reproduced with permission.[139] Copyright 2020, Wiley-VCH.

owing to the complexity of the wound tissue, the healing process and parameters are dynamically altered with time, which may result in the single wound dressings hardly meeting each phase during the entire wound healing process. Furthermore, cells- and cytokines-loaded wound dressings are typically required for a specific duration, while they may play an opposite role in other time periods. Thus, designing hydrogels that can achieve different functions over time is a direction for future academic study.

5. Conclusion and future prospects

Self-healing hydrogels have emerged as highly competitive biomedical materials in recent years and show great potential in the biomedical fields. Herein, we provide a comprehensive summary of the hydrogel preparation, self-healing mechanism, as well as their biomedical applications. It was believed that the self-healing hydrogels will propel the biomedical field to new heights in the future.

Although the self-healing hydrogels show much promise, the self-healing process is required to be stimulated *via* external stimuli, such as pH, heat, and light, which significantly restricts their applications *in vivo*. For example, self-healing hydrogels formed through disulfide bonds require UV light irradiation to initiate the healing process, which is inconvenient to operate and can also be toxic to the tissues. In addition, the mechanical strength of the reported dynamic hydrogels is relatively low, which hardly matches well with the native tissues. Thus, enhancing the mechanical properties of dynamic hydrogels without affecting their dynamic properties is still a significant challenge in the academic exploration stage. As an alternative and promising approach, it is crucial to explore the innovative dynamic crosslinks and self-healing mechanisms including chemistry, kinetics, and thermodynamics.

Although many successes have been achieved in the dynamic hydrogel research and clinical translation, several limitations still exist. Biocompatibility of the crosslinking chemistries, selected materials, byproducts, and even the resulting degradation products is an overwhelmingly critical factor to consider. Among the various well-established dynamic interactions, imine bonds are the primary dynamic covalent bonds that have been successfully utilized in the construction of dynamic hydrogel products for clinical translation until now. However, the materials that were chosen as the hydrogel building blocks are largely limited to natural materials (*e.g.*, collagen, albumin, and chitosan), and very few synthetic polymers, except for PEG, have been utilized. Apart from the imine bonds, for the other dynamic interactions, although one or two of them may commonly exist in most hydrogel systems, such as the hydrogen bonding and hydrophobic interactions, it should be noted that few such dynamic interactions have reached the clinic by now, which may be due to their intrinsic incompatibility and synthetic complexities. An effective method to utilize these reactions may be anchoring these reaction moieties onto the natural polymers. However, biodegradation and safety are still pressing issues to address in the academic exploration stage.

With the increasing requirements in clinical applications, the functions of self-healing hydrogels have evolved from simple physical coverage and water retention to encompass multiple bioactive functions and they even exhibit intelligent characteristics. Considering the complexity and dynamic nature of the tissue repairing process, tissue microenvironment-responsive dynamic hydrogels are preferred for biomedical applications. Also, owing to their function of serving as delivery vehicles, drugs, cells, and other bioactive molecules can be incorporated into the hydrogel. For example, incorporating antibacterial agents and cytokines into the dynamic hydrogel systems can not only provide self-healing and injectable properties, but also enhance antibacterial effects and tissue regeneration. In addition, the properties of the hydrogel can be well-tailored according to the characteristics of the tissue itself. As an example, conductive hydrogels are generally employed for repairing hearts damaged by heart attacks. The emergence of intelligent hydrogels, which are used to detect the tissue healing process, is a major direction for the future development. In the end, we firmly believe that the challenges mentioned above require researchers from different fields to collaborate in order to find solutions, which could not only push forward the development of self-healing hydrogels, but

also open up exciting possibilities for their widespread utilization in the biomedical field.

Author contributions

Conceptualization and supervision: Y. J. Zhao; writing –original draft: X. Y. Ding; writing–review & editing: L. Fan, L. Wang, M. Zhou, and Y. X. Wang.

Conflicts of interest

There are no conflicts to declare.

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