

## REVIEW

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## Engineered cyclodextrin-based supramolecular hydrogels for biomedical applications

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Cyclodextrin (CD)-based supramolecular hydrogels are polymer network systems with the ability to rapidly form reversible three-dimensional porous structures through multiple cross-linking methods, offering potential applications in drug delivery. Although CD-based supramolecular hydrogels have been increasingly used in a wide range of applications in recent years, a comprehensive description of their structure, mechanical property modulation, drug loading, delivery, and applications in biomedical fields from a cross-linking perspective is lacking. To provide a comprehensive overview of CD-based supramolecular hydrogels, this review systematically describes their design, regulation of mechanical properties, modes of drug loading and release, and their roles in various biomedical fields, particularly oncology, wound dressing, bone repair, and myocardial tissue engineering. Additionally, this review provides a rational discussion on the current challenges and prospects of CD-based supramolecular hydrogels, which can provide ideas for the rapid development of CD-based hydrogels and foster their translation from the laboratory to clinical medicine.

## 1. Introduction

Cyclodextrins (CDs), first discovered by Villers in 1891, are a class of naturally occurring water-soluble macrocyclic compounds consisting of multiple D-glucopyranose units linked by  $\alpha$ -1,4 glycosidic bonds.<sup>1</sup>  $\alpha$ -CDs,  $\beta$ -CDs, and  $\gamma$ -CDs are the three most common types of CDs, composed of six, seven, and eight D-glucopyranose units, respectively, with different cavity

sizes.<sup>2</sup> The hydrophilicity of CDs is conferred by the secondary hydroxyl group located at the C2/3 position of the larger open end of the outer surface and the primary hydroxyl group located at the C6 position of the smaller open end, while the hydrophobicity is conferred by the shielding effect of the C-H bonds that form the hydrophobic cavities.<sup>3,4</sup> Due to the unique properties of CDs' hydrophilic outer edges and hydrophobic inner cavities, they can effectively serve as hydrophobic binding sites for various guest molecules.<sup>5</sup> The interactions between CDs and guest molecules involve van der Waals (homogeneous, dispersive, and induced forces), coulombic, hydrophobic, and hydrogen bonding forces.<sup>6</sup> Furthermore, the abundance of reactive hydroxyl groups in CDs can be chemically modified to result in a wide variety of functional cyclodextrin

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derivatives.<sup>7</sup> These unique properties of CDs have been of widespread interest in the construction of supramolecular injectable hydrogels.<sup>8</sup>

There are two main methods for the preparation of CD-based supramolecular hydrogels. One method involves forming a poly(pseudo)rotaxane (PPR) structure, where linear polymer chains penetrate into the cavities of the CD.<sup>9</sup> The other method involves forming an inclusion complex between the CD and the guest molecule. CD-based supramolecular hydrogels are distinguished by dynamically reversible non-covalent bonding, such as host-guest interactions and hydrogen bonding, making them shear-thinning and self-healing.<sup>10</sup> For example, the hydrogel transitions to a flowable state when sufficient shear stress is applied during the injection process, and then recovers to a gel state when the high shear stress is removed.<sup>11</sup> This makes supramolecular hydrogels suitable for forming drug reservoirs in target tissues in a mini-invasive manner and allows for continuous and controllable drug release.<sup>12</sup> However, the weak mechanical strength and large pore structure of CD-based supramolecular hydrogels severely limit their effectiveness in controlled drug release, stability, and therapeutic ability. To overcome this limitation, a frequent strategy is to regulate the mechanical behavior of supramolecular hydrogels by adjusting the number of host and guest molecules.<sup>13,14</sup> However, due to the special structure of macromolecule CDs, the efficiency of CD modification of the macromolecule chain is limited, and fails to significantly improve the mechanical properties of hydrogels. Therefore, in-depth elaboration of the cross-linking of CD-based supramolecular hydrogels is essential to optimize their mechanical properties and drug loading modes, which are major priorities for their effective use in the treatment of various diseases.

Several recently published reviews on CD-based supramolecular materials primarily focus on the preparation, stimuli-

responsive drug delivery, and other biological applications of these materials.<sup>8,15–18</sup> However, there is, to our knowledge, a lack of detailed discussion regarding the optimization of the mechanical properties and the different drug loading and release modalities of CD-based supramolecular hydrogels.<sup>19–21</sup> CD-based supramolecular hydrogels have garnered significant attention due to their self-healing and shear-thinning properties. Nonetheless, the tradeoff between the self-healing properties and mechanical strength of these hydrogels severely limits their practical applications in various biomedical fields.<sup>22</sup> Therefore, there is considerable scope to clarify the underlying relationship between the self-healing properties and mechanical strength for the development of CD-based supramolecular hydrogels with balanced properties. For example, supramolecular hydrogel dressings with excellent self-healing and mechanical properties can prevent bacterial infection or premature drug leakage caused by structural damage.<sup>23</sup> High-strength supramolecular hydrogels can provide mechanical support in bone/cartilage repair.<sup>24</sup> Hydrogels with favorable mechanical strength enable more controllable, stable, and effective drug delivery. Furthermore, the appropriate drug loading and release modalities of supramolecular hydrogels are crucial for the effective treatment of various diseases.<sup>12</sup>

As detailed above, this review aims to fill the existing gap in the current systematized knowledge by conducting comprehensive investigations on the crosslinking mechanism, optimization of mechanical properties, drug loading and release modalities of CD-based supramolecular hydrogels. In addition, the advantages of CD-based supramolecular hydrogels for targeted drug delivery in specific diseases, such as tumor, bone/cartilage defect, and myocardial infarction, are systematically summarized. Finally, the challenges and opportunities for promoted clinical translations of CD-based supramolecular hydrogels are proposed (Scheme 1). This review is expected to serve as valuable guidance for the next generation of advanced



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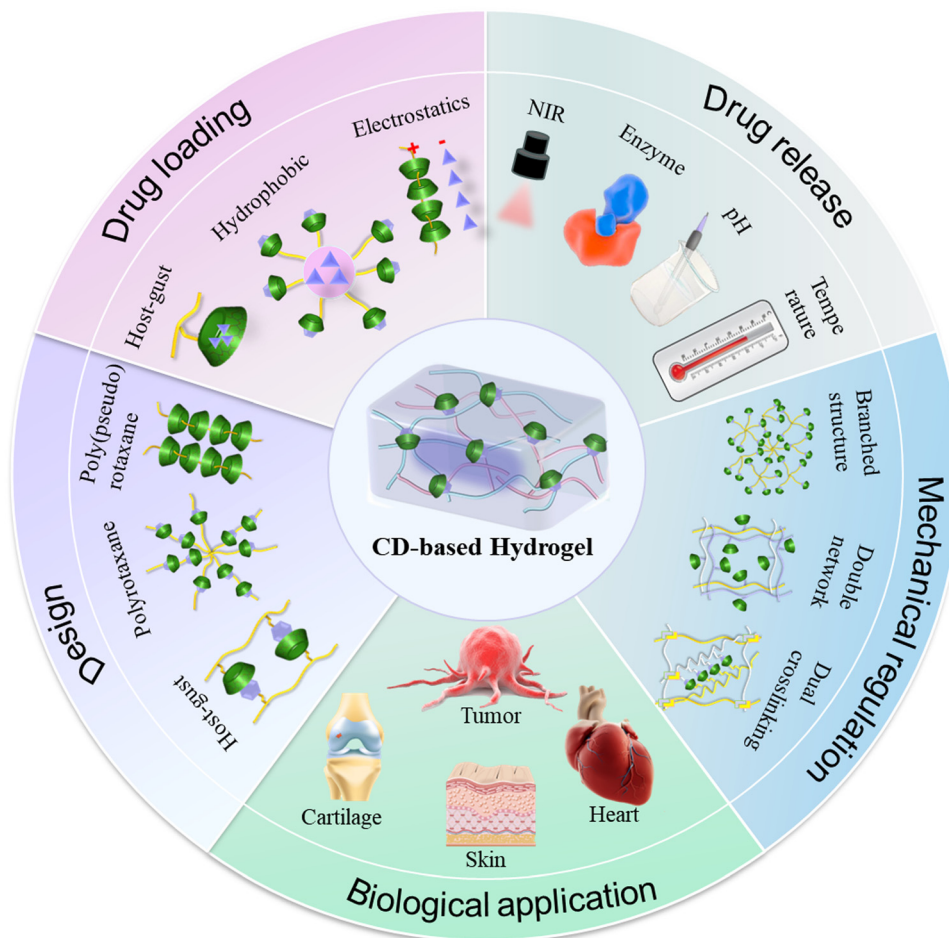
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Scheme 1 Schematic illustration of the design and biological applications of CD-based supramolecular hydrogels.

CD-based supramolecular hydrogels in the field of biomedicine from bench to bedside.

## 2. Design strategy of CD-based supramolecular hydrogels

### 2.1 Hydrogen bonding

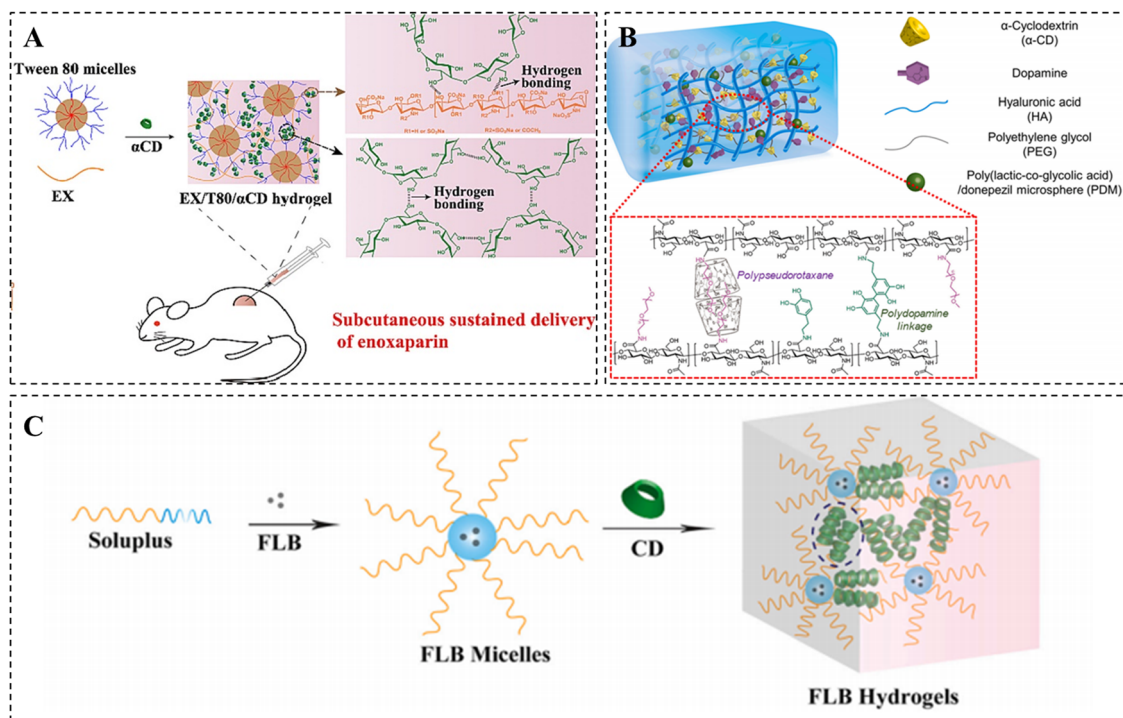
Polyrotaxane (PR) and poly(pseudo)rotaxane (PPR) are unique supramolecular structures that consist of a “necklace” of molecules. These structures are formed by threading multiple cyclodextrin (CD) molecules onto polymer chains, which may or may not have bulky end groups. The presence of cyclodextrins on neighboring polymer chains allows for strong hydrogen bonding interactions, leading to cross-linking of the PR or PPR structures. This cross-linking is responsible for the formation of CD-based PR or PPR supramolecular hydrogels.<sup>25–27</sup>

The size match between the polymer chain and the CD cavity is crucial for the formation of PPR.  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CDs have different cavity sizes and can form PPR structures with various polymer chains.<sup>28–31</sup> Among them, the combination of  $\alpha$ -CD and PEG is currently the most frequently used. Harada *et al.* initially reported that  $\alpha$ -CD can form  $\alpha$ -CD/PEG supramolecular

hydrogels using PEG with a molecular weight greater than 2 kDa in aqueous solution. The mechanical properties of hydrogels gradually enhanced with the increasing molecular weight of PEG.<sup>32,33</sup>

These  $\alpha$ -CD/PEG PPR hydrogels often face challenges such as rapid drug release and inadequate mechanical properties due to weak non-covalent cross-linking. Although the mechanical properties of hydrogels can be improved with an increased molecular weight of PEG, the poor biodegradability associated with the high molecular weight of PEG in turn limits their biological applications. To achieve a balanced performance between the biodegradability and mechanical properties, various biodegradable linear block copolymers, star polymers, PEG-grafted polymers, or nanoparticles have been frequently incorporated into PPR hydrogels to overcome these limitations.<sup>34–37</sup> The incorporation of diverse polymers or nanoparticles enhances the multifunctionality of PPR hydrogels, thereby expanding their applications in biomedicine.<sup>37</sup> For example, Tween 80 (T80) is a surfactant that can self-assemble and form micellar structures containing a hydrophilic PEG shell at a specific concentration.<sup>38</sup> Tang *et al.* demonstrated the development of a PPR hydrogel with tunable stiffness *via* the complexation between T80 and  $\alpha$ -CDs, as well





**Fig. 1** Construction of CD-based supramolecular hydrogels based on PPR. (A) Enoxaparin-loaded supramolecular hydrogel prepared via inclusion complexation between Tween 80 and  $\alpha$ -CDs, as well as hydrogen bonding between  $\alpha$ -CDs. Reproduced with permission from ref. 39. Copyright 2022, Elsevier. (B) PDM-loaded hydrogel based on PPR and polydopamine. Reproduced with permission from ref. 40. Copyright 2021, Elsevier. (C) FLB hydrogel cross-linked by host-guest recognition between the Soluplus micelles and  $\gamma$ -CDs, as well as the strong hydrogen bonding between  $\gamma$ -CDs. Reproduced with permission from ref. 43. Copyright 2022, Elsevier.

as the hydrogen bonding between  $\alpha$ -CDs. The hydrogen bonding between CDs and low molecular weight heparin (LMWH) enabled the effective loading and sustained release of LMWH (Fig. 1A).<sup>39</sup> Additionally, PEG can be modified on the polymer chain to further enhance the cross-linking density of the hydrogel due to its branching structure. Hwang *et al.* synthesized hyaluronic acid modified with PEG and dopamine, and then constructed a physical-chemical double cross-linked injectable self-healing hydrogel using the PPR structure formed by PEG and  $\alpha$ -CD, as well as the autopolymerization of dopamine in an alkaline environment (Fig. 1B).<sup>40</sup>

In contrast to  $\alpha$ -CD,  $\gamma$ -CD allows for the simultaneous cross-linking of two PEG chains due to its larger cavity size.<sup>41,42</sup> For instance, Fang *et al.* prepared a shear-thinning supramolecular hydrogel platform based on  $\gamma$ -CD for efficient and safe delivery of ocular drugs (Fig. 1C).<sup>43</sup> The crosslinking of this hydrogel primarily relies on the host-guest recognition between the PEG of Soluplus micelles and  $\gamma$ -CDs, as well as the hydrogen bonding interactions between  $\gamma$ -CDs. The drug flurbiprofen (FLB) was loaded into the hydrophobic core of Soluplus micelles. The results demonstrated that FLB hydrogels significantly decreased the dosing frequency and effectively suppressed intraocular inflammation compared to drug solutions and micelles.

## 2.2 Host-guest interactions

Besides PPR hydrogels formed by hydrogen bonding, a significant component of CD-based supramolecular hydrogel is

host-guest supramolecular hydrogels. This type of hydrogel is commonly cross-linked through host-guest recognition between a range of size-matched guest molecules and the unique hydrophobic cavities of CDs.<sup>6,12</sup>  $\beta$ -CD is the most commonly utilized in the preparation of host-guest inclusion due to its moderate cavity size, good modifiability, and low cost. The major guest molecules compatible with  $\beta$ -CD include adamantane, azobenzene, ferrocene, and cholesterol.<sup>44,45</sup> CD-based host-guest supramolecular hydrogels are increasingly employed in biomedical and other fields due to the strong attraction provided by the dynamic reversibility of host-guest interactions.<sup>18,46</sup> In the next sections, an introduction to CD-based supramolecular hydrogels based on host-guest interactions will be provided.

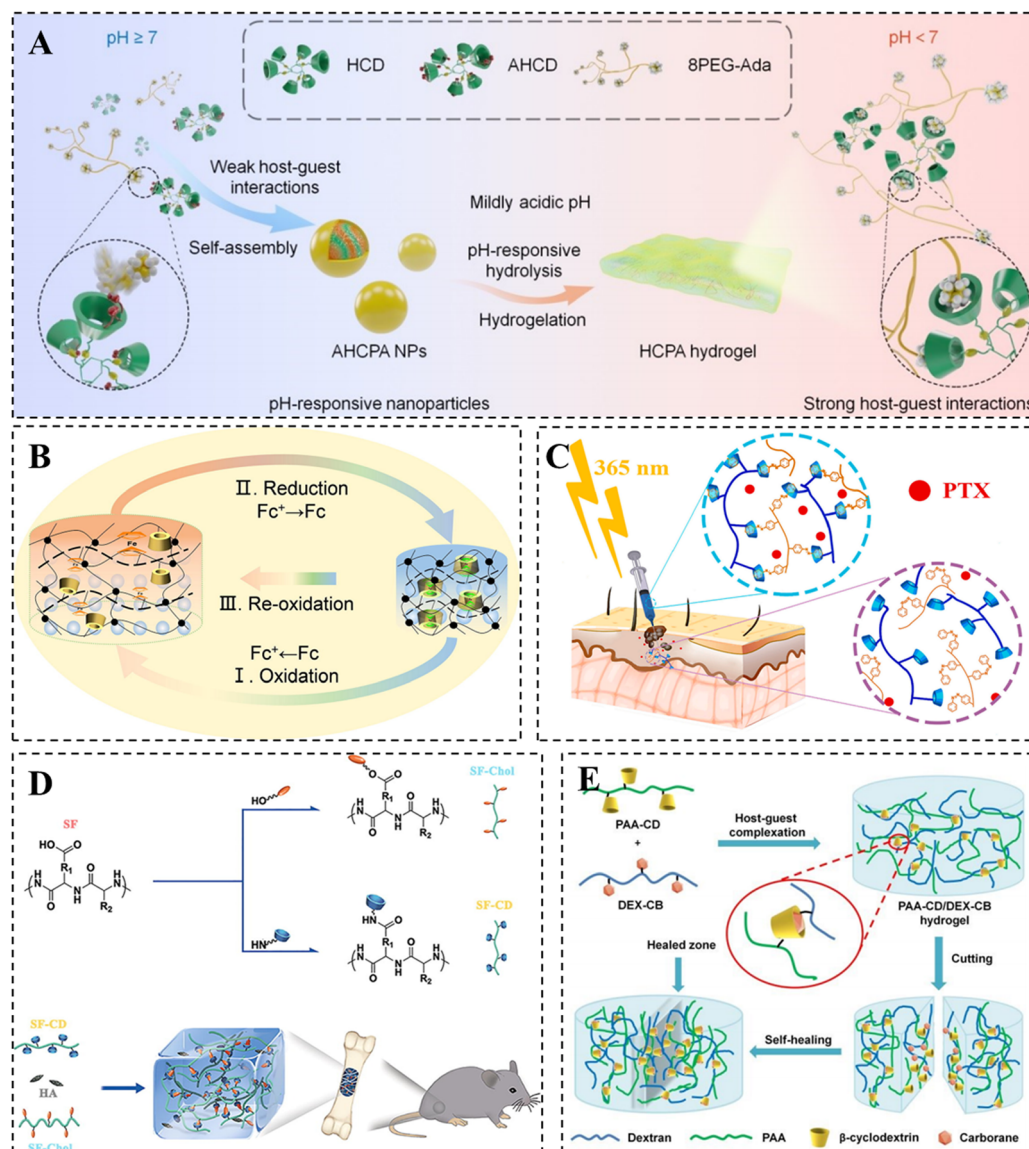
**2.2.1 Adamantane.** Adamantane (Ad) is a hydrophobic molecule that fits well into the hydrophobic cavity of  $\beta$ -CD and can form a stable 1:1 complex with  $\beta$ -CD.<sup>47</sup>  $\beta$ -CD/Ad supramolecular hydrogels are commonly cross-linked through reversible host-guest interactions between  $\beta$ -CD and Ad-modified polymers. These supramolecular hydrogels possess injectable and self-healing properties, making them promising materials for the delivery of bioactive molecules and human tissues.<sup>48–50</sup>

However, the mechanical properties of hydrogels based on CD host-guest interactions are significantly hampered by the weak noncovalent interactions and the low cross-linking density owing to the generally low modification efficiency of  $\beta$ -CD



on the macromolecular chains. Unlike previous investigations where  $\beta$ -CD/Ad host-guest hydrogels were formed by modifying CDs and Ads on polymer chains, Chen *et al.* successfully constructed a robust and self-healing  $\beta$ -CD/Ad host-guest PAM hydrogel using novel cyclodextrin topology nanoparticles (TNPs) as physical cross-linking agents.<sup>51</sup> The unique topology of TNPs and the host-guest cross-linking mechanism contributed significantly to the improvement of the hydrogel's mechanical strength and self-healing capabilities. This innovative approach presents a novel method for enhancing the mechanical properties of CD-based hydrogels.

More interestingly, Li *et al.* utilized the different strengths of the  $\beta$ -CD/Ad host-guest interactions to convert nanoparticles into hydrogels. They developed a multifunctional hydrogel platform that can respond to both physiological and pathological acidic microenvironments (Fig. 2A).<sup>52</sup> To achieve this, they synthesized a pH-responsive multivalent hydrophobic host compound, AHCD, by conjugating  $\beta$ -CD to cyclic hexachlorocyclotriphosphazene (HCTP) and acetalization. Subsequently, they prepared pH-responsive ACPA NPs by nanoprecipitation of AHCD with Ad-modified 8-armed PEG, relying on weak host-guest interactions. Under an acidic environment, AHCD underwent hydrolysis, resulting in the production of the hydrophilic



**Fig. 2** Construction of CD-based supramolecular hydrogels based on host-guest interactions. (A)  $\beta$ -CD/Ad host-guest supramolecular hydrogel converted from nanoparticles under acidic conditions. Reproduced with permission from ref. 52. Copyright 2022, Wiley. (B) Supramolecular photonic hydrogel based on  $\beta$ -CD/Fc host-guest interactions for use in a biosensor. Reproduced with permission from ref. 60. Copyright 2023, Elsevier. (C) PTX-loaded photo/thermal dual-responsive supramolecular hydrogel based on  $\beta$ -CD/Azo host-guest interactions for use in tumor therapy. Reproduced with permission from ref. 69. Copyright 2023, Elsevier. (D) Hydroxyapatite-loaded hydrogel based on  $\beta$ -CD/chol host-guest interactions for use in bone repair. Reproduced with permission from ref. 82. Copyright 2020, Elsevier. (E) Supramolecular hydrogel based on  $\beta$ -CD/CB host-guest interactions. Reproduced with permission from ref. 88. Copyright 2020, Royal Society of Chemistry.

host compound HCD. The enhanced host-guest interactions resulted in the conversion of the nanoparticles into a hydrogel. These pH-responsive nanoparticles were successful in protecting mice from ethanol- or drug-induced gastric injury by forming a protective hydrogel barrier on the gastric mucosa after oral administration. This finding has significant clinical implications.

**2.2.2 Ferrocene.** Ferrocene (Fc) exhibits weaker interaction with CD compared to Ad, resulting in limited applications of Fc. However, Fc can form host-guest complexes with all three types of CDs. Specifically, Fc is expected to form stable 1:1 complexes with  $\beta$ -CD or  $\gamma$ -CD, while tending to form 1:2 complexes with  $\alpha$ -CD.<sup>53</sup> This difference can be attributed to the varying sizes of the hydrophobic cavities of CDs. Furthermore, Fc has garnered significant attention due to its excellent oxidation-reduction reversibility. It can undergo a reversible transition between the hydrophobic reduced state and the hydrophilic oxidation state under external stimuli, allowing for the assembly and dissociation of CD/Fc inclusion complexes.<sup>54–56</sup>

The introduction of Fc and its derivatives in CD-based supramolecular hydrogels has the potential to facilitate the development of redox-responsive smart hydrogel systems with promising applications in biomedicine.<sup>57–59</sup> For example, Qin *et al.* designed a supramolecular photonic hydrogel with self-regulation based on the reversible  $\beta$ -CD/Fc host-guest complexation (Fig. 2B).<sup>60</sup> In the presence of horseradish peroxidase/ $\text{H}_2\text{O}_2$  and glucose oxidase/*D*-glucose, the contraction or swelling of the hydrogel can be observed as a result of the complexation or dissociation of the  $\beta$ -CD/Fc host-guest complex. The volume change of the hydrogel was simultaneously accompanied by its color variation due to the presence of photonic structures, which confirmed the hydrogel to be a potential candidate as a biosensor for detecting the concentration of  $\text{H}_2\text{O}_2$  and glucose as well as enzyme activity.

Currently, most CD/Fc supramolecular hydrogels achieve drug release or other functions by inducing a sol-gel transition with externally provided redox stimuli. Chiang *et al.* took an interesting approach by utilizing the release of reducing agents loaded in the hydrogel to accelerate both the self-healing procedure and the restoration of mechanical properties. It was considered to be an effective approach to the problem of substantial reduction of the host-guest hydrogel's mechanical properties with the swelling process or external stimuli. In their study, they developed an injectable HA-pAA hydrogel with CD/Fc supramolecular interactions to deliver GSH-loaded LbL-PPMM magnetic microcapsules and chondrocytes.<sup>61</sup> By slowly releasing the reducing agent GSH from LbL-PPMM, the self-healing rate of the hydrogel was significantly accelerated, and the mechanical strength of the hydrogel was restored to its initial level due to the gradual reduction of the oxidized Fc.

**2.2.3 Azobenzene.** Azobenzene (Azo) is commonly utilized in the construction of CD-based supramolecular hydrogels due to its strong binding affinity with  $\beta$ -CD. Azo is a photo-responsive molecule that can undergo reversible *cis-trans* transitions when exposed to UV light or visible light.<sup>62</sup> This

transition leads to a sol-gel transformation in  $\beta$ -CD/Azo supramolecular hydrogels, creating favorable conditions for the development of photo-responsive hydrogels and further expanding their potential for various biological applications.<sup>63–66</sup>

Azo-based UV-responsive hydrogels show promise as platforms for smart drug delivery in superficial tissues, allowing for remote and precise spatiotemporal modulation of drug release.<sup>67,68</sup> For example, Pourbadiei *et al.* synthesized the photo/thermal responsive copolymer NIPAZO by using Azo and NIPAM. They then prepared the DAS@SCD/NIPAZO hydrogel through host-guest recognition between NIPAZO and CD-modified starch (Fig. 2C).<sup>69</sup> At physiological temperature, the paclitaxel-loaded hydrogel exhibited a slow and sustainable release of paclitaxel within 96 hours. However, the CD/Azo host-guest interaction in the hydrogel gradually broke when exposed to 365 nm UV illumination, resulting in an increased release rate of paclitaxel and a significant inhibitory effect on tumor growth.

Unfortunately, the limited tissue penetration of UV light has hindered extensive research on CD/Azo hydrogels in various biomedical applications, including deep tissue repair. Red or near-infrared light (600–900 nm) offers deeper penetration and causes less photodamage compared to UV light.<sup>70</sup> Previous studies have demonstrated that the activated light of Azo is able to be red-shifted *via* chemical modification of the electron-donating or electron-withdrawing groups on the benzene ring.<sup>71,72</sup> Wu *et al.* designed a red light-sensitive hyaluronic acid (HA) hydrogel by utilizing tetra-ortho-methoxy-substituted azobenzene (mAzo) and  $\beta$ -CD through host-guest recognition.<sup>73</sup> The combination of red-shifted-photoisomerized Azo and HA confers enhanced hydrogen bonding and reduced photoisomerization of the polymeric guest. Compared to conventional CD/Azo hydrogels, this hydrogel avoids the problem of rapid drug release brought about by a complete red light-responsive gel-sol transition, making it a promising candidate for sustained drug release.

**2.2.4 Cholesterol.** Cholesterol (Chol) plays a crucial role in the formation of cell membranes in animal tissue cells.<sup>74</sup> Compared to other guest molecules such as adamantane and ferrocene, Chol exhibits superior biocompatibility and biodegradability, making it a subject of considerable interest in cyclodextrin host-guest supramolecular chemistry.<sup>75</sup> Hennink *et al.* successfully developed an 8-arm star-shaped PEG supramolecular hydrogel using  $\beta$ -CD/chol host-guest interactions. This hydrogel displayed thermal reversibility, and its properties, including viscoelasticity and mechanical characteristics, could be adjusted by manipulating the polymer concentration,  $\beta$ -CD/chol molar ratio, and PEG molecular weight.<sup>76</sup>

However, polymers such as PEG and polyacrylamide, while exhibiting good biocompatibility, suffer from disadvantages such as poor biodegradability and lack of bioactivity. Poly-L-glutamic acid (PLGA), similar to proteins found in the extracellular matrix, is an ideal peptide material due to its excellent biocompatibility, biodegradability, and ability to promote tissue repair and cell growth through its degradation products.<sup>77</sup>

Li *et al.* developed a degradable and self-healing  $\beta$ -CD/chol host-guest peptide hydrogel using PLGA. The hydrogel demonstrated the highest energy storage modulus when the  $\beta$ -CD/chol molar ratio was 1:1, and the mechanical properties of the hydrogel were progressively enhanced with increasing molecular weight of PLGA.<sup>78</sup>

Although the  $\beta$ -CD/chol host-guest hydrogels offer the ability to adjust their mechanical properties, hydrogels formed from a single network of host-guest crosslinking remain mechanically weak. Compared to other natural polymers, silk fibroin (SF) demonstrates exceptional mechanical strength as SF molecules can transition from randomly curled to a stable  $\beta$ -folded structure, forming  $\beta$ -sheet nanocrystalline structures primarily driven by hydrogen bonding.<sup>79,80</sup> To address the mechanical limitations of  $\beta$ -CD/chol hydrogels, Bai *et al.* developed HG-SF hydrogels by utilizing the  $\beta$ -CD/chol dynamic host-guest interactions with the layered structure of SF. The hydrogel demonstrated outstanding mechanical strength, self-healing, with a maximum compressive stress of up to 3.16 MPa, and achieved a healing efficiency of 93.78% after 2 hours.<sup>81</sup> In addition, the research team incorporated hydroxyapatite nanoparticles with good osteoconductivity into HG-SF hydrogels to form organic-inorganic hybrid hydrogels, which were utilized for bone repair (Fig. 2D).<sup>82</sup> In summary, cholesterol, commonly used as a guest molecule for cyclodextrins, offers advantages in biological applications because of its outstanding biocompatibility and biodegradability.

**2.2.5 Other guest molecules.** Besides the previously mentioned well-known guest molecules, other guest molecules that have well-matched CD cavity dimensions have also been used for the preparation of CD-based host-guest supramolecular hydrogels.<sup>6</sup> *N*-Isopropylacrylamide (NIPAM) is a representative temperature-responsive molecule frequently utilized in the creation of temperature-responsive self-healing hydrogels.<sup>83</sup> Previous studies have demonstrated that the hydrophobic isopropyl group in NIPAM is capable of engaging in host-guest recognition with  $\beta$ -CD.<sup>84</sup> Deng *et al.* proposed the preparation of a temperature-responsive self-healing hydrogel by host-guest recognition between  $\beta$ -CD and NIPAM. To enhance its electrical conductivity, nanostructured polypyrrole (PPY) and multiwalled carbon nanotubes (CNTs) were simultaneously incorporated into the hydrogel.<sup>85</sup> Carboranes (CBs) are a class of boron-rich icosahedral cluster compounds. Their appropriate size and hydrophobicity make them suitable guest molecules for  $\beta$ -CD.<sup>86,87</sup> Xiong *et al.* developed a novel self-healing hydrogel based on the strong  $\beta$ -CD/CB host-guest interactions using CB-grafted dextran and  $\beta$ -CD-grafted polyacrylic acid (Fig. 2E).<sup>88</sup> The hydrogel exhibited excellent self-healing properties within minutes and achieved a storage modulus of approximately 10 kPa.

In addition to CBs, many other naturally occurring hydrophobic small molecules are capable of host-guest complexation with CDs.<sup>89</sup> Coumarin (COU) is a light-sensitive small molecule that exhibits interesting changes when irradiated with light at wavelengths of 365 nm and 254 nm.<sup>90</sup> Furthermore, COU has been extensively studied as a guest molecule in host-guest

complexation.<sup>91</sup> Liu *et al.* constructed a bimodal supramolecular hydrogel by forming a 2:1 host-guest complex between COU and  $\gamma$ -CD.<sup>92</sup> Notably, the mechanical strength of the hydrogel is able to be controlled by switching the weak physical cross-linking sites to strong chemical cross-linking sites using UV irradiation. Specifically, the encapsulated COU in  $\gamma$ -CD undergoes dimerization under 365 nm UV irradiation, resulting in a change of the cross-linking interaction from host-guest recognition to COU-COU covalent bonding. As a result, the hydrogel's storage modulus increases to 2.3 MPa. Nevertheless, the COU-COU covalent bonds are broken, and the hydrogel returns to its soft physically cross-linked state. This unique property makes the hydrogel a promising material for self-healing applications due to its reversible stiffness tunability and self-healing properties.

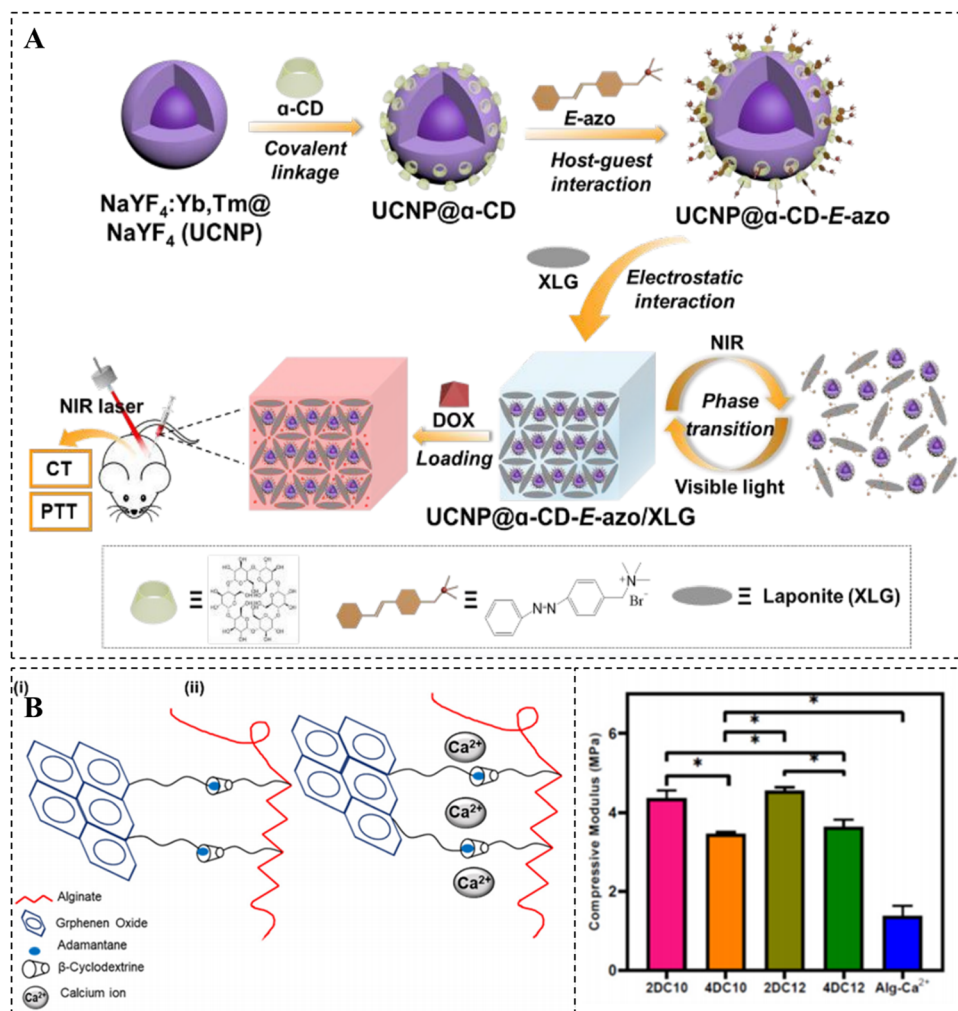
### 2.3 Ionic interactions

Compared to other noncovalent interactions, such as hydrogen bonding and host-guest interactions, ionic interactions are more robust and play an essential role in the formation of CD-based supramolecular hydrogels.<sup>93</sup> Host-guest interactions have been extensively recognized to make a substantial contribution to the favorable self-healing properties of hydrogels while limiting their mechanical properties. To address the trade-off between these two properties in CD-based supramolecular hydrogels, ionic interactions have often been combined with the most extensively used host-guest interactions. There are two primary strategies for constructing hydrogels of this nature.

One approach involves modifying CD molecules or guest molecules with charged groups, such as guanidino groups, to create charged polymers or nanoparticles through host-guest interactions. Subsequently, supramolecular hydrogels are prepared by utilizing electrostatic interactions between charged nanoparticles and charged inorganic materials, such as LAPONITE<sup>®</sup>. The incorporation of inorganic nanomaterials can further enhance the mechanical properties of the hydrogels.<sup>94</sup> Zhang *et al.* developed a supramolecular hydrogel that is highly loaded with drugs and responsive to near-infrared (NIR) light by using upconverting nanoparticles (UCNP),  $\alpha$ -CD/Azo, and LAPONITE<sup>®</sup> (Fig. 3A).<sup>95</sup> Specifically, UCNP@ $\alpha$ -CD-E-azo nanoparticles were obtained by host-guest recognition of  $\alpha$ -CD covalently coated UCNP and azobenzene quaternary ammonium salt. This was immediately followed by the preparation of a supramolecular hydrogel *via* electrostatic interactions between the quaternary ammonium salt and LAPONITE<sup>®</sup>. UCNP has the ability to convert absorbed NIR light into UV light and heat, causing a gel-sol phase transition and facilitating the effective release of drugs. The combination of photothermal therapy and chemotherapy in this hydrogel system effectively inhibits tumor growth, making it a promising controlled drug delivery platform for cancer treatment.

Another approach is to utilize host-guest interactions as the initial cross-linking mechanism in hydrogels. In this method, electrostatic interactions occur between polymer chains that are enriched with charged groups, such as carboxyl groups, and





**Fig. 3** Construction of CD-based supramolecular hydrogels based on ionic interactions. (A) NIR-responsive hydrogel via electrostatic interaction between  $\text{UCNP@}\alpha\text{-CD-E-azo}$  and LAPONITE<sup>®</sup> and its pH/NIR-responsive DOX release. Reproduced with permission from ref. 95. Copyright 2020, Royal Society of Chemistry. (B) Crosslinking mechanism of the nanohybrid Alg-GO hydrogel with adjustable mechanical properties. Reproduced with permission from ref. 96. Copyright 2021, Elsevier.

ions serve as the second cross-linking agent. It should be noted that ionic interactions do not take place on CDs or their guest molecules. For example, Kharaziha *et al.* successfully prepared a nanohybrid double crosslinked hydrogel by employing host-guest interactions between  $\beta$ -CD grafted sodium alginate (Alg-CD) and Ad-modified graphene oxide (Ad-GO), as well as the ionic interactions between  $\text{Ca}^{2+}$  and Alg (Fig. 3B).<sup>96</sup> The incorporation of  $\text{Ca}^{2+}$  significantly strengthened the shear-thinning properties of the hydrogel. Moreover, the hydrogel demonstrated adjustable mechanical and biological properties due to the ability to control the crosslink density and network structure. This characteristic makes it highly promising as a minimally invasive injectable material.

Overall, the introduction of ionic interactions in host-guest supramolecular hydrogels is a well-established and effective method for enhancing their mechanical properties. Moreover, these ionic interactions facilitate the efficient encapsulation of charged drugs in CD-based supramolecular hydrogels.

### 3. Strategies to improve the mechanical properties of CD-based supramolecular hydrogels

Currently, increasing research interests have been concentrated on CD-based supramolecular hydrogels due to their shear-thinning and self-healing properties. However, their generally weak mechanical properties limit the potential applications in certain fields.<sup>22</sup> For wound healing applications, supramolecular hydrogel dressings are expected to possess not only favorable self-healing properties but also appropriate mechanical properties, thus avoiding bacterial infections or premature drug leakage caused by structural damage from external pressure during the application process.<sup>23</sup> In the field of bone and cartilage tissue engineering, it is necessary for hydrogels to have mechanical strength comparable to those of natural bone and cartilage to improve the quality of repair.<sup>24</sup> The elastic modulus of articular cartilage can reach up to 950 kPa, while

that of bone is even higher than 1 MPa.<sup>97</sup> Unfortunately, CD-based supramolecular hydrogels typically fail to achieve such high mechanical strength values due mainly to the following three factors, (i) the crosslinking of supramolecular hydrogels is primarily based on the reversible non-covalent interactions, (ii) the low grafting efficiency of the host and guest molecules onto the polymer chain results in a low cross-linking density, and (iii) the steric hindrance of the polymer backbone also accounts somewhat for the compromised mechanical properties of the hydrogels.

One of the simplest and most direct methods to improve the mechanical properties of hydrogels is to increase the polymer concentration or the amount of host-guest crosslinking sites. For instance, Ren *et al.* designed a supramolecular hydrogel with high adhesion properties by the host-guest interactions between  $\beta$ -CD and dopamine co-grafted alginate and adamantane-grafted polyacrylamide (Fig. 4A).<sup>98</sup> The results demonstrated the effectiveness of this approach in enhancing

the mechanical properties of the hydrogel. In another study, Lee *et al.* developed F127-Ad/CDP hydrogels for protein drug delivery by crosslinking Pluronic F127 modified with single or multiple Ads and  $\beta$ -CD polymers *via* host-guest interactions (Fig. 4B).<sup>99</sup> The formation of F127 micelles not only conferred thermally responsive sol-gel transition properties, but also enhanced the mechanical properties of the hydrogel. As the number of Ads attached to F127 increased, the polymer concentration required for hydrogel formation gradually decreased, resulting in improved mechanical properties of the hydrogel.

In addition, incorporating multiple cross-linking mechanisms is a common method for enhancing the mechanical properties of CD-based supramolecular hydrogels. One strategy involves introducing chemical covalent crosslinking to create a highly crosslinked rigid network in addition to a relatively relaxed host-guest crosslinked network. Wang *et al.* initially synthesized three-armed host-guest supramolecules (HGSMs) through appropriate host-guest interactions between

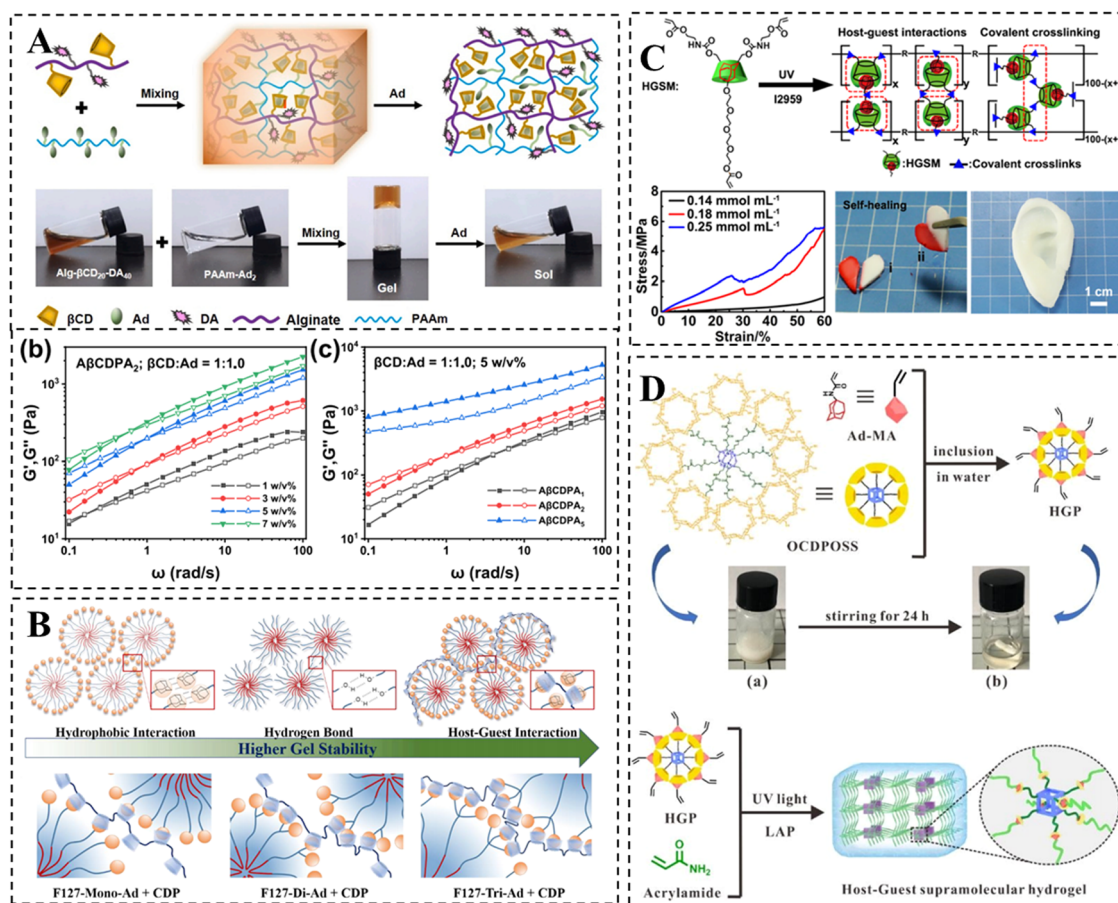


Fig. 4 Strategies to improve the mechanical properties of CD-based supramolecular hydrogels. (A) Schematic representation of alginate/polyacrylamide host-guest supramolecular hydrogels. The mechanical properties are improved by increasing the concentration or adamantane substitution of PAAm-Ad polymer. Reproduced with permission from ref. 98. Copyright 2023, Elsevier. (B) Schematic representation of ADA-F127 supramolecular hydrogel. The mechanical properties may be improved by increasing the substitution of adamantane and using the F127 micellar structure as secondary cross-linking. Reproduced with permission from ref. 99. Copyright 2021, Elsevier. (C) Schematic representation of the self-healing HGSM supramolecular hydrogel. The mechanical properties are improved via a combination of multiple cross-linking mechanisms. Reproduced with permission from ref. 100. Copyright 2018, Wiley. (D) Schematic representation of the preparation for the HGP hydrogel. The mechanical properties are improved via the incorporation of POSS and a combination of multiple cross-linking mechanisms. Reproduced with permission from ref. 102. Copyright 2020, Royal Society of Chemistry.

$\beta$ -CD-AOI<sub>2</sub> (the host molecule) and A-TEG-Ad (the guest molecule), thus avoiding the spatial site-barriers of the polymer chains that lead to inadequate cross-linking. Subsequently, they covalently polymerized HGSM with double bonds under UV light initiation to obtain HGSM hydrogels (Fig. 4C).<sup>100</sup> This physical/chemical dual crosslinked network significantly enhanced the mechanical strength of CD-based hydrogels, making them promising candidates for regenerative medicine applications such as cartilage repair. However, the irreversible nature of covalent interactions leads to a partial loss of the self-healing properties of hydrogels. To strengthen the mechanical properties while realizing the intact retention of the inherent dynamic properties of supramolecular hydrogels, the combination of multiple non-covalent interactions is more popular. Chen *et al.* employed a kinetic interlocking multiple unit (KIMU) strategy to introduce two types of host-guest interactions, CB[8]-Phe and  $\beta$ CD-Ad, into a hyaluronic acid hydrogel system.<sup>48</sup> This approach successfully incorporated the hydrogel into the system without sacrificing self-healing and shear dilution properties, while increasing the hydrogel's storage modulus by 78%. This KIMU effect inhibits the cascade disintegration of the two host-guest complexes, leading to higher dynamic stability.

Finally, the incorporation of rigid inorganic nanomaterials into CD-based hydrogels has been found to strengthen their mechanical properties. Among the various organic-inorganic hybrid silica nanoparticles, POSS, as the smallest, has been shown to play a crucial role in improving the mechanical properties of hydrogels.<sup>101</sup> Zhou *et al.* developed star-type HGP crosslinkers using POSS,  $\beta$ -CD and adamantane. The star-type HGP crosslinkers were created through host-guest interaction, and subsequently, HGP supramolecular hydrogels were formed *via* covalent polymerization of double bonds (Fig. 4D).<sup>102</sup> Comparatively, the HGP hydrogels exhibited a 2.7-fold increase in tensile modulus and demonstrated excellent ductility when compared to the HGM hydrogels lacking POSS. Moreover, the storage modulus of hydrogels improved with a higher HGP cross-linker concentration.

## 4. Drug loading and release of CD-based supramolecular hydrogels

### 4.1 Drug loading

Drug-loading methods for CD-based supramolecular hydrogels can be categorized into two types: (1) loading the drug into the hydrogel *via* non-covalent interactions, like electrostatic interactions, hydrophobic interactions, and hydrogen-bonding interactions; and (2) covalent modification of the drug onto the molecular chains of the hydrogel.<sup>103–105</sup> Hydrophilic drugs can be directly physically encapsulated into hydrogels, and their release rate is related to the dimension of the drugs and the affinity between the drugs and the hydrogel matrix. Compared to hydrophilic drugs, hydrophobic drugs are less efficiently loaded into hydrogels due to difficulties in dissolution leading to their poor loading.<sup>12,106</sup>

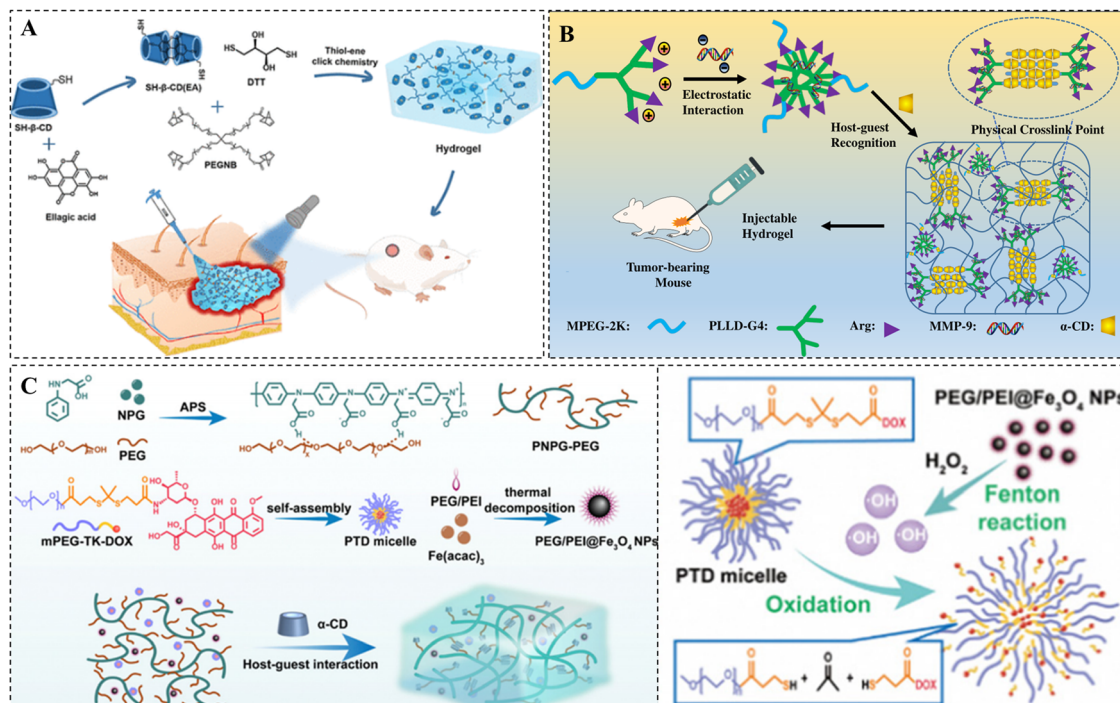
**4.1.1 Drug physical encapsulation.** In CD-based supramolecular hydrogels, the hydrophobic cavities of CDs can be used for efficient loading of hydrophobic drugs, which not only improves the loading efficiency of the drugs, but also maximizes their bioactivity.<sup>107</sup> For example, Feng *et al.* developed a supramolecular gelatin-based hydrogel through host-guest interactions between aromatic residues and acrylated  $\beta$ -CD, and utilized the excess  $\beta$ -CD cavities in the hydrogel to enhance the storage and slow release of the drug by combining  $\beta$ -CD with the hydrophobic drug dexamethasone.<sup>108</sup> Zhang *et al.* developed an inclusion complex of the hydrophobic drug ellagic acid (EA) with SH- $\beta$ -CD in a 1 : 2 molar ratio, and formed an EA-loaded hydrogel through the photoinitiated click reaction between the inclusion complex as cross-linking agents and tetra-armed poly(ethylene glycol)-norbornene (Fig. 5A).<sup>109</sup> The release rate of the EA depended on the stability of the hydrogen bond between the EA and cyclodextrin, the pore size of the hydrogel, and the degradation of the hydrogel.

In addition, hydrophobic drugs can also be efficiently loaded into nanocarriers, such as micelles, liposomes, and metal nanoparticles, through covalent or noncovalent interactions, and then these nanocarriers can be further loaded into supramolecular hydrogels for efficient loading of hydrophobic drugs.<sup>110–112</sup> Domiński *et al.* developed pH-responsive drug-loaded nanomicelles by encapsulating DOX into their hydrophobic core. Next, they mixed these nanomicelles with a solution of  $\alpha$ -CD and 8-hydroxyquinoline glycoconjugate affixes to form supramolecular hydrogels loaded with both hydrophobic DOX and hydrophilic 8-hydroxyquinoline glycoconjugate affixes.<sup>113</sup> The structures showed that this drug-loaded hydrogel displayed accelerated drug release under acidic conditions.

For negatively charged gene drugs, they are often loaded into hydrogels by forming complexes with cationic polymers in the hydrogel matrix. Xue *et al.* synthesized poly(L-lysine) dendrimer molecules functionalized with PEG and arginine (MPEG-PLLD-Arg), which were bound to pMMP-9 *via* electrostatic interactions to form nanocomplexes. After mixing these complexes with  $\alpha$ -CD, a PPR hydrogel for local delivery of pMMP-9 was prepared (Fig. 5B).<sup>114</sup> This hydrogel not only maintains the high bioactivity and stability of pMMP-9 for a long time, but also has a well-established slow-release effect on pMMP-9.

**4.1.2 Drug covalent coupling.** Drugs are able to be integrated into hydrogels *via* covalent bonding with the hydrogel polymer chains.<sup>115</sup> This involves the formation of unstable covalent bonds, like ester, imine, and acylhydrazone bonds, to ensure efficient retention and release of the drug.<sup>116</sup> Among these unstable covalent bonds, the ester bond is commonly used because it can be hydrolyzed *in vivo* by esterases.<sup>117,118</sup> Dai *et al.* prepared CMC-BA prodrugs by modifying the hydrophilic molecule PEG and the hydrophobic drug betulinic acid (BA) on carboxymethyl cellulose (CMC) using readily hydrolyzable ester bonds. These prodrugs were then self-assembled with hydroxycamptothecin (HCPT) to form nanoparticles. The nanoparticles were mixed with  $\alpha$ -CD to create an injectable thermosensitive supramolecular hydrogel.<sup>119</sup> Upon increasing the temperature to 37 °C, the hydrogel underwent a gel-sol





**Fig. 5** Drug loading methods of CD-based supramolecular hydrogels. (A) Schematic representation of EA-loaded thiol-ene hydrogels for wound healing. EA is loaded into hydrogels *via* host-guest complexation with β-CD. Reproduced with permission from ref. 109. Copyright 2023, American Chemical Society. (B) Schematic representation of pMMP-9-loaded PPR supramolecular hydrogels for tumor therapy. pMMP-9 is loaded into hydrogels based on electrostatic interaction with MPEG-PLL-Arg. Reproduced with permission from ref. 114. Copyright 2017, Elsevier. (C) Schematic representation of NIR-responsive supramolecular hydrogels containing mPEG-TK-DOX micelles and PEG/PEI@Fe<sub>3</sub>O<sub>4</sub> nanoparticles for tumor therapy. DOX is loaded into hydrogels by linking to mPEG *via* TK bonds. Reproduced with permission from ref. 130. Copyright 2023, Royal Society of Chemistry.

transition, resulting in accelerated drug release. Furthermore, in the presence of esterases, the ester bond was rapidly hydrolyzed, leading to a significantly faster release rate of BA.

In addition to easily hydrolysable ester bonds, there are numerous other covalent bonds that can be cleaved in response to external environmental changes. For example, pH-responsive imine bonds, acylhydrazone bonds, and acetal bonds.<sup>120–122</sup> Li *et al.* modified DOX onto β-CD *via* imine bonding, and prepared DOX-loaded PPR supramolecular hydrogels by utilizing the host-guest interactions between Pluronic F-127 and β-CD and α-CD.<sup>123</sup> As a result of the presence of acylhydrazone bonds, these hydrogels displayed pH-sensitive DOX release. Furthermore, the acylhydrazone bonds demonstrated better stability at lower pH levels. Li *et al.* prepared DOX-loaded supramolecular hydrogels by utilizing interactions between acid-sensitive PEGylated polyphosphoester-doxorubicin precursors (PBYP-g-PEG-g-DOX) and α-CD.<sup>124</sup> The acid sensitivity of the precursor was mainly attributed to the introduced acylhydrazone and acetal bonds. The results showed that under acidic conditions, the acetal and acylhydrazone bonds facilitated cleavage, leading to degradation of the hydrogel and the release of DOX.

Redox-responsive covalent bonds, such as disulfide, diselenide, and thioketal bonds, are frequently employed for drug modification.<sup>125–127</sup> Thioketal (TK) bonds are considered to be one of the most efficient reactive oxygen species (ROS)-responsive bonds and can rapidly oxidize to thiols under high

levels of ROS.<sup>128,129</sup> Huang *et al.* developed a NIR-responsive supramolecular hydrogel using conjugated poly(*N*-phenylglycine)-poly(ethylene glycol) (PNPG-PEG) and α-CD. They encapsulated PEG/PEI@Fe<sub>3</sub>O<sub>4</sub> nanoparticles with DOX-loaded nanomicelles within the hydrogel (Fig. 5C).<sup>130</sup> The drug-loaded nanomicelles were self-assembled by the amphiphilic precursors mPEG-TK-DOX linked *via* TK bonds. The PEG/PEI@Fe<sub>3</sub>O<sub>4</sub> nanoparticles in this hydrogel could utilize the Fenton reaction to generate •OH, which led to an increase of ROS and induced the breakage of the ROS-responsive TK bond, thereby promoting sustained DOX release.

Overall, the covalent modification of drugs on CD-based supramolecular hydrogels substantially extends the duration of drug release and enhances intelligent responsiveness.<sup>131</sup> This modification also prevents the elimination of drug molecules (particularly peptide drugs) by the immune system.<sup>132,133</sup>

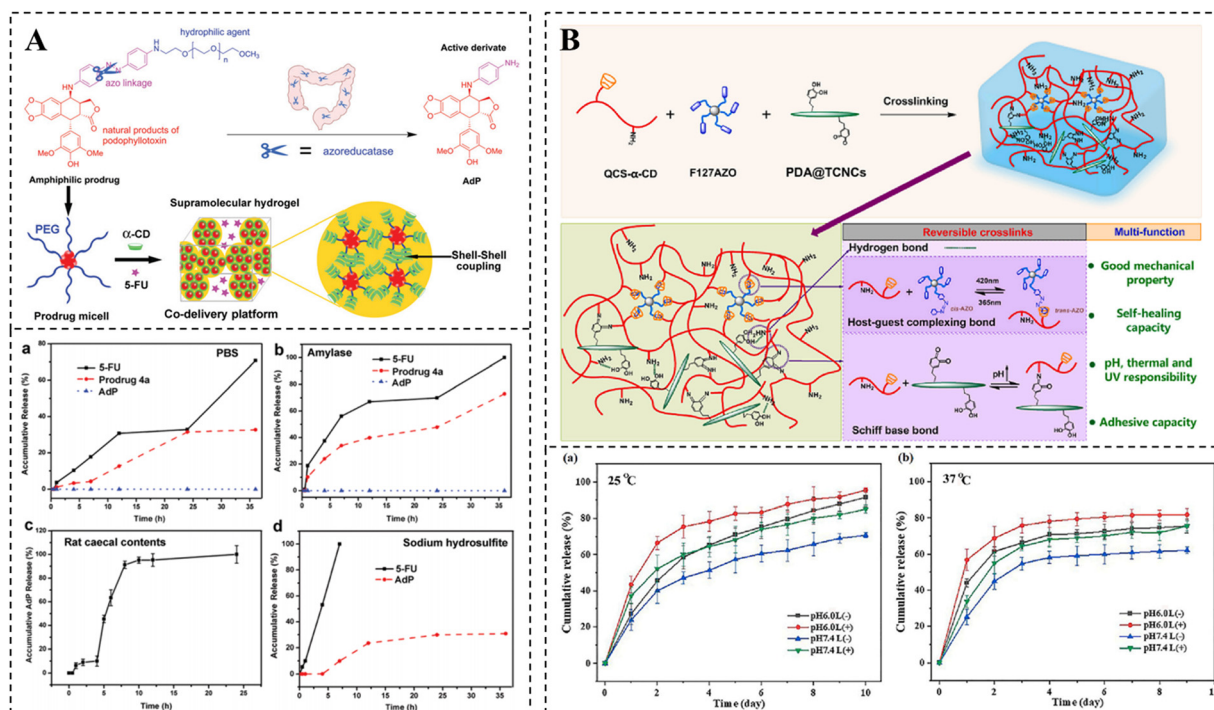
## 4.2 Drug release

The release rate of drugs physically encapsulated in hydrogels relies mainly on the pore size of hydrogels and the dimension of drugs.<sup>134–136</sup> If the hydrogel possesses a larger pore size than the dimension of drugs, the release rate of drugs has nothing to do with the pore size of the hydrogel, but is associated with the affinity between the hydrogel matrix.<sup>137,138</sup> If the hydrogel possesses a pore size close to the dimension of the drugs, the release rate of drugs depends mainly on the degradation rate of

the hydrogel and the interaction between drugs and the hydrogel.<sup>139,140</sup> If the hydrogel possesses a smaller pore size than the dimension of the drugs, the hydrogel pores may cause a strong spatial site resistance, preventing the diffusion of drugs, and the release rate of drugs mainly depends on the swelling or shrinkage and degradation of the hydrogel.<sup>136</sup> For example, after a change in the external environment, the electrostatic or hydrogen bonding interactions between hydrophilic groups and water molecules in the hydrogel are enhanced, resulting in water-absorbing swelling of the hydrogel, which accelerates the release of the drug.<sup>141,142</sup> Conversely, if there are more hydrophobic groups in the hydrogel, dominated by hydrophobic interactions, the formation of hydrogen bonds between the hydrophilic groups and external water molecules is hindered. This leads to shrinkage of the hydrogel, generating a squeezing effect, which promotes drug release.<sup>143</sup> In addition, when there are easily hydrolyzable bonds in the hydrogel structure, such as ester and peptide bonds, the pore size of the hydrogel gradually increases with the degradation of the hydrogel network, which in turn achieves a slow release of the drug.<sup>144–146</sup>

Drugs are loaded into hydrogels as chemical couplings, and their release rate depends greatly on the breakage rate of covalent bonds. Stable covalent bonds, such as amide bonds, achieve slow drug release mainly through degradation of the hydrogel network, whereas covalent bonds that can respond to cleavage, such as imine and disulfide bonds, can achieve controlled drug release in response to external environmental

changes.<sup>10</sup> Currently pH-responsive bonds such as imine bonds and acylhydrazone bonds, redox-responsive bonds including disulfide bonds and thioketal bonds, as well as enzyme-responsive bonds, have been extensively utilized for covalently modifying drugs on hydrogels.<sup>123,130,147–149</sup> These modified drug-loaded hydrogels exhibit more precise on-demand drug release and higher therapeutic efficiency compared to physically embedded drug-loaded hydrogels. For instance, Ha *et al.* developed amphiphilic prodrugs by conjugating podophyllotoxin with PEG and self-assembled them to form nanomicelles. Subsequently, the nanomicelles were further self-assembled into supramolecular hydrogels using the strong hydrogen bonding force between PEG and  $\alpha$ -CD. The water-soluble anti-cancer drug 5-Fu was loaded in a physically embedded manner within these supramolecular hydrogels (Fig. 6A).<sup>150</sup> It is demonstrated that  $\alpha$ -CD was slowly degraded by amylase, resulting in the disruption of the hydrogel structure and, consequently, an accelerated release of 5-Fu. Additionally, the presence of  $\text{Na}_2\text{S}_2\text{O}_4$ , a biomimetic azo reductase, caused the cleavage of the Azo bond in the amphiphilic prodrug, leading to the formation of 4'-O-demethyl-4 $\beta$ -(4''-aminoanilino)-4-desoxy-podophyllotoxin (AdP). This also disrupted the nanocellular structure and further facilitated the release of both 5-Fu and active AdP. Due to the specific secretion of amylase and azo reductase by colonic flora, this hydrogel enables responsive drug release at the colonic site, thereby demonstrating more precise on-demand effects in the therapy of diseases related to the colon.



**Fig. 6** Drug release of CD-based supramolecular hydrogels. (A) Schematic diagram of the preparation of PPR hydrogel coloaded with AdP and 5-Fu and its amylase or azo reductase responsive release kinetics. Reproduced with permission from ref. 150. Copyright 2021, Royal Society of Chemistry. (B) Schematic illustration of the preparation of curcumin-loaded hydrogel and its multi-responsive release kinetics (light, pH, and temperature). Reproduced with permission from ref. 155. Copyright 2023, Elsevier.

Achieving controlled release based on effective loading and release of drugs is essential for disease treatment. It is fascinating that stimuli-responsive hydrogels allow for the responsive release of drugs in specific environments, thus improving the efficacy of drugs. CD-based supramolecular hydrogels are an ideal smart drug delivery system that can form drug reservoirs in target tissues in a mini-invasive manner and realize controlled release of therapeutic drugs in time and space by responding to stimuli such as pH, redox, and light. Studies have shown that CD-based supramolecular self-assembly systems can effectively react to external stimuli, leading to the assembly and dissociation of the system. For example, the pH sensitivity of the  $\beta$ -CD/benzimidazole system,<sup>151–153</sup> the redox responsiveness of the  $\beta$ -CD/Fc,<sup>56,154</sup> and the UV light sensitivity of the  $\beta$ -CD/Azo have been investigated.<sup>67,68</sup> These host-guest interactions offer promising conditions for the exploitation of stimuli-responsive CD-based supramolecular hydrogels.

In contrast to hydrogels that respond to single stimuli, multi-responsive hydrogels based on CD are capable of responding to multiple stimuli simultaneously. Such hydrogels can also demonstrate greater sensitivity to small environmental changes at the lesion site, resulting in more accurate drug release and more effective disease treatment. For example, Liu *et al.* prepared a supramolecular hydrogel that is responsive to both light and heat by using  $\alpha$ -CD-grafted quaternized chitosan and Azo-modified Pluronic F127. Furthermore, polydopamine-coated tunicate cellulose nanocrystals were dispersed homogeneously in the hydrogel through Schiff base bonding and hydrogen bonding. This not only introduced pH responsiveness to the hydrogel, but also improved its mechanical properties and adhesion (Fig. 6B).<sup>155</sup> As a multi-responsive delivery platform for curcumin, this supramolecular hydrogel can release curcumin on demand in response to low pH and high-temperature environments at the wound site, as well as external UV irradiation, thereby effectively promoting wound healing. However, current research on CD-based multi-stimulus-responsive hydrogels is still in its early stages and requires further development.

## 5. Biological applications of CD-based hydrogels

Hydrogels have been broadly utilized in regenerative medicine, drug delivery, and biosensing due to their excellent biocompatibility and adjustable pore size and stiffness.<sup>156,157</sup> Among hydrogels, supramolecular hydrogels crosslinked by noncovalent interactions exhibit unique properties, such as injectability, self-healing, and stimulus responsiveness, which greatly expand the biological applications of hydrogels.<sup>20,158,159</sup> CDs are of vital importance in the development of drug carriers, which can not only increase the solubility and bioavailability of insoluble drugs, but also enable sustained drug release, thereby optimizing therapeutic effects.<sup>15–17,160,161</sup> In summary, the combination of multifunctional CD units and supramolecular hydrogels represents an effective strategy for maximizing the

safety and efficacy of therapeutic molecules, providing a promising approach for the exploitation of functional hydrogels and broadening the applications of hydrogels in disease treatment.<sup>12</sup> Recent advancements in CD-based supramolecular hydrogels for tumor therapy, bone and cartilage repair, myocardial repair, and wound healing are briefly described below.

### 5.1 Tumor treatment

One of the most pressing health issues in contemporary society is cancer, with the number of cancer-related deaths steadily increasing each year. The current approach to treating cancer is shifting towards a synergistic model that combines multiple therapies, with chemotherapy remaining the most crucial strategy.<sup>162,163</sup> However, the clinical applications of most anti-cancer drugs are limited due to their low solubility, poor stability, and inadequate tumor targeting. A solution to these challenges is provided by CD-based supramolecular hydrogels. These hydrogels enable the effective loading of anticancer drugs and facilitate local sustained release through intratumoral or peritumoral injection.<sup>164</sup> By delivering anticancer drugs locally, the concentration of the drugs can be maximized, enhancing their effectiveness against tumor cells while minimizing unnecessary side effects on healthy tissues.<sup>165</sup>

Hydrophobic chemotherapeutic drugs such as paclitaxel (PTX) and doxorubicin (DOX) are often loaded into hydrogels for the treatment of various tumors.<sup>166–169</sup> Song *et al.* developed thermo-responsive supramolecular hydrogels using two host-guest interactions to achieve sustained delivery of anticancer drugs, including DOX (Fig. 7A).<sup>170</sup> Specifically, the researchers assembled thermo-responsive pseudo-block copolymers ( $\beta$ CD-(PNIPAAm)<sub>4</sub>/Ad-PEG) through host-guest recognition between  $\beta$ CD-core PNIPAAm 4-armed star polymers and Ad-modified PEG. These copolymers formed supramolecular micelles when the temperature exceeded the LCST. The bis-supramolecular hydrogels were then created by aggregating the PPR structure formed between PEG and  $\alpha$ -CD. The resulting bis-supramolecular hydrogels exhibited significantly improved mechanical properties and enhanced slow-release properties of DOX compared to the single PPR supramolecular hydrogel at temperatures up to 37 °C. Moreover, the hydrogel demonstrated superior antitumor effects in multi-drug resistant cancer cells.

Compared to the treatment of a single chemotherapy drug, combination therapy with multiple chemotherapeutic drugs is considered a more effective anti-tumor strategy. The combination of hydroxycamptothecin (HCPT) and betulinic acid (BA) has been speculated to enhance tumor inhibition. Therefore, Dai *et al.* utilized the amphiphilic precursor 8 arm-PEG-BA to self-assemble with hydrophobic HCPT, forming drug-loaded micelles and achieving simultaneous and efficient loading of the two drugs.<sup>171</sup> The temperature-sensitive hydrogel was then formed through the package interaction between  $\alpha$ -CD and PEG in the micelles. The hydrogel could be injected intratumorally for local delivery and temperature-sensitive controlled release



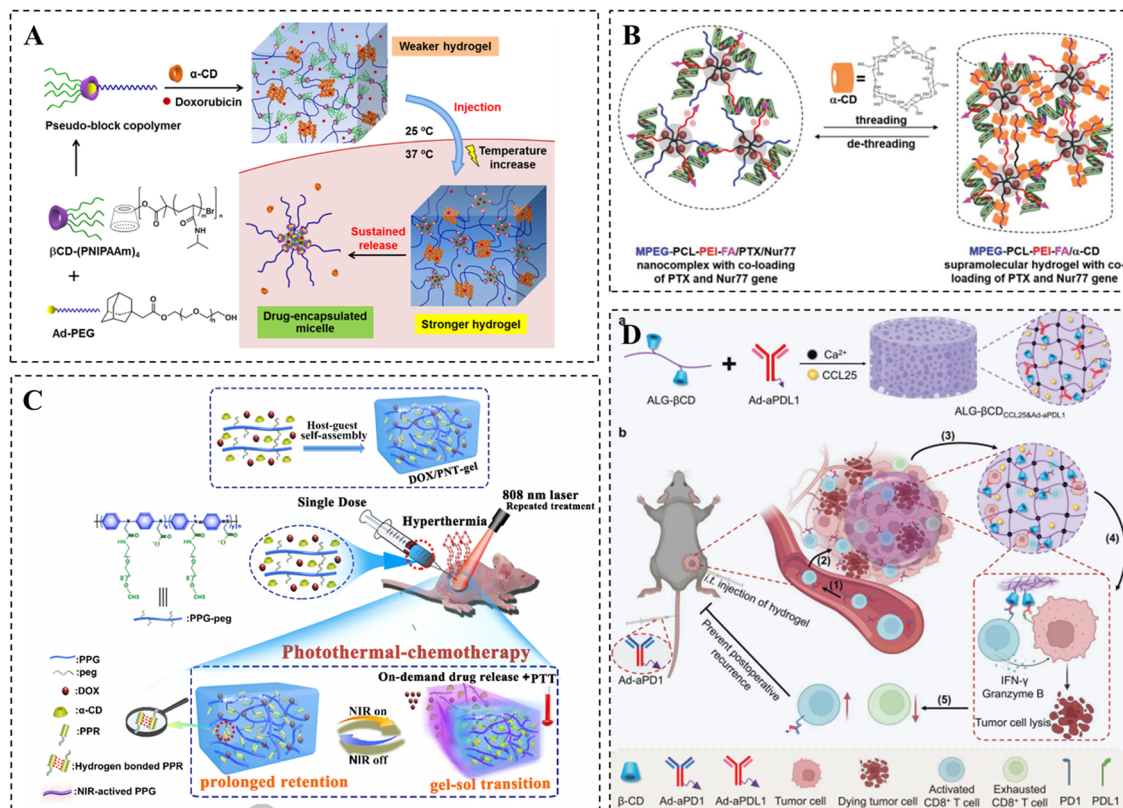


Fig. 7 CD-based supramolecular hydrogels for tumor therapy. (A) Schematic diagram of DOX-loaded PPR supramolecular hydrogels for tumor therapy and its thermo-responsive drug release. Reproduced with permission from ref. 170. Copyright 2020, American Chemical Society. (B) Schematic representation of PTX and Nur77 co-loaded PPR hydrogels for tumor therapy. Reproduced with permission from ref. 175. Copyright 2019, Wiley. (C) Schematic representation of the DOX/PNT-gel for photothermal-chemotherapy treatment. Reproduced with permission from ref. 178. Copyright 2019, Elsevier. (D) Schematic representation of the ALG-βCD hydrogels for tumor therapy. Reproduced with permission from ref. 180. Copyright 2023, Wiley.

of BA and HCPT, exhibiting more favorable anti-tumor effects compared to monotherapy.

In addition to delivering chemotherapeutic drugs, CD-based supramolecular hydrogels can also serve as an attractive bio-material for the delivery of antitumor gene drugs.<sup>172</sup> Gene drugs can form complexes with PEG-modified cationic polymers or polycations, as they have a negative charge. Consequently, CD-based PPR hydrogels can be prepared *via* the host-guest interaction between these complexes and α-CD.<sup>173</sup> These CD-based PPR hydrogels can act as local gene reservoirs, ensuring the sustained availability of DNA vectors in specific locations over a long period, thus demonstrating their potential as a platform for gene drug delivery. Liu *et al.* utilized MPEG-PCL-PEI triblock copolymers to bind the Bcl-2 converted Nur77 gene, resulting in the formation of MPEG-PCL-PEI/Nur77 complex micelles through hydrophobic interaction.<sup>174</sup> Subsequently, a PPR hydrogel was obtained through mixing complex micelles with α-CD. This hydrogel could be formed *in situ* at the tumor site and exhibited a desirable slow-release effect on pDNA (Nur77) for up to 7 days. Notably, it demonstrated significant inhibitory effects on drug-resistant tumors with high expression of Bcl-2.

To achieve the synergistic delivery of chemotherapeutic drugs and gene drugs, as well as more precise drug therapy,

the research group made further modifications to the MPEG-PCL-PEI triblock copolymers. They incorporated a folic acid targeting moiety and mixed it with α-CD to create a supramolecular hydrogel. This hydrogel allowed for the co-loading of the chemotherapeutic drug PTX and Nur77 gene (Fig. 7B).<sup>175</sup> After injecting the hydrogel near the tumor, the MPEG-PCL-PEI-FA/PTX/Nur77 complex was released and targeted the tumor cells with high FR expression. The hydrogel degraded and gradually released PTX and Nur77 genes. Compared to the untargeted hydrogel, the targeted hydrogel showed significantly enhanced inhibition of drug-resistant tumors.

In addition, the synergistic effects of photothermal therapy and chemotherapy have been shown to enhance anti-tumor effects.<sup>176,177</sup> Shen *et al.* prepared NIR-responsive injectable hydrogels *via* supramolecular assembly between α-CD and PEG using PEG-modified poly-*N*-phenylglycine (PPG) as a photothermal backbone (Fig. 7C). The PPG backbone endowed the hydrogel with photothermal conversion capabilities, which can induce gel-sol conversion by absorbing external NIR light (808 nm) and converting it into heat, thus realizing the precise release of DOX on demand.<sup>178</sup> It was indicated that this hydrogel achieved almost complete eradication of 4T1 breast cancer by synergizing photothermal therapy and chemotherapy, making it an attractive and multifunctional tumor therapeutic platform.

Immunotherapy has emerged as a novel and effective anti-tumor therapy in recent years, which can enhance the recognition and killing of tumor cells by modulating the immune system.<sup>179</sup> Zhu *et al.* presented an alginate hydrogel for the multifaceted promotion of the recruitment, engagement, and rejuvenation of T cells (Fig. 7D).<sup>180</sup> It was demonstrated that following the recruitment of CCR9<sup>+</sup>CD8<sup>+</sup> T cells by the chemokine CCL25 released from the hydrogel, the engagement of CD8<sup>+</sup> T cells with tumor cells was further facilitated by the anti-PDL1 antibody and anti-PD1 antibody immobilized in the hydrogel *via* CD/Ad host-guest interactions. Meanwhile, CD8<sup>+</sup> T cells were rejuvenated to avoid depletion, ultimately achieving enhanced T cell-mediated immunotherapy efficacy. Overall, CD-based supramolecular hydrogels show broad application prospects in tumor therapy, and more of their applications in tumor therapy are summarized in Table 1.

## 5.2 Bone/cartilage repair

Throughout the regeneration of bone and cartilage, the extracellular matrix (ECM) is known to be critical in facilitating signal and material exchange. CD-based supramolecular hydrogels exhibit similarities to the natural ECM and can create a suitable microenvironment for cell and tissue repair.<sup>184,185</sup> Moreover, these hydrogels possess shear-thinning properties, enabling them to be administered through minimally invasive injections, thereby replacing traditional implantation procedures.<sup>105</sup> Furthermore, their malleability allows them to be molded into various shapes to accommodate irregular bone defect sites.<sup>186</sup>

To enhance the regeneration of bone and cartilage defects, various approaches have been explored, involving the integration of growth factors, metal ions, and nanomaterials into hydrogels. These additives serve to improve the osteogenic activity of the hydrogels. For example, metal ions such as Ca<sup>2+</sup>, Mg<sup>2+</sup>, Zn<sup>2+</sup>, Cu<sup>2+</sup>, and Sr<sup>2+</sup> have been found to possess

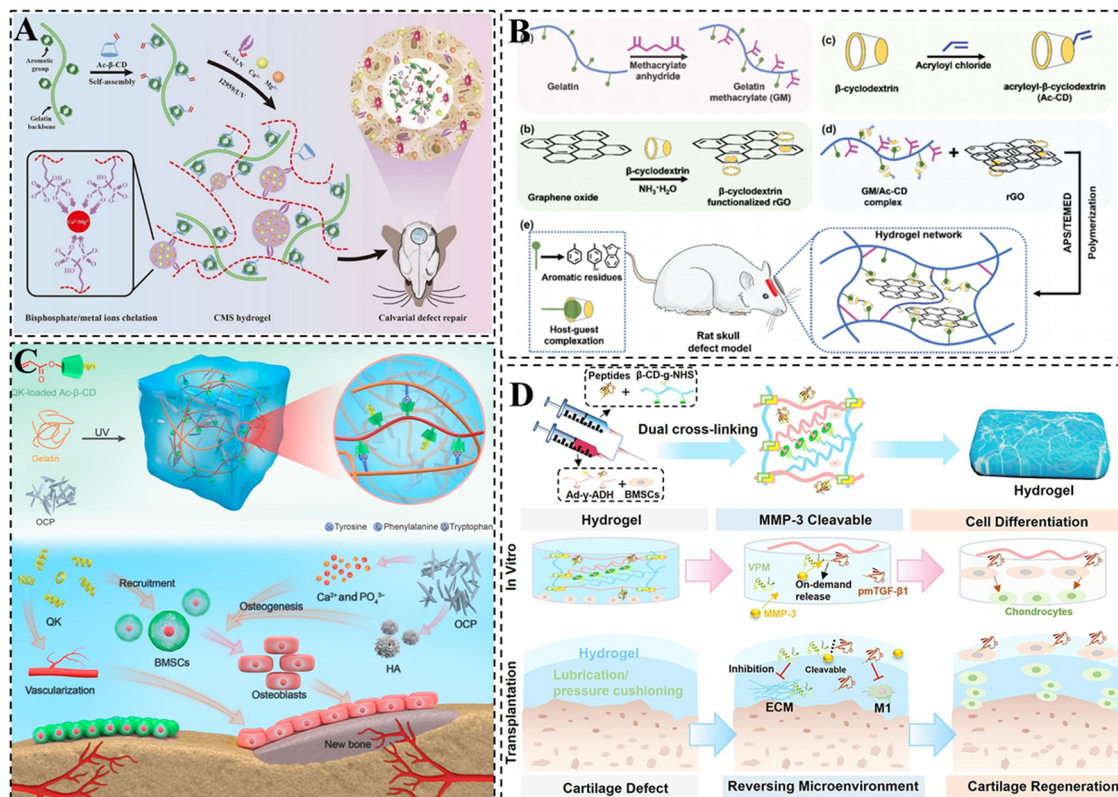
favorable pro-angiogenic and osteogenic properties.<sup>187,188</sup> Yu *et al.* developed supramolecular hydrogels for bone repair with the use of host-guest interactions between gelatin aromatic residues and CDs (Fig. 8A).<sup>189</sup> Meanwhile, the hydrogel was reinforced with the strong coordination between alendronate (ALN) and Ca<sup>2+</sup>/Mg<sup>2+</sup> to enhance its osteogenic activity and mechanical properties. The study demonstrated that the presence of ALN and Ca<sup>2+</sup>/Mg<sup>2+</sup> significantly facilitated osteogenic differentiation of stem cells and bone regeneration within the hydrogel, thus establishing it as an ideal platform for bone repair.

In addition, previous studies have demonstrated that the incorporation of conductive materials can effectively enhance the bone repair capabilities of hydrogels.<sup>190</sup> Among these materials, reduced graphene oxide (rGO) stands out as an ideal choice due to its ability to not only promote the osteogenic differentiation of MSCs but also contribute to a significant improvement in the mechanical properties of hydrogels.<sup>191,192</sup> Taking this into account, Li *et al.* developed a multifunctional hydrogel scaffold that combines good mechanical, photothermal, conductive, and low swelling properties by incorporating CDs, rGO, and gelatin. The formation of the hydrogel primarily relied on double-bond polymerization and host-guest cross-linking between CDs and gelatin (Fig. 8B).<sup>193</sup> It is noteworthy that the non-covalent supramolecular interactions within the hydrogel were found to enhance its toughness, while the presence of rigid rGO conferred improved mechanical, electrical conductivity, and photothermal antimicrobial properties to the hydrogel. The efficacy of the multifunctional hydrogel in promoting the proliferation and differentiation of MC3T3-E1 cells was further confirmed, thus facilitating the repair of skull defects.

Octacalcium phosphate (OCP) exhibits enhanced osteoinduction as a precursor of hydroxyapatite (HA). It is capable of converting to HA and releasing Ca<sup>2+</sup> at physiological pH, which

**Table 1** Cyclodextrin-based supramolecular hydrogels for tumor therapy

Hydrogel components	Drugs delivered	Therapeutic strategies	Tumor types	Ref
βCD-PNIPAAm/Ad-PEG/α-CD	DOX	Sustained controlled release of DOX to overcome multidrug resistance (MDR) in tumor cells	AT3B-1 cells	170
DAS@SCD/NIPAZO	PTX	UV-responsive PTX delivery	Melanoma therapy	69
HPG-PCL-MPEG/α-CD	CPT/DOX	Combination therapy with multiple chemotherapy drugs	HNE-1 tumor	181
8 arm-PEG-BA/α-CD	BA/HCTP	Combination therapy with multiple chemotherapy drugs	LLC tumor	171
MPEG-PLLD-Arg/α-CD	pMMP-9	Gene therapy	HNE-1 tumor	114
MPEG-PCL-PEI/α-CD	Bcl-2 conversion Nur77 gene	Gene therapy	Hepatocarcinoma	174
MPEG-PCL-PEI-FA/α-CD	PTX/Nur77	Combination therapy with chemotherapy drugs and therapeutic genes	Hepatocarcinoma	175
4-PEG/α-CD	G4/Adv	Viral immunotherapy	Murine melanoma	182
PNPG-PEG/α-CD	CDDP	NIR-triggered cisplatin delivery and combined chemo-photothermal therapy	Triple-negative breast cancer	183
PPG-peg/α-CD	DOX	NIR-triggered DOX delivery and combined chemo-photothermal therapy	4T1 breast cancer	178
PNPG-PEG/PTD micelles/PEG/PEI@Fe <sub>3</sub> O <sub>4</sub> NPs/α-CD	DOX	ROS-responsive DOX release and synergistic chemo-photothermal therapy	4T1 breast cancer	130
ALG-βCD/Ad-aPDL1/Ca <sup>2+</sup>	aPDL1/CCL25	T cell-mediated immunotherapy	B16-F10 tumor	180
OSA-βCD/Ca <sup>2+</sup>	WA-cRGD/(aPD-L1)	Ferroptosis-immunotherapy	B16-F10 tumors	179



**Fig. 8** CD-based supramolecular hydrogels for bone/cartilage repair. (A) Schematic representation of CMS supramolecular hydrogel with dual physical cross-linking for cranial bone restoration. Reproduced with permission from ref. 189. Copyright 2023, Elsevier. (B) Schematic illustration of the GM/Ac-CD/rGO hydrogel for cranial bone repair. Reproduced with permission from ref. 193. Copyright 2022, Royal Society of Chemistry. (C) Schematic representation of dual network supramolecular hydrogel loaded with OCP and QK and its mechanism of building angiogenic and osteogenic microenvironments for bone repair. Reproduced with permission from ref. 197. Copyright 2023, American Association for the Advancement of Science. (D) Schematic representation of peptide-based supramolecular hydrogel encapsulated with BMSCs and MMP-3 cleavable VPM-pmTGF- $\beta$ 1 integrative peptide. Reproduced with permission from ref. 206. Copyright 2023, Elsevier.

promotes the osteogenic differentiation of stem cells.<sup>194–196</sup> Therefore, Li *et al.* prepared an injectable hydrogel for bone repair through the double-bond polymerization of Ac- $\beta$ -CD and the host-guest interaction between CD and aromatic groups (Fig. 8C).<sup>197</sup> OCP (an HA precursor that releases  $\text{Ca}^{2+}$ ) and QK (a VEGF-mimetic peptide) were simultaneously added into the hydrogel to further enhance its osteoconductive properties, angiogenic capacity and mechanical properties. It was demonstrated that the integration of QK and OCP into the dual-network hydrogel could synergistically contribute to the regeneration of skull bone defects *via* the construction of angiogenic and osteogenic microenvironments, indicating promising application prospects in the field of bone repair.

Due to the fact that there are no blood vessels, lymphatic or nervous systems, stem cells face difficulties migrating to the cartilage injury site, resulting in limited self-repair of damaged cartilage tissue.<sup>198–200</sup> It is generally accepted that the delivery of stem cells is of crucial importance in the regeneration of cartilage tissue.<sup>201</sup> The use of CD-based supramolecular hydrogels offers multiple properties that can potentially enable highly active delivery of stem cells.<sup>202–204</sup> Furthermore, CDs can form complexes with the aromatic residues of natural collagen or hydrophobic drug molecules *via* host-guest

interaction, which enhances the tissue adhesion of the hydrogel, as well as the loading efficiency of hydrophobic drugs. Xu *et al.* formed a supramolecular gelatin hydrogel using  $\beta$ -CDs. The excess  $\beta$ -CD cavities in the hydrogel facilitated the effective loading and slow release of the hydrophobic small molecule drug kartogenin (KGN).<sup>205</sup> Additionally, the hydrogel was able to directly encapsulate hydrophilic protein growth factor (TGF- $\beta$ 1) and BMSCs. In a knee cartilage defect model, it was demonstrated that the hydrogel exhibited a significant contribution to cartilage regeneration. In addition, our group prepared a peptide-based hydrogel with both favorable self-healing and mechanical properties by integrating  $\beta$ -CD/Ad host-guest interactions, hydrogen bonding as well as amide bonding (Fig. 8D). The hydrogel effectively inhibited cartilage inflammation and promoted BMSC differentiation with the delivery of BMSC and MMP-3 cleavable VPM-pmTGF- $\beta$ 1 integrative peptide, achieving efficient restoration of damaged cartilage tissue.<sup>206</sup>

To achieve the simultaneous repair of cartilage and subchondral bone, an injectable, *in situ*-forming biphasic hydrogel was developed by Liu *et al.* This was accomplished by covalently photo-crosslinking double-bond-modified CDs with hyaluronic acid methacrylate (HAMA) and gelatin methacryloyl (GelMA),



Table 2 Cyclodextrin-based supramolecular hydrogels for bone/cartilage repair

Hydrogel components	Osteogenic/chondrogenic active ingredients	Therapeutic strategies	Animal models	Ref.
PAMAM-Ad/ $\beta$ -CD-g-PNIPAM/ChS-F/PEG-AMI	ChS	Mechanical properties of hydrogels under dynamic conditions can mimic dynamic bone tissue and ChS can confer hydrogel bone repair capabilities	Rat right limb bone defect model	208
Gelatin/Ac- $\beta$ -CD	Icaritin/MSCs	Icariin promotes endogenous cell recruitment and infiltration, as well as osteogenic differentiation of MSCs, thereby accelerating the bone regeneration.	Steroid-associated osteonecrosis	209
GelMA/Ac- $\beta$ -CD	Kartogenin/TGF- $\beta$ 1/hBMSCs	Continuous release of KGN and TGF- $\beta$ 1 promotes chondrogenic differentiation of hBMSC for cartilage regeneration.	Osteochondral defects in rat knee joints	205
HA-CD/HA-Ad	MSCs	Spatio-temporal controlled delivery of MSC for cartilage regeneration.	Rat osteochondral defect model	204
HAMA/GelMA/ $\beta$ -CD-AOI <sub>2</sub>	Melatonin/Kartogenin/MSCs	The release of KGN and MLT induces chondrogenic and osteogenic differentiation for simultaneous repair of cartilage and subchondral bone.	Rabbit osteochondral interface defect model	207
SF-CD/SF-Chol/HA	Hydroxyapatite	The introduction of HA promotes the differentiation of stem cells to osteoblasts.	Rat femoral defect model	82
GM/Ac-CD/rGO	rGO	The rigid rGO endowed the hydrogel with enhanced mechanical, electrical conductivity, and photothermal antimicrobial properties, which effectively promoted the repair of skull defects.	Rat skull defect model	193
Gelatin/Ac- $\beta$ -CD/Ac-ALN/Ca <sup>2+</sup> /Mg <sup>2+</sup>	ALN/Ca <sup>2+</sup> /Mg <sup>2+</sup>	The addition of ALN with metal ions such as Ca <sup>2+</sup> /Mg <sup>2+</sup> significantly improves bone regeneration because of the excellent osteogenic activity.	Rat skull defect model	189
Gelatin/Ac- $\beta$ -CD	Octacalcium phosphate (HA precursor)/QK (VEGF-mimicking peptide)	The introduction of OCP and QK improves the mechanical properties, osteoconductive properties, and angiogenic capacity of hydrogels, which can synergistically promote the repair and regeneration of cranial bone defects by constructing angiogenic and osteogenic microenvironments	Rat skull defect model	197

respectively.<sup>207</sup> To promote chondrogenic and osteogenic differentiation, the drugs KGN and melatonin (MLT) were separately encapsulated into the CD cavities within the hydrogel through host-guest interactions. The slow release of KGN and MLT from the cartilage and subchondral bone layers induced chondrogenic and osteogenic differentiation, ultimately realizing the simultaneous regeneration of both cartilage and subchondral bone. Table 2 provides a thorough summarization of the recent applications of CD-based supramolecular hydrogels in bone and cartilage repair.

### 5.3 Myocardial repair

Myocardial infarction (MI) is a prevalent cardiovascular disease characterized by impaired vascularization and the loss of cardiomyocytes, ultimately leading to ventricular remodeling or sudden death.<sup>210</sup> The use of biomaterials for sustainable delivery of bioactive agents or stem cells to damaged tissues is an effective approach to treating MI, as it reduces side effects and improves therapeutic efficacy.<sup>211–213</sup> CD-based supramolecular hydrogels show promise as prospective platforms for drug or stem cell delivery because of their injectability and favorable biocompatibility.<sup>214</sup> While erythropoietin (EPO) has been found to have anti-apoptotic and angiogenic effects in the treatment of MI, it can also lead to adverse effects such as erythrocytosis.<sup>215</sup> To minimize these adverse effects, Wang *et al.* incorporated linear MPEG-PCL-MPEG polymers into  $\alpha$ -CD cavities and formed a supramolecular hydrogel through hydrogen bonding between the  $\alpha$ -CDs for the sustained delivery of EPO to the myocardial site.<sup>216</sup> The study demonstrated that

this supramolecular hydrogel enhanced the therapeutic efficacy of EPO and improved cardiac function without causing erythrocytosis. Similarly, Wang *et al.* encapsulated BMSCs into  $\alpha$ -CD/MPEG-PCL-MPEG hydrogels for the treatment of MI.<sup>217</sup> It was shown that the supramolecular hydrogel loaded with BMSCs increased the left ventricular ejection function and attenuated left ventricular dilatation.

In addition, previous studies have demonstrated that extracellular vesicles (EVs) derived from endothelial progenitor cells (EPC) play a beneficial role in cardiac repair.<sup>218</sup> Chen *et al.* conducted a study in which EPC-derived EVs were loaded into a hyaluronic acid hydrogel formed by  $\beta$ -CD/Ad supramolecular interactions.<sup>219</sup> This study showed that intramyocardial delivery of EPC-derived EVs through shear-thinning hydrogels not only improved angiogenesis and hemodynamic function at the site of MI, but also maintained the ventricular geometry intact, thereby facilitating myocardial repair.

Gene drugs have emerged as a highly promising therapeutic approach for MI in recent years.<sup>220</sup> To enhance the efficacy of gene drugs, supramolecular hydrogels have already been employed for the local and continuous release of gene drugs. For instance, Burdick *et al.* designed a self-healing hyaluronic acid hydrogel using CD/Ad host-guest interactions (Fig. 9A).<sup>221</sup> Chol-modified miR-302 was embedded into the hydrogel *via* host-guest recognition. The results demonstrated that the sustained delivery of miR-302 in hydrogels effectively promoted the proliferation and regeneration of cardiomyocytes after MI. Another study by the same research group designed a dynamic acylhydrazone-bonded cross-linked hydrogel for local delivery

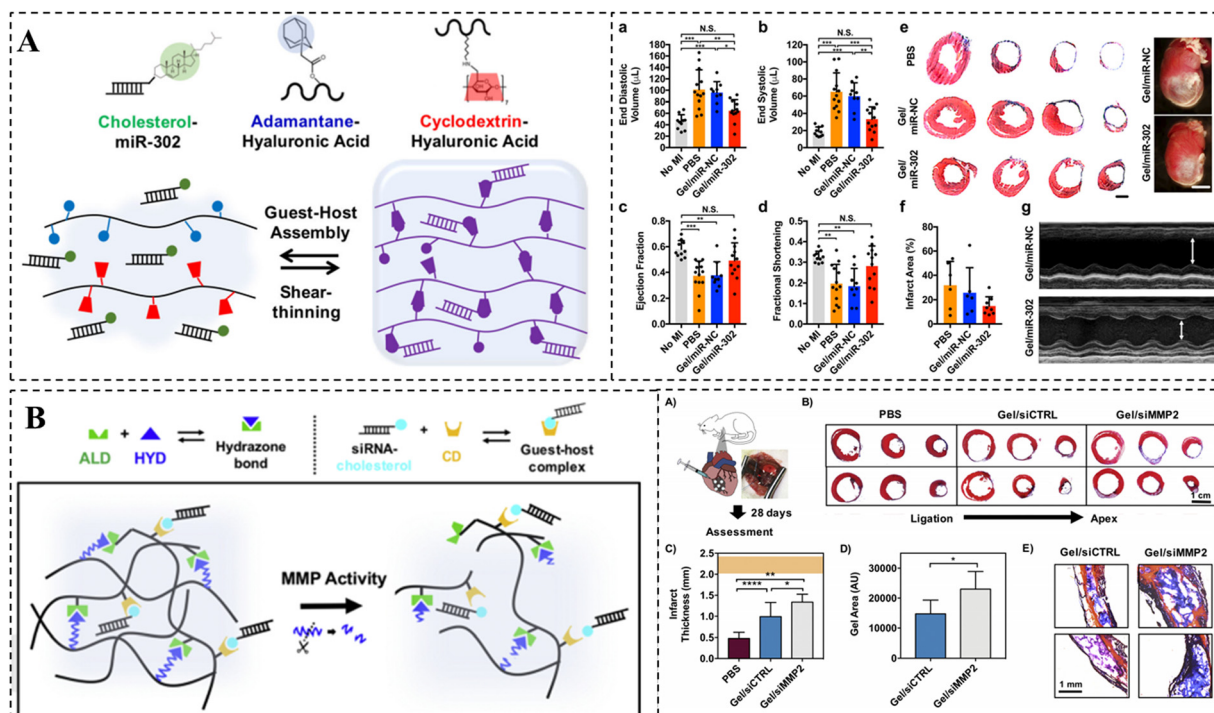


Fig. 9 CD-based supramolecular hydrogels for myocardial repair. (A) Schematic representation of the CD/Ad supramolecular hydrogel and its *in vivo* therapeutic effect. miR-302-chol was loaded into the hydrogel via CD/Chol host-guest interactions. Reproduced with permission from ref. 221. Copyright 2017, Springer Nature. (B) Schematic illustration of a protease-degradable, injectable hydrogel for delivery of siRNA to the heart site and its *in vivo* therapeutic effect. Reproduced with permission from ref. 222. Copyright 2018, Elsevier.

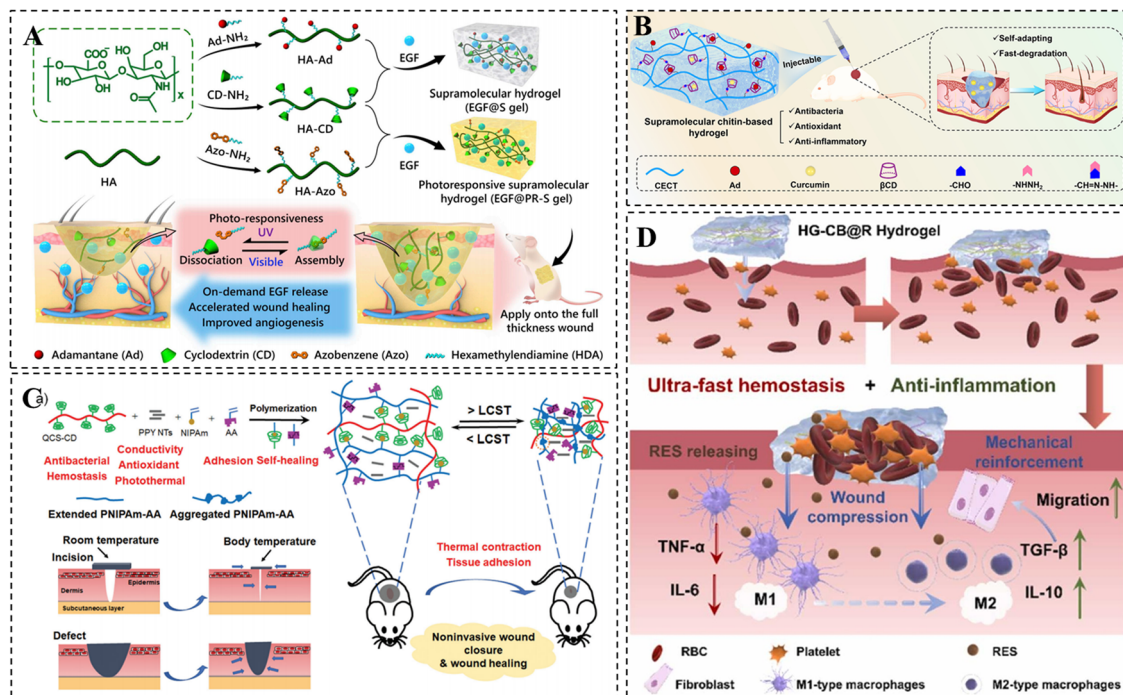
of siMMP2 (Fig. 9B).<sup>222</sup> In this case, CDs were modified on HA to form complexes with chol-modified siRNAs, thereby restricting the passive diffusion of siRNAs within the hydrogels. Moreover, MMP-responsive peptide was also integrated into the crosslinks, enabling the hydrogels to erode and release siMMP2 in response to MMP2. The findings demonstrated that siMMP2 could slow down hydrogel erosion by silencing MMP2 expression, thereby reducing infarct enlargement and remodeling, and improving myocardial function.

#### 5.4 Wound repair

CD-based supramolecular hydrogels have garnered significant attention in the field of wound dressings and have demonstrated considerable application value in recent years.<sup>223</sup> In comparison to traditional hydrogels, CD-based supramolecular hydrogels offer distinct advantages in the field of wound repair due to their injectability, shape adaptability, and favorable self-healing ability.<sup>224</sup> The utilization of anti-inflammatory drugs or bioactive molecules, such as epidermal growth factors (EGF) at the wound site has emerged as an effective therapeutic approach to accelerate wound healing.<sup>225–227</sup> CD-based supramolecular hydrogels can serve as drug reservoirs for the continuous delivery of drugs or bioactive molecules, resulting in the acceleration of the wound healing process.<sup>228</sup> Zhao *et al.* constructed a light-responsive hyaluronic acid hydrogel by harnessing the photoisomerization property of Azo (Fig. 10A).<sup>229</sup> The study demonstrated that the CD/Azo host-guest cross-links in the hydrogel were disrupted under the

irradiation of UV light, resulting in the rapid release of EGF at the wound site and consequently facilitating wound healing. Similarly, a curcumin-loaded chitin supramolecular hydrogel was prepared by Shi *et al.* via  $\beta$ -CD/Ad host-guest interactions as well as dynamic Schiff base bonding (Fig. 10B).<sup>230</sup> Curcumin, a hydrophobic drug with antioxidant and anti-inflammatory activities, was loaded into the excess CD cavity in the hydrogel. The study indicated that the curcumin-loaded hydrogel effectively promoted wound healing with favorable drug release kinetics.

In addition to delivering anti-inflammatory drugs for their anti-inflammatory effects, ideal hydrogel dressings are expected to possess antimicrobial, angiogenic, and conductive properties to prevent wound infections and accelerate wound healing.<sup>231,232</sup> Currently, hydrogel platforms that integrate multiple functions are becoming popular in the field of wound healing.<sup>233</sup> Yu *et al.* developed an injectable thermosensitive hydrogel by utilizing the host-guest complexation of *N*-isopropylacrylamide (NIPAM) with CD and hydrogen bonding between adenine (Fig. 10C).<sup>234</sup> This hydrogel was endowed with various bioactivities such as photo-thermal antimicrobial, electrical conductivity, antioxidant, and hemostatic properties through the incorporation of CD-grafted quaternized chitosan and polypyrrole nanotubes. These properties effectively reduced inflammation and promoted skin repair. Moreover, the presence of adenine facilitated excellent tissue adhesion, while the thermal contraction behavior provided by PNIPAM allowed for rapid contraction of the wound defect site, enabling



**Fig. 10** CD-based supramolecular hydrogels for wound repair. (A) Schematic diagram of UV-responsive hyaluronic acid supramolecular hydrogels loaded with EGF for skin repair. Reproduced with permission from ref. 229. Copyright 2020, Elsevier. (B) Schematic representation of curcumin-loaded chitin-based hydrogels for wound healing. Reproduced with permission from ref. 230. Copyright 2023, Elsevier. (C) Schematic illustration of PNIPAm-AA/QCS-CD/PPY hydrogel for non-invasive mouth closure and wound healing. Reproduced with permission from ref. 234. Copyright 2022, Wiley. (D) Schematic representation of HG-CB@R hydrogels for therapeutic rapid hemostasis and wound healing. Reproduced with permission from ref. 235. Copyright 2023, Elsevier.

non-invasive wound closure. The hydrogel shows great promise for the non-invasive closure of large open wounds and enhanced wound healing. A resveratrol-loaded HG-CB@R hydrogel for therapeutic rapid hemostasis was prepared by Tan *et al.* using host-guest interactions and double-bond radical polymerization (Fig. 10D). It was shown that blood coagulation could be accelerated by rapid absorption of water from the wound site. In addition, the cross-linking density of the hydrogel can be further increased *via* the coordination of bisphosphonate groups with  $\text{Fe}^{3+}$  in the blood, improving its mechanical properties and avoiding secondary bleeding from hydrogel rupture.<sup>235</sup>

## 6. Summary and outlook

In this review, we present a comprehensive summary of the preparation of CD-based supramolecular hydrogels and the optimization strategy for enhancing their mechanical properties. Additionally, we provide a detailed description of the different methods for loading drugs into CD-based supramolecular hydrogels and their responsive drug release modes, highlighting their applications as stimuli-responsive drug carriers in various biomedical fields including oncology therapeutics, bone/cartilage repair, myocardial repair, and skin repair. CD-based supramolecular hydrogels exhibit intriguing features like self-healing, injectability, shear-thinning, and stimulus

responsiveness, which contribute to their practicality and intelligence. It is evident that with the continuous optimization of the mechanical properties, loading methods, and the introduction of stimuli-responsive units, CD-based supramolecular hydrogels have vast potential and will find broader applications in the future. Although numerous functions of CD-based supramolecular hydrogels have been validated in laboratory settings, and positive results have been obtained in animal models for various biological applications, theoretical studies of these hydrogels are still in their early stages, and there remain significant clinical requirements that have not been addressed. Consequently, the translation of CD-based supramolecular hydrogels from laboratory research to clinical medicine poses a substantial challenge.

To further advance the biomedical application of CD-based supramolecular hydrogels and expedite their clinical transformation, it is imperative to enhance research in the following areas: (i) Strengthening research on the encapsulation performance of different CD hosts and guests is necessary. This will help elucidate the various factors that affect encapsulation efficiency and gradually develop theories to provide theoretical guidance for the fabrication of CD-based hydrogels. Additionally, the advantages of CDs in the long-term controlled release of drug molecules should be fully utilized, combined with stimuli-responsive building units, and extended to the application of these materials in biomedicine or tissue engineering. (ii) Further research should be conducted on CD-based



supramolecular hydrogels with superior mechanical properties to enhance their applicability in tissue engineering, particularly in bone repair, where mechanical support is crucial. Moreover, efforts should be made to improve the functionalization and intelligence of CD-based supramolecular hydrogels, enabling them with a wider variety of characteristics like electrical conductivity, multi-stimulus responsiveness, and antimicrobial properties, thereby moving them towards true functional diversification. (iii) In the early stages of designing CD-based supramolecular hydrogels, it is crucial to fully consider the biodegradability and biocompatibility of the hydrogels. Additionally, efforts should be made to minimize the foreign body reaction (FBR) of the hydrogels *in vivo* in order to ensure their *in vivo* safety and enhance their potential for clinical translation. (iv) To facilitate clinical translation, research systems should steer clear of overly complex designs and prioritize the safety and feasibility of the materials used. It is also of importance to take the reproducibility and stability of experimental results into consideration, as well as the suitability of the hydrogels for scaled-up industrial production in the early stages of development. Although numerous investigations focus on the design of CD-based supramolecular hydrogels and their initial application to specific diseases, clinical translation remains a distant goal. However, it is worth trusting that CD-based supramolecular hydrogels hold promise for future multifunctionality, intelligence, and disease-specific adaptability. These hydrogels have the potential to integrate diagnostics, treatment, and detection, thereby improving patient compliance, meeting growing clinical needs, and ultimately achieving clinical translation.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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