

## REVIEW

# Recent advances in polysaccharide-based hydrogels for synthesis and applications

Zili Li | Zhiquan Lin 

School of Materials Science and Engineering,  
Georgia Institute of Technology, Atlanta, Georgia,  
USA

**Correspondence**

Zhiquan Lin, School of Materials Science and  
Engineering, Georgia Institute of Technology,  
Atlanta, GA 30332, USA.  
Email: [zhiquan.lin@mse.gatech.edu](mailto:zhiquan.lin@mse.gatech.edu)

**Abstract**

Hydrogels are three-dimensional (3D) crosslinked hydrophilic polymer networks that have garnered tremendous interests in many fields, including water treatment, energy storage, and regenerative medicine. However, conventional synthetic polymer hydrogels have poor biocompatibility. In this context, polysaccharides, a class of renewable natural materials with biocompatible and biodegradable properties, have been utilized as building blocks to yield polysaccharide-based hydrogels through physical and/or chemical crosslinking of polysaccharides via a variety of monomers or ions. These polysaccharide-derived hydrogels exhibit peculiar physicochemical properties and excellent mechanical properties due to their unique structures and abundant functional groups. This review focuses on recent advances in synthesis and applications of polysaccharide-based hydrogels by capitalizing on a set of biocompatible and biodegradable polysaccharides (i.e., cellulose, alginate, chitosan, and cyclodextrins [CDs]). First, we introduce the design and synthesis principles for crafting polysaccharide-based hydrogels. Second, polysaccharide-based hydrogels that are interconnected via various crosslinking strategies (e.g., physical crosslinking, chemical crosslinking, and double networking) are summarized. In particular, the introduction of noncovalent and/or dynamic covalent interactions imparts polysaccharide-based hydrogels with a myriad of intriguing performances (e.g., stimuli–response and self-recovery). Third, the diverse applications of polysaccharide-based hydrogels in self-healing, sensory, supercapacitor, battery, drug delivery, wound healing, tissues engineering, and bioimaging fields are discussed. Finally, the perspectives of polysaccharide-based hydrogels that promote their future design to enable new functions and applications are outlined.

**KEYWORDS**

applications, double-network, dynamic covalent interactions, noncovalent interactions, polysaccharide-based hydrogels

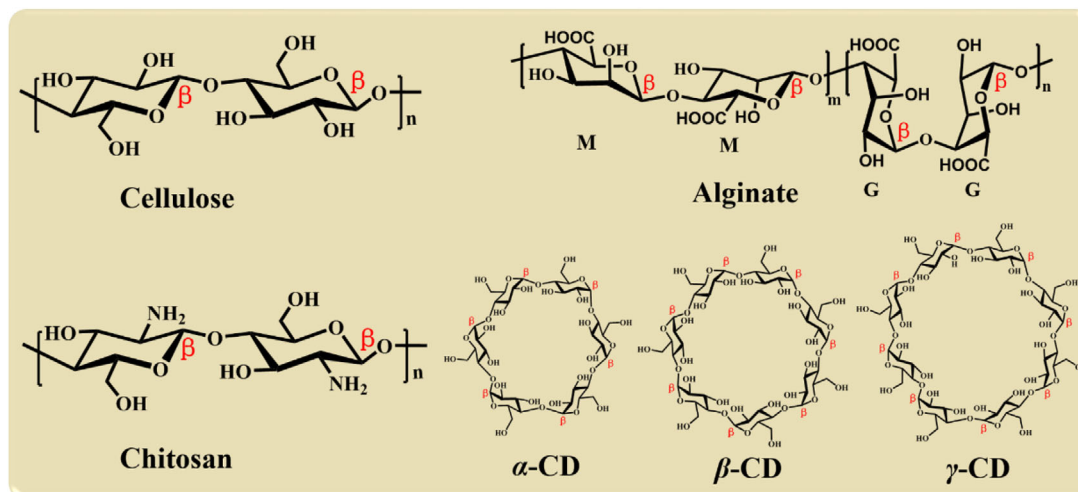
## INTRODUCTION

Hydrogels represent a class of materials that are composed of crosslinked hydrophilic polymer networks filtered with solvents (e.g., water, organic solvent/water mixture). They find a broad spectrum of applications in biomedical,<sup>[1]</sup> self-healing,<sup>[2]</sup> sensory,<sup>[3]</sup> energy, and water sustainability fields.<sup>[4]</sup> These hydrophilic polymer networks can be produced via in situ physical and/or chemical crosslinking. Generally, chemical crosslinking can be achieved using redox-, thermal-, photo-, or radiation-initiated free radical polymerization. On the other hand, noncovalent interactions (e.g., hydrogen bonding, metal coordination, hydrophobic

interaction, and host–guest interaction) have also been widely employed to construct physical networks, thereby imparting hydrogels with attractive self-healing properties.<sup>[5]</sup> This intriguing characteristic can be used to distinguish the hydrogels formed via covalent or noncovalent crosslinking. Due to the low binding strength of single polymer chains, and weak noncovalent interactions, hydrogels usually display poor tensile strength. Many strategies, such as double-network,<sup>[6]</sup> topological structure,<sup>[7]</sup> multi-interaction,<sup>[8]</sup> and nanocomposite<sup>[9]</sup> have been implemented to improve mechanical properties. However, most synthetic polymer hydrogels cannot concurrently render biocompatibility and high strength in emerging biological materials.

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**FIGURE 1** Chemical structures of cellulose, alginate (partial chemical structure containing G and M repeating unit sequences is selected for clarity of illustration), chitosan, and CDs

Significant progresses have been achieved in engineering hydrogels using natural biomass resource materials. Recently, with the development of biological applications of flexible materials and environmental concerns, biological hydrogels created using natural resources (e.g., cellulose, alginate, chitosan, and cyclodextrins [CDs]; Figure 1) have been extensively exploited as alternative renewable materials to alleviate the increasing global energy crisis.<sup>[10–13]</sup> These materials can be classified as polysaccharide biomass resources consisting of monosaccharides repeating units.<sup>[14,15]</sup> They play a crucial role in supplying energy for living organisms and can be readily found in plants, animals, or microbial worlds. Polysaccharides possess a set of compelling attributes, including abundance, cost saving, biocompatibility, nontoxicity, and regeneration, compared to synthetic polymer counterparts. In addition, ample hydroxyl groups (-OH), carboxyl acid (-COOH), or amine (-NH<sub>2</sub>) are covalently anchored on the periphery of the glucose unit, thereby providing a versatile platform for functionalization and postmodification.

As described above, polysaccharides have intrinsic functional moieties, thus polysaccharide-based hydrogels have been engineered by employing various physical noncovalent or chemical covalent crosslinking strategies. Nonetheless, it remains challenging to dissolve cellulose and chitosan to prepare hydrogels in an aqueous solution due to the tremendous amount of inter- and intra-chain hydrogen bonding.<sup>[15]</sup> To overcome this issue, some solvents such as aqueous base/urea systems have been developed to dissolve cellulose and chitosan via the cyclic freezing–thawing process and form gelation through regeneration from hot water.<sup>[16]</sup> Alternatively, modification of polysaccharides via oxidation is also an important method to yield carboxylated polysaccharides.<sup>[17]</sup> The polysaccharide derivatives could form gelation via intermolecular hydrogen bonding,<sup>[18]</sup> ionic interactions with metal ions<sup>[19–21]</sup> and organic molecules,<sup>[22]</sup> or host–guest interactions.<sup>[23,24]</sup> In particular, alginate could produce egg-box–like dimer structure crosslinking with Ca<sup>2+</sup> ions,<sup>[21]</sup> and the cavities of CDs could form inclusion complexes with various guest molecules via host–guest interaction to form hydrogels.<sup>[24]</sup> In addition, dynamic covalent interactions (e.g., Diels–Alder [D-A] cycloaddition linkages, boronate ester bonds, disulfide moieties, imine bonds) have

also been utilized to crosslink hydrogels. These interactions confer polysaccharide-based hydrogels with many intriguing features (e.g., stimuli–response and self-healing) yet exhibiting low mechanical performances and poor stability. In this context, double-network strategy based on chemical and physical crosslinking paves a promising way to engineer polysaccharide-based hydrogels with excellent strength and toughness as well as high stability. Tremendous efforts have been centered on crafting polysaccharide-based hydrogels due to their outstanding characteristics. Notably, they have been extensively exploited in an array of applications such as catalysts,<sup>[15]</sup> tissue engineering,<sup>[25]</sup> sensors,<sup>[26]</sup> self-healing,<sup>[27]</sup> and energy storage and conversion.<sup>[28]</sup>

This review aims to provide comprehensive guidelines for rational design and synthesis of polysaccharide-based hydrogels by capitalizing on commonly used biomass materials such as cellulose, sodium alginate, chitosan and CD, and their potential applications. Starting with the design and synthesis principles for polysaccharide-based hydrogels, hydrogels based on different substrates and crosslinking methods over the past decade are first summarized. Subsequently, the cellulose-, alginate-, chitosan-, and CD-based hydrogels crafted using various strategies are introduced. Thereafter, recent progresses of polysaccharide-based hydrogels for self-healing, sensors, energy storage and conversion, and biomedical applications are discussed. Finally, the future outlook of polysaccharide-based hydrogels is outlined.

## SYNTHESIS OF POLYSACCHARIDE-BASED HYDROGELS

Hydrogels are soft 3D framework polymers and its intrinsic characteristic is crosslinking existed in those materials.<sup>[29–31]</sup> In this regard, crosslinking density makes a critical difference in dominating the performances of hydrogels. Crosslinking can be achieved via forming covalent or noncovalent bonds. Chemical crosslinking is permanent and the structure is very stable, while physical crosslinking is dynamic and the structural stability is highly dependent on external environments. Those characteristics endow hydrogels with distinct performances based on the variable bond strength.<sup>[32]</sup>

**TABLE 1** Selective represents of polysaccharide-based hydrogels

Materials	Functional moieties	Modification methods	Crosslinkers	Crosslinking mechanism	Ref.
CNC	–COOH	TEMPO oxidation	–	Hydrogen bonding	18
CNC	–NH <sub>2</sub>	Amidation reaction	–	Hydrogen bonding	18
CNC	–SO <sub>3</sub> H	Sulfuric acid hydrolysis	–	Electrostatic interaction	36
CMC	–COOH	Etherification	Fe <sup>3+</sup> and Ru <sup>3+</sup>	Metal coordination	52
CNC, PVA	–OH	–	Borax	Hydrogen bonding, boronate ester bonds	59
CNC, PVA	Viologen, naphthyl	ATRP	CB[8]	Host–guest	23
CNC, PAM	–OH	–	MBA	Covalent bonds	76
CNC	Dihydrazide	Amidation reaction	PEG	Acylhydrazone, disulfide bonds	84
Alginate	–COOH	–	Ca <sup>2+</sup>	Metal coordination	101
Alginate	–COOH	–	Chitosan	Electrostatic interaction	113
Alginate	Furan	Amidation reaction	Bismaleimide	Diels–Alder addition	134
Alginate	Phenylboronic acid	Amidation reaction	PVA	Metal coordination, boronate ester bonds	102
Alginate, PAM	–COOH	–	MBA	Metal coordination, covalent bonds	139
Chitosan	–NH <sub>2</sub>	–	–	Hydrogen bonding	16
Chitosan	–NH <sub>2</sub>	–	Metal ions	Metal coordination	20
Chitosan	–NH <sub>2</sub>	–	TPP	Electrostatic interaction	159
Chitosan	–NH <sub>2</sub>	–	SDS	Electrostatic interaction	22
Chitosan	–NH <sub>2</sub>	–	Cellulose	Imine bonds	184
Chitosan	Double bond, catechol	Amidation reaction	–	Electrostatic interaction, covalent bonds	194
Cyclodextrin (CD)	–	–	PEG	Inclusion complexation	215
CD	–	–	Ad	Host–guest interaction	225
CD	–	–	PNIPAM	Host–guest interaction	235

Polysaccharides have numerous intrinsic functional groups on their repeating units and these can serve as covalent and noncovalent crosslinking or decorative points for the fabrication of hydrogels with tunable architectures. In addition, different polysaccharides have different intrinsic properties, for instance, cellulose exhibits a one-dimensional (1D) structure, sodium alginate, and chitosan can be considered as anionic and cationic polyelectrolyte, respectively, whereas CD is a cyclic molecule. The chemical and physical modifications of polysaccharides not only increase the solubility (e.g., modified cellulose can dissolve in most of the common solvents) but also incorporate functional moieties for crosslinking. In addition, polysaccharide composites (e.g., nanoparticles and polymers) can improve the mechanical performances or processibilities of the resulting hydrogels because of the crosslinking or the flexibility of matrices. With the remarkable tunability of the crosslinking points (e.g., chemical and physical crosslinking including host–guest, hydrophobic, metal coordination, and hydrogen bonding interactions) and compositions (e.g., cellulose, alginate, chitosan, and CD), polysaccharide-based hydrogels are capable of providing self-healing, high strength, excellent flexibility and enhanced ionic conductivity.<sup>[17,23]</sup> Table 1 summarizes the selective represents of polysaccharide-based hydrogels with diverse crosslinking approaches.

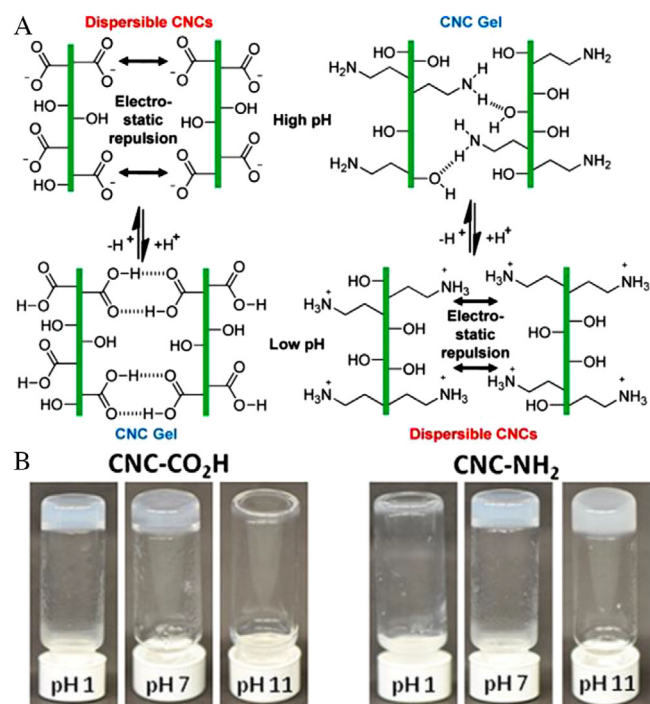
## Cellulose-based hydrogels

Cellulose is the most abundant polysaccharide biomass resource in nature, which exhibits fascinating 1D morphology due to its rigid backbone.<sup>[33]</sup> Moreover, cellulose

possesses many hydroxyl groups along its backbone, thus leading to poor dispersibility in common solvents arising from the formation of intermolecular and intramolecular hydrogen bonding among cellulose backbones.<sup>[17]</sup> Therefore, the main obstacle to synthesize cellulose-based hydrogels is finding appropriate solvents to dissolve cellulose, because hydrogels are fabricated via a two-step process involving dissolution followed by crosslinking.<sup>[17]</sup> There are two strategies exploited to dissolve cellulose: (i) using ionic liquids or base/urea aqueous solution to dissolve raw cellulose;<sup>[34]</sup> (ii) modification of cellulose to increase solubility in common solvents. It is worth noting that commercial cellulose derivatives (e.g., hydroxypropyl cellulose [HPC] and carboxymethyl cellulose [CMC]) are available and they can dissolve in a common solvent. These methods provide great opportunities for preparing cellulose-based hydrogels with tailorable performances.

## Physically crosslinked cellulose-based hydrogels

Physically crosslinked cellulose-based hydrogels have been explored with various types of nanocellulose bearing different functional groups.<sup>[35]</sup> Cellulose nanocrystal (CNC) is an important class of nanocellulose with high crystalline regions, which can be obtained via acid hydrolysis of raw cellulose. CNC exhibits 1D rod- or whisker-like morphology, and its diameter ranges from 3 to 50 nm, and length in 50–500 nm.<sup>[17]</sup> It has been reported that CNC has partial dispersibility in aqueous solution because of the surface introduced negatively charged –SO<sub>3</sub>H moieties during the



**FIGURE 2** (A) Schematic representation of the proposed interactions between CNC-COOH and CNC-NH<sub>2</sub> at high and low pH conditions. (B) Images of aqueous dispersions of 2.7 wt % CNC-COOH and 2.7 wt % CNC-NH<sub>2</sub> at pH of 1, 7, and 11. Adapted with permission.<sup>[18]</sup> Copyright 2012 American Chemical Society

hydrolysis process with sulfuric acid.<sup>[36]</sup> The sulfonated CNCs transform into the birefringent gel at a concentration >12.6 vol% due to the complications of electrostatic repulsion and its rod-like morphology with polydispersity.<sup>[17]</sup> Uncharged CNCs can be obtained via hydrolysis with hydrochloric acid, but they could not disperse in an aqueous solution. In order to improve the dispersibility of CNCs, surface oxidation is usually employed to obtain carboxylic acid moieties by using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).<sup>[35]</sup> The carboxylated CNCs form gelation at low pH because of the attractive hydrogen bonding among carboxylic acid groups, which forms a percolating network through the interacting CNC fibers (Figure 2(A)).<sup>[18]</sup> In addition, the surface acid groups can convert into amine moieties with amidation reaction in a one-step process. Conversely, the amine-functionalized CNCs exhibit hydrogel formation at high pH conditions due to the hydrogen bonding between the amine and hydroxyl groups.<sup>[18]</sup> As the gel formation of the CNCs is highly dependent on pH conditions, they can be easily applied to fabricate pH-responsive hydrogels (Figure 2(B)).

Cellulose nanofiber (CNF) is another kind of nanocellulose that has been extensively exploited to engineer hydrogels. CNFs have similar widths to that of CNCs, but the length is much longer than that of CNCs and it can reach up to micrometer scale.<sup>[17]</sup> CNFs consist of significant amorphous regions, thus they exhibit increased flexibility and propensity for entanglement. Such a unique characteristic renders CNFs able to form hydrogels exhibiting high moduli with less amount as a result of the entanglement among CNFs. CNF concentration dominates the mechanical performances of the hydrogels. For instance, TEMPO-oxidized

CNFs spontaneously align in water, leading to the formation of unprecedentedly stiff hydrogels with CNFs concentration as low as 0.1% w/v %.<sup>[37]</sup> Except for the introduction of carboxylic acid on CNF surface with TEMPO oxidation, other methods (e.g., carboxymethylation, carboxylation using nitric acid/sodium nitrite, and periodate–chlorite oxidation) for preparing carboxylated CNFs are also exploited. In particular, the hydroxyl group at the second and third carbon positions of polysaccharides could be oxidized by sodium periodate to form two aldehyde functional groups as intermediates, which could be further oxidized to acid groups under sodium chlorite.<sup>[35]</sup> All carboxylated CNFs could form hydrogels at optimized conditions. Additionally, with a consecutive pretreatment of CNFs with periodate and bisulfite, sulfonated CNFs with lower charge densities than CNFs prepared by periodate–chlorite oxidation are nanofibrillated to form a viscous clear gel.<sup>[38]</sup> Very recently, negatively charged CNFs bearing phosphoric acid groups on the surfaces were produced via an emerging phosphorylation treatment with less toxic chemicals. The phosphorylated CNFs produce a transparent gel-like suspension at approximately 2 wt %.<sup>[39]</sup> It should be noted that cellulose-based foams followed by freeze-drying of hydrogels show excellent flame-retardant properties attributing mainly to the intrinsic charring ability and the formation of heat-protective intumescent-like barriers.<sup>[40]</sup> Furthermore, CNFs with positive charges can also be applied to prepare hydrogels. 2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC) is the most commonly used reagent for the cationization of cellulose via ring-opening reaction by –OH groups in the presence of varying amounts of bases, after cationization in the organic solvent, the CNFs form a gel-like suspension in water.<sup>[41]</sup>

Hemicelluloses are a heterogeneous, branched group of polysaccharides made up of pyranoses and furanoses sugar units, which can further subdivide into four groups, xylans, mannans, xyloglucans, and  $\beta$ -1,3;1,4-glucans, based on structural features.<sup>[42]</sup> Hemicelluloses are noncrystalline because of the shorter chains and branched structure. However, hemicelluloses are not characterized as being cellulose. In addition, hemicelluloses have various compositions and structures depending on different sources of biomass (e.g., hardwoods and softwoods).<sup>[43]</sup> A distinct characteristic of hemicelluloses is their hydrophilic nature and they can dissolve in water above the temperature of 150°C.<sup>[44]</sup> Similarly, hemicelluloses have many intrinsic active groups such as –OH and –COOH, thus, it is easy to do modification via various physical and chemical reactions. Therefore, hemicellulose-based hydrogels have been studied for various applications due to the merits of hemicelluloses (e.g., water solubility, functional groups, and branched structure).<sup>[45]</sup> For instance, the cyclic freezing–thawing technique has been employed to prepare hemicellulose/polyvinyl alcohol (PVA)/chitin composite hydrogels with high strength. Notably, the repeated cycles, polymer concentration, and reaction time of the freezing–thawing process affect the final properties of hydrogels.<sup>[46]</sup> Hemicellulose-based hydrogels exhibit weak mechanical properties compared to other cellulose-based hydrogels because of their low molecular weight and noncrystalline nature. Chemically crosslinking of hemicellulose is the alternative robust pathway to prepare hydrogels with high performances.<sup>[45,47]</sup>

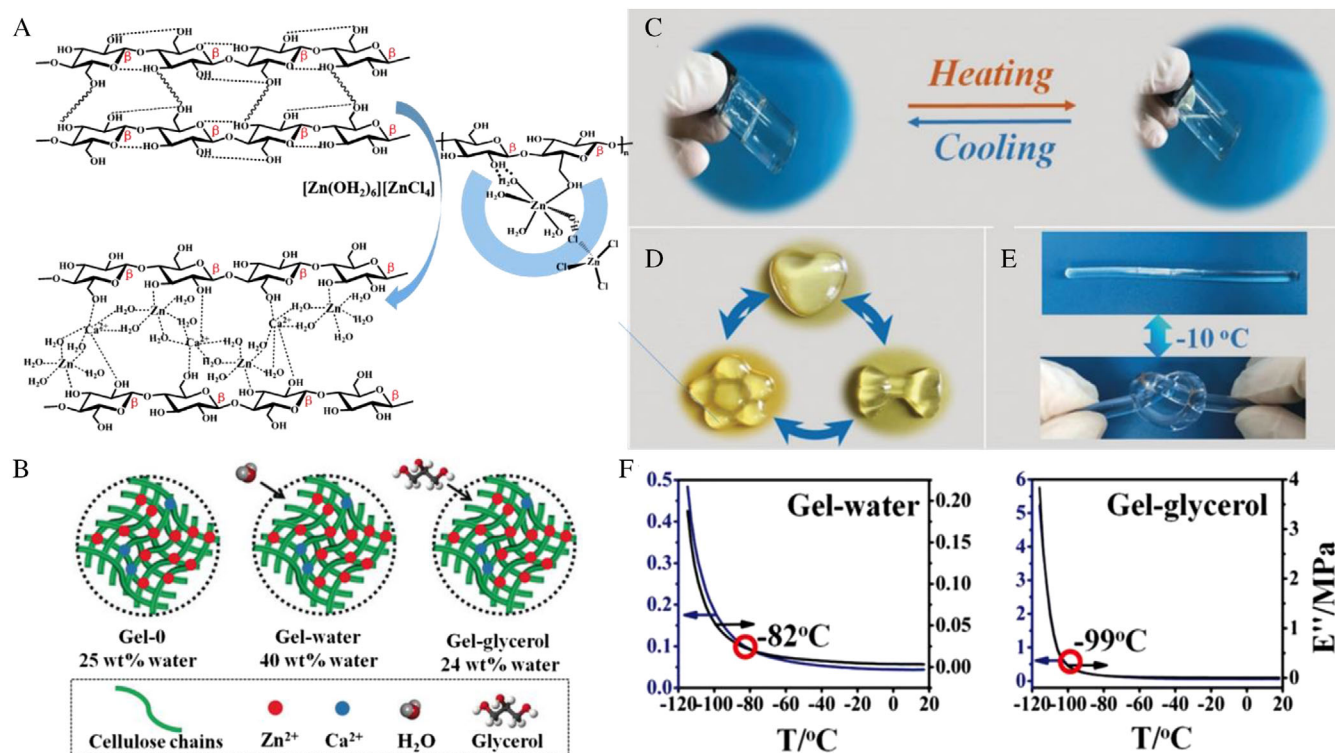


It has been demonstrated that the electrostatic repulsion can be suppressed by improving the ionic strength of CNC suspensions due to the decrease of Debye length of charged CNCs, thus attractive forces are dominated in the system and consequently lead to gelation with low concentration.<sup>[48–50]</sup> In addition, carboxylate exhibits strong coordination with metal ions, especially transition metal cations, forming robust metal–carboxylate complexes. The influence of metal cations with multiple valences (e.g.,  $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Al}^{3+}$ , and  $\text{Fe}^{3+}$ ) on CNF-based hydrogel formation has been systematically explored recently.<sup>[48]</sup> It was found that the strong cation–carboxylate interactions that form ionic crosslinking and screen the repulsive charges on the CNFs dominate the hydrogel formation. Alkaline metal cations have lower binding energies to carboxylate than the transition cations. In addition, divalent cations exhibit weaker binding energies with carboxylate groups than the trivalent cations.<sup>[48]</sup> Notably, sulfonated CNCs showed a similar tendency to ion-mediated gelation. The stronger side-by-side CNC association coordinated by cations results in a stiffer network.<sup>[49]</sup> The comprehensive study demonstrated that both the charge numbers and ionic radii of cations played a crucial role in forming hydrogels.<sup>[49]</sup> Increasing cation charge number decreased the Debye length of the CNCs, leading to the formation of gel networks with higher stiffness and thicker mesh walls. The hydrogels became stiffer when the cation increase of ionic radius was similar to the Debye length of the CNCs. Regardless of the cations types added, the CNCs suspension showed a minimum threshold value of  $\sim 1.5$  wt %, and the moduli of the hydrogels displayed higher dependence on CNC contents than salt concentration.<sup>[49]</sup> Even though monovalent cations had weak metal–ligand coordination with carboxylate groups, adding  $\text{AgNO}_3$  also favored the association into a network structure. The silver nanoparticles could be in situ synthesized in the matrix as a result of the reduction induced by hydroxyl moieties on CNFs.<sup>[50]</sup>

It is worth noting that the physically crosslinked cellulose hydrogels are based on hydrogen bonding or metal–carboxylate interactions. Generally, the stability of these weak noncovalent interactions lies in the surrounding environment such as heat, light, and pH. For example, TEMPO-oxidized cellulose and amine-functionalized cellulose showed distinct sol–gel transition under variable pH conditions, because the hydrogen bonds were broken and reconstructed because of the protonation and deprotonation of the moieties.<sup>[18]</sup> Light-induced control over elasticity of various polysaccharide-based hydrogels formed via  $\text{Fe}^{3+}$ –carboxylates reaction has been reported.<sup>[51]</sup> Upon irradiation with UV light, the hydrogels quickly transferred into sol state in 10 s, because the iron–carboxylate system absorbed light, and the excited electrons transferred from carboxylate to  $\text{Fe}^{3+}$ , leading to the formation of  $\text{Fe}^{2+}$  and carboxylate radical species as well as  $\text{CO}_2$  release. However, the response for light was irreversible due to the irreversible photochemical reaction.<sup>[51]</sup> Redox-responsive metal–carboxylate complexes (e.g.,  $\text{Fe}^{3+}$  and  $\text{Ru}^{3+}$ ) could be reversibly controlled in carboxymethylcellulose hydrogels. The  $\text{Fe}^{3+}$  or  $\text{Ru}^{3+}$  ions could coordinate with three carboxylate moieties forming hydrogels with high storage modulus, while reduction of the metal ions with ascorbic acid yields hydrogels with lower stiffness. The  $\text{Fe}^{3+}$  or  $\text{Ru}^{3+}$  ions could be regenerated via reverse oxidation with sodium persulfate, forming stiffer hydrogels.<sup>[52]</sup>

Very recently, binary  $\text{ZnCl}_2/\text{CaCl}_2$  systems were integrated into cellulose hydrogel networks to prepare thermally reversible hydrogels (Figure 3).<sup>[19]</sup> It is well known that  $\text{ZnCl}_2$  hydrate demonstrates extraordinary hydrogen-bond-donating ability deriving from its existing form of the ionic liquid ( $[\text{Zn}(\text{OH})_6][\text{ZnCl}_4]$ ). Particularly,  $\text{Zn}^{2+}$  ions coordinate with hydroxyl groups along cellulose chains, while five additional  $\text{H}_2\text{O}$  molecules absorbed around  $\text{Zn}^{2+}$  ions. Therefore, the formation of the first hydration shell weakens the intrinsic hydrogen bonding of cellulose. This promoted the dissolution process of cellulose in an aqueous solution.  $\text{Ca}^{2+}$  ions acted as a gelling agent, which could form ionic crosslinking and hydrogen bonding with adjacent Zn–cellulose junction zones. Moreover, glycerol exhibited excellent hydrogen-bond-donating ability, which could induce fast gelation in 30 s. Benefiting from the noncovalent interactions, cellulose hydrogels demonstrated reversible sol–gel transition upon heating–cooling cycle treatment. In addition, the hydrogels exhibited excellent antifreezing properties (Figures 3(E) and 3(F)).<sup>[19]</sup> Very recently, bisphosphonate (BP) groups were conjugated to cellulose derivatives through photo-induced polymerization. The dynamic complexing capacity of BPs toward  $\text{Ca}^{2+}$  ions<sup>[53]</sup> or iron oxide ( $\text{Fe}_3\text{O}_4$ ) nanoparticle<sup>[54]</sup> makes it easy to prepare injectable hydrogels.

Despite a huge number of cations that have been employed to prepare hydrogels based on the metal-complexation crosslinking in aqueous solution, the strength of the obtained hydrogels is limited due to the limited valences of inorganic cations. Polymers could have plenty of functional groups on the backbone, and they could act as multiple binders to crosslink the celluloses for gelation. Celluloses themselves can serve as macromolecular crosslinkers. For example, different types of hemicellulose have been introduced into CNFs as crosslinkers to manipulate the architectures and mechanical performances of hydrogels.<sup>[55,56]</sup> Alternatively, water-soluble synthetic polymers are the straightforward candidates to physically crosslink the celluloses to engineering hydrogels, and the CNCs or CNFs can functionalize as filler or reinforcing agents to enhance the mechanical properties. PVA is one of the most significant synthetic polymers due to its excellent strength and flexibility, superior oxygen barrier, as well as ease film-forming characteristics, which has been widely exploited to prepare cellulose-based composite hydrogels.<sup>[57–59]</sup> Cyclic freezing–thawing process is usually used to achieve the gelation of PVA aqueous solution derives from the phase separation. Enhanced mechanical performances of PVA/CNC hydrogels arising from the synergistic effect of hydrogen bonding between PVA and CNCs as well as reinforcement of rigid rod-like CNCs was reported.<sup>[60]</sup> In order to further improve the mechanical strength and toughness of hydrogels, three types of borax chemical crosslinking (e.g., CNC and CNC, PVA and PVA, CNC and PVA) are developed into the system. CNCs act as multifunctional interpenetrating crosslinkers and fillers to chemically and physically crosslink the hydrogel network.<sup>[59]</sup> Both of these two types of crosslinking could be manipulated to produce desirable hydrogels with enhanced mechanical performances and intriguing properties. It was found that advanced hydrogels with fascinating properties can be readily achieved by the introduction of dynamic boronate ester bonds combining with the



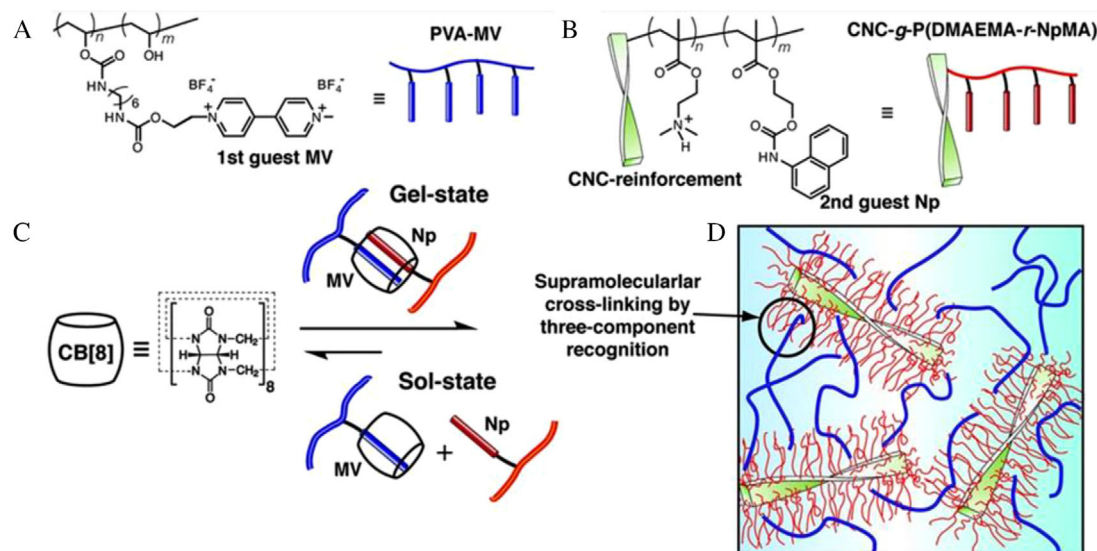
**FIGURE 3** Schematic illustration of (A) the dissolution of cellulose in aqueous  $\text{ZnCl}_2/\text{CaCl}_2$  system and (B) the preparation and components of three cellulose hydrogels. The appearance of cellulose hydrogels under different conditions, (C) thermal reversibility, (D) remoldability, (E) good stretchability at  $-10^\circ\text{C}$ . (F) Dynamic mechanical analysis (DMA) as a function of temperature for cellulose hydrogels. Adapted with permission.<sup>[19]</sup> Copyright 2019 John Wiley & Sons Inc

merits of natural polymers, such as glucose-responsivity and self-healing.<sup>[61]</sup>

Surface modification of cellulose is emerging research for promoting its diverse applications in high-strength hydrogels. Among the various modification methods, grafting small molecules or polymer chains on the CNCs is a fascinating and versatile strategy in practical terms.<sup>[17]</sup> This method could not only introduce functional moieties but also improve the cellulose solubility in other solvents. For instance, tannic acid (TA) is a low-cost and biocompatible plant polyphenol, which has been utilized as an alternative to PDA for designing functional surfaces to mimic mussel-inspired materials.<sup>[62–64]</sup> TA can be readily converted to high molecular weight polymers via in situ oxidative polymerization under alkaline conditions.<sup>[62]</sup> The resulting TA can deposit on the surface of CNC through intermolecular interactions and introduce more catechol groups on the surface, which can act as crosslinking sites. When the TA-coated CNCs were incorporated into  $\text{Al}^{3+}$ -containing polyacrylic acid (PAA) gel solution, conductive ionic hydrogels with remarkable self-healing and mechanical properties were achieved due to the synergistic multiple coordination interactions (e.g., metal–phenolic coordination between TA-coated CNCs, metal–carboxylate coordination between PAA chains, as well as hybrid bridging between TA-coated CNCs and PAA).<sup>[62]</sup> Notably, the ionic gel exhibited super toughness with stretching reaching up to 2900% without fracture, which is 43 times higher than that of pristine PAA gels.<sup>[62]</sup> Recently, TA-coated CNCs were exploited as a dynamic connected bridge for the fabrication of bio-based PVA composite hydrogels via strong multiple hydrogen bonding among the PVA and TA-coated CNCs.<sup>[63]</sup> In order to further increase the mechanical

performances, reversible covalent boronate–diol bonds were introduced into the system. The synergistic effect of dynamic boronate–diol bonds and hydrogen bonding imparted the crosslinked hydrogels with rapid self-healing behaviors and enhanced mechanical performances.<sup>[64]</sup>

Covalent grafting of small molecules or polymers on cellulose is another important method to achieve surface modification.<sup>[17]</sup> As the cellulose surfaces bearing plenty of  $-\text{OH}$  groups, they can readily react with active groups, such as isocyanate<sup>[65,66]</sup> and epoxy group<sup>[67]</sup>. Recently, free radical polymerization is used to graft poly (ionic liquid) on CNCs, superior mechanical PVA-based hydrogels can be obtained upon CNC loading via ionic interaction and hydrogen bonding.<sup>[58]</sup> More specifically, grafting charged monomers via advanced polymerization techniques resulted in cellulose with controlled functionality and structures.<sup>[23]</sup> The second-guest polymer was prepared via surface-initiated atom transfer radical polymerization (SI-ATRP) of monomers, dimethylaminoethyl methacrylate (DMAEMA) and naphthyl-functionalized methacrylate (NpMA), yielding naphthyl-functionalized polymer brushes (CNC-g-P(DMAEMA-r-NpMA)). Thereafter, the host molecule, cucurbit[8]uril (CB[8]) was introduced into the homogeneous mixture of CNC-g-P(DMAEMA-r-NpMA) and viologen-functionalized PVA (PVA-MV),<sup>[66]</sup> the strong host–guest interactions drove the formation of reversible crosslinked hydrogels (Figure 4).<sup>[23]</sup> Thereafter, this method was extended to prepare nanocomposite hydrogels with polymer brush-grafted CNC (hard) and “soft” polymeric domains in the presence of CB[8].<sup>[65]</sup> As the polymer brushes on CNCs were prepared through controlled SI-ATRP, the density of recognition sites could be rationally tuned. The storage



**FIGURE 4** Schematics and architectures of (A) PVA containing the first-guest methyl viologen functionality (PVA-MV) and (B) CNCs containing copolymer grafts of second-guest naphthyl moieties (CNC-g-P(DMAEMA-r-NpMA)). (C) CB[8] as the host motif. (D) Selective supramolecular crosslinks based on three-component recognition by CB[8] binding together the modified PVA and the CNC-grafts into dynamic hydrogels. Reproduced with permission.<sup>[23]</sup> Copyright 2014 John Wiley & Sons Inc

modulus reached up to 10 kPa, almost 10 times enhancement than previous small molecule-decorated CNC hydrogels.<sup>[23,66]</sup>

In order to explore the influence of cellulose on increasing the mechanical properties of nanocomposite hydrogels, straightforward physical incorporation of cellulose as reinforcing agents into covalent polymeric hydrogels. The commonly exploited networks are based on water-soluble PAA,<sup>[62]</sup> polyacrylamide (PAM),<sup>[68]</sup> poly(*N*-isopropyl acrylamide) (PNIPAM),<sup>[69]</sup> and poly(ethylene glycol) (PEG),<sup>[70]</sup> and so on.<sup>[71]</sup> The covalent networks are in situ formed within cellulose suspensions in the presence of monomers and crosslinkers with redox-free radical polymerization or UV/ $\gamma$ -ray irradiation techniques at room temperature to avoid the bubbles under heating conditions. Notably, the mechanical properties of the resulting hydrogels are higher than physically crosslinked hydrogels due to the stronger binding energy of covalent bonds.<sup>[71]</sup> Generally, the physical loading of CNCs in the covalent hydrogel networks is operated at low concentration. It should be noted that the enhancement of mechanical performances of the hydrogels ranges from several to tens of times, which results from the rigid rod-like CNCs and the hydrogen bonding interactions between CNC and the network stands.<sup>[71]</sup>

## Chemically crosslinked cellulose-based hydrogels

Though the aforementioned cellulose could enhance the mechanical performances, in most cases the cellulose or its derivatives are physically entrapped in the systems, the weak physical interactions limit the improvement of hydrogels. To further promote the enhancements of cellulose, chemical incorporation of celluloses into hydrate polymer networks is the priority to achieve this objective. In this case, celluloses are covalently bonded with surrounding hydrogel phases, thus the performances and stability of hydrogels can be

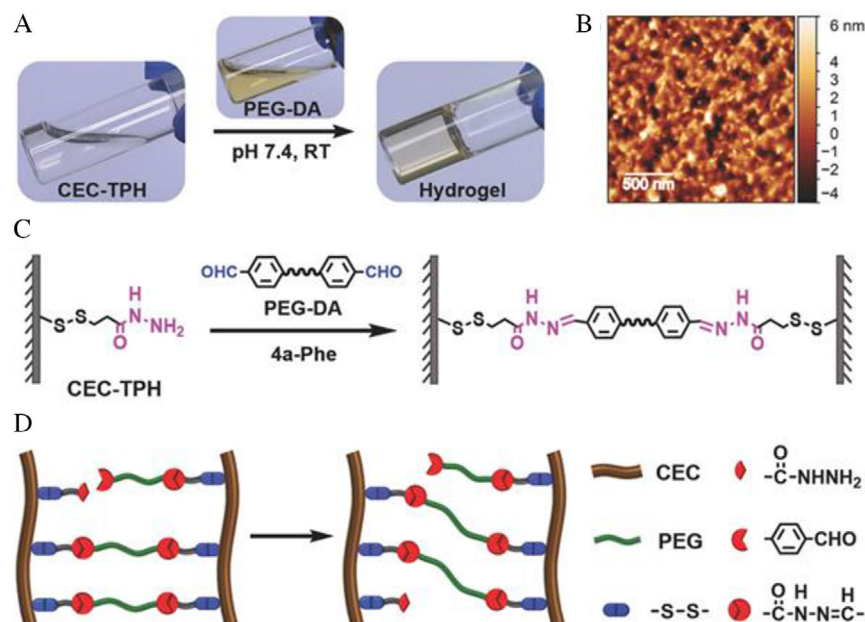
significantly improved compared to physically incorporated hydrogels because celluloses act as rigid fillers and covalent crosslinking points. Generally, there are two strategies to chemically entrap celluloses into hydrogels: (i) cellulose itself serves as a crosslinker and (ii) cellulose connects with other polymer chains forming a covalent network. Therefore, this provides a versatile platform to prepare high-strength covalently crosslinked hydrogels due to the various crosslinking strategies and crosslinking chemistries.

The easiest way to covalently introduce cellulose into hydrogel networks is through a radical mechanism initiated by redox polymerization<sup>[72]</sup> as well as high-energy irradiations (e.g., UV,<sup>[73]</sup>  $\gamma$ -ray,<sup>[74]</sup> and electron-beam radiation<sup>[75]</sup>). It was found that the active sulfate anion radicals generated from persulfate initiator decomposition could extract hydrogen from the  $-OH$  groups in the cellulose, producing more active alkoxy radicals, then those radical could initiate the vinyl monomers growing. Whereas the celluloses during the polymerization serve as multiple functional crosslinkers.<sup>[76,77]</sup> For instance, CMC grafted copolymerization of AA/AM/2-acrylamido-2-methyl-1-propanesulfonic acid and methylene bis(acrylamide) (MBA) crosslinker has been achieved and used as superabsorbents.<sup>[77]</sup> High-energy irradiation does not require any additional chemicals, random recombination of the polymers and crosslinkers leads to the formation of networks because the irradiation-initiated active radicals from  $H_2O$  molecules results in polymerization and crosslinking.<sup>[75]</sup> Additionally, electron-beam radiation could avoid the involvement of a radioactive source, which is hazardous toxicity to human bodies.<sup>[75]</sup>

Vinyl bonds can be directly incorporated into celluloses via surface modification with silane treatment, which can act as multifunctional crosslinks to initiate polymerization and engineer networks.<sup>[73,78,79]</sup>  $\gamma$ -Methacryloxypropyl trimethoxy silane is the most used coupling agent to decorate cellulose with double bonds. The modified CNCs in situ copolymerized with AA,<sup>[79]</sup> or *N,N*-dimethyl acrylamide,<sup>[78]</sup> or NIPAM<sup>[73]</sup> without the addition of crosslinker, producing



**FIGURE 5** (A) Photographs of the precursor solutions (CEC-TPH and PEG-DA) and the resultant hydrogels. (B) AFM image of the hydrogel surface. (C) The gelation mechanism of the hydrogels. (D) Schematic illustration for the dynamic hydrogel networks through the reversible breaking and regeneration of the acylhydrazone bonds. Reproduced with permission.<sup>[84]</sup> Copyright 2014 John Wiley & Sons Inc



flexible hydrogels due to the interactions between CNCs and polymers, which could dissipate energy during the deformation process. When lignin-based micelles capped with primary amines were introduced into the CNFs-PNIPAM-based hydrogels, thermo- and pH-responsive hydrogels with fast self-recovery could be produced because of the dynamic hydrogen bonding between CNCs and micelles as well as covalent crosslinking.<sup>[73]</sup>

As the celluloses still have abundant hydroxyl groups even after surface oxidation, high efficient reactions such as esterification with an anhydride,<sup>[80]</sup> and etherification with epichlorohydrin (ECH),<sup>[81]</sup> or epoxy-functionalized PEG,<sup>[82]</sup> have been extensively utilized to crosslink celluloses, yielding covalently crosslinked hydrogels. In the chemical crosslinking hydrogels, physical crosslinking arising from hydrogen bonding, and cellulose chain entanglement, as well as crystallite hydrates of cellulose could also improve the mechanical properties of hydrogels.<sup>[81]</sup> Moreover, the covalent crosslinking density could be readily manipulated by the concentration of crosslinkers. It should be noted that additional functionality can be incorporated by the crosslinkers. For instance, when the esterification with anhydride occurred, a subsequent generation of free carboxyl groups endows hydrogels with superabsorbent ability.<sup>[80]</sup> However, the formed covalent bonds are very stable, which restrict the variability of the resulting hydrogels.

Dynamic covalent bonds have been developed as attractive crosslinking for designing self-healing hydrogels. Cellulose can be straightforwardly oxidized with sodium periodate to impart aldehyde groups on the surface,<sup>[35]</sup> which show great potential to react with amine groups forming dynamic and reversible imine linkages with high efficiency at room temperature. In addition, the aldehyde-modified CNCs (CHO-CNCs) still maintain their rigid rod-like morphologies.<sup>[83]</sup> Meanwhile, commercial CMC can be readily converted to dihydrazide-modified carboxymethyl cellulose (CMC-NHNH<sub>2</sub>) via condensation of hydrazides with carbonyl groups.<sup>[84]</sup> When the CHO-CNCs mixed with CMC-NHNH<sub>2</sub>, robust crosslinked gelation occurred within seconds. Upon adding a third component, aldehyde-

modified dextran (dextran-CHO), into the system, injectable hydrogels with high stability are produced.<sup>[85]</sup> Zhang et al. prepared CMC-NHNH<sub>2</sub> by conjugating dithiodipropionate dihydrazide with CMC, introducing the disulfide bonds into the celluloses, followed by the addition of dibenzaldehyde-terminated PEG (PEG-DA) to induce the gelation under optimal conditions (Figure 5).<sup>[84]</sup> The resulting hydrogel exhibited a homogeneously interconnected porous structure (Figure 5(B)). Additionally, it also displayed dual responsive sol-gel transitions under pH and redox conditions due to the dynamic acylhydrazone and disulfide bonds in the hydrogels. HCl and trimethylamine (TEA) were applied to adjust the reversible pH-responsive sol-gel transition. Moreover, the hydrogel decomposed after adding 1,4-dithiol-dl-threitol (DTT) and regenerated again under H<sub>2</sub>O<sub>2</sub> oxidation. Both sol-gel transitions could be repeated for several cycles because of the reversible breaking and regeneration of acylhydrazone and disulfide bonds in the hydrogels (Figure 5).<sup>[84]</sup> Alternatively, small molecule cystamine dihydrochloride (CYS) containing disulfide bonds was utilized to conjugate cellulose acetoacetate, forming pH/redox dual-responsive hydrogels.<sup>[86]</sup> D-A reaction is another well-known chemical reaction forming dynamic bonds, which could be reversibly cleaved and recombined via thermal treatment.<sup>[87,88]</sup> Bionanocomposite hydrogels were demonstrated by using maleimide-functionalized CNCs and furan-modified gelatin via D-A reaction.<sup>[87]</sup> It was reported that tough and self-healing nanocomposite hydrogels were prepared using furan-modified CNCs and maleimide-terminated PEG. The hydrogels displayed outstanding mechanical performances of high fracture strain of 690% and fracture strength up to 0.3 MPa.<sup>[88]</sup>

## Double-network cellulose-based hydrogels

PAM and polyacrylate-based networks are the most widely studied systems because of the relatively convenient polymerization and crosslinking with commercial chemicals. In most cases, commercial crosslinkers such as MBA or



water-soluble poly(ethylene glycol) diacrylate (PEGDA) derivatives are applied to create the covalent networks. While another network is formed through another mechanism, interpenetrating with the covalent mechanism. Generally, the covalent crosslinking confers elasticity, and the second network (physical crosslinking) can be broken and regenerated to dissipate mechanical energy endowing hydrogels with toughness in the double-network systems. Recently, CNC-reinforced PAM hydrogels were demonstrated with redox polymerization, and the mechanical properties increase with CNCs contents. The double-network combining hydrogen bonding between CNCs and amine groups of PAM chains as well as chemical crosslinking PAM network endows the hydrogels enhanced mechanical performances.<sup>[68]</sup> Alternatively, UV-induced polymerization of acrylamide (AM), NIPAM, or acrylic acid (AA) in CNCs suspensions was found highly effective to obtain hydrogels with the long-range chiral nematic structure above a critical CNCs concentration.<sup>[89]</sup> The resulting hydrogels exhibited stimuli responsiveness (e.g., solvent, pH, and temperature) through the choice of suitable hydrogel monomers.<sup>[89]</sup> Pal et al. reported that preparation of composite hydrogels via UV initiated crosslinking of NIPAM and triethylene glycol dimethacrylate, and the hydrogels exhibited tunable optical properties and wavelength bandpass selectivity, which was indicative of thermal responsiveness.<sup>[69]</sup> PEG is the most extensively explored biocompatible hydrophilic polymer in biological applications. In situ UV-initiated polymerization of PEGDA in CNCs dispersion leads to the crosslinking of hydrogels, which possess higher strength and toughness than pristine PEG hydrogels due to the extensive hydrogen bonding among PEG matrix and CNCs.<sup>[70]</sup> However, an excessive amount of CNCs results in poor mechanical performances due to the inhomogeneity of the system.<sup>[70]</sup> Besides the free radical crosslinking, other highly effective reactions have also been utilized to produce covalent networks. Aldehyde- and hydrazide-functionalized PEG precursors could strongly adsorb the CNCs surface, and simultaneously the PEG precursors could be crosslinked by dynamic covalent hydrazone bonds.<sup>[90]</sup> The physically entrapped CNCs within the network significantly enhances the mechanical properties and lowers the degradation compared to the pristine PEG hydrogels.<sup>[90]</sup>

## Alginate-based hydrogels

Alginate is a kind of natural anionic polymer typically derived from seaweed, which has been extensively applied for a variety of applications such as biomedical fields,<sup>[91]</sup> food industry,<sup>[92]</sup> and water treatment,<sup>[93]</sup> as a result of its biocompatibility, low toxicity, and low cost. Alginate comprises 1,4-linked mannuronic acid (M unit) and guluronic acid (G unit), which form consecutive G block, M block, and alternating G and M blocks.<sup>[21]</sup> It was found that the G and M contents, as well as the length of each block, are highly dependent on the sources. The G block from different alginate chains could form intermolecular crosslinking with divalent cations (e.g.,  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$ ).<sup>[21]</sup> In addition, the M block could produce cytokine production via human monocytes, making it is favorable for wound healing.<sup>[91]</sup> Therefore, the G/M block ratio, as well as their block length and sequence play a critical

role in dominating the properties of alginates. These unique characteristics provide highly favorable suitability in more advanced fields.<sup>[94]</sup>

## Physically crosslinked alginate-based hydrogels

Due to the intrinsic anionic feature, alginates could readily combine with plenty of metal cations via electrostatic interactions and coordination. Generally, divalent cations such as  $\text{Cd}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Pb}^{2+}$ , and  $\text{Zn}^{2+}$ ,  $\text{Ca}^{2+}$  are favorable for ionic or coordination crosslinking between G blocks and the cations, forming egg-box-like dimer structure (each cation is coordinated by four guluronate units) at optimal concentration.<sup>[21]</sup> It has been demonstrated that transition metal ions show strong coordination to carboxylate groups with unidentate binding, while ionic bonds are preferred to form between alkaline earth cations and alginates.<sup>[95]</sup> Nevertheless, monovalent cations are not suitable for coordination.<sup>[96]</sup> The chelation at the G blocks from two different alginate molecules in combination with the van der Waal forces between alginate segments results in gelation.<sup>[97]</sup> The higher the G block content, the stronger strength of the hydrogels. It should be noted that the strength and selectivity of binding were dominated by the size of metal ions and packing degree of the alginate chains around the metal ions, which further determined the strength and Schwann cell viability of the resultant hydrogels.<sup>[98]</sup> A larger ionic radius facilitated a higher extent of cooperative binding with G blocks.<sup>[99]</sup> In addition, the conditions (e.g., temperature and pH) for gelation were also inescapable to achieve high-strength hydrogels. In some cases, glacial acetic acid was added to adjust the calcium ions released from calcium carbonate, controlling the gelation process. Alternatively, external trisodium citrate, which could compete with alginates for free  $\text{Ca}^{2+}$ , was also utilized to control the gelation. Therefore, the performances of hydrogels are strictly dependent on the chemical structure and composition of alginates, metal cations as well as gelation conditions.<sup>[97]</sup>

Ionic crosslinking is the most frequently used approach to fabricate physically crosslinked alginate hydrogels. Among the various cations,  $\text{Ca}^{2+}$  is the most commonly applied cation to crosslink the alginate hydrogels, and there are two approaches to achieve this process.<sup>[100]</sup> (i) External diffusion-crosslinking strategy, wherein the cations diffuse into the alginate solution. The easiest way to perform this method is to mix the alginate solution with  $\text{CaCl}_2$  solution to form a homogeneous system and incubate for a certain time. Yet, the slow diffusion process often leads to the random distribution of cations, yielding heterogeneous hydrogels. (ii) Internal in situ crosslinking strategy, in which the insoluble calcium salts such as  $\text{CaCO}_3$  as a calcium source disperse in alginate solution, controlled release of  $\text{Ca}^{2+}$  triggered by pH (releasing from *D*-glucono- $\delta$ -lactone) leads to the gelation. Nonetheless, the pH will also induce the hydrolysis of the glycosidic bonds in alginates with a three-step degradation process.<sup>[100]</sup> Photo-induced crosslinking of alginates was also reported by introducing photosensitive  $\text{Ca}^{2+}$  cages. Upon light exposure,  $\text{Ca}^{2+}$  cages release the free  $\text{Ca}^{2+}$  cations, resulting in the crosslinking of alginates.<sup>[101]</sup> It has been reported that the  $\text{Ca}^{2+}$  can be either extracted by carbonate ions or complexed by more competitive ligand such as

ethylenediaminetetraacetic acid disodium salt (EDTA·2Na), leading to the decomplexation between alginate and  $\text{Ca}^{2+}$  cations.<sup>[102]</sup>

Though the “egg-box” model has been proposed to explain the crosslinking mechanism of the resultant hydrogels, actually, the gelation of  $\text{Ca}^{2+}$  to alginate is a multiple-step binding process with  $\text{Ca}^{2+}$  concentration increases.<sup>[103]</sup> At low concentration, the  $\text{Ca}^{2+}$  selectively coordinates with the single G unit to form a complex. Increasing the concentration leads to the formation of egg-box dimers composed of 2/1 helical chains. Finally, multimers will be formed as a result of the association of egg-box dimers at a higher concentration.<sup>[103]</sup> Consequently, the concentration of  $\text{Ca}^{2+}$  significantly affects the mechanical performances and morphology of alginate hydrogels. With a higher concentration of  $\text{CaCO}_3$ , stiffer hydrogels with smaller pore sizes were demonstrated via ionic crosslinking, indicating that more cations bound to the binding sites, giving rise to high crosslinking density.<sup>[104]</sup> Recently, the effect of metal coordination and M/G ratio on the mechanical performances of alginate hydrogel films was systematically explored by immersing the film in  $\text{CaCl}_2$  solution.<sup>[105]</sup> The tensile strength of the crosslinked films increased with  $\text{CaCl}_2$  concentration as well as G/M ratio, whereas the elongation-at-break, moisture content, solubility, and swelling index values decreased with the increasing of the variables.<sup>[105]</sup>

Iron cations have also been employed to crosslink the alginates to form stable alginate hydrogels, which show enhanced cell adhesion compared to  $\text{Ca}^{2+}$ -crosslinked alginate hydrogels.<sup>[106]</sup> However, the huge difference between  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions leads to distinctly different coordination chemistry.  $\text{Fe}^{2+}$  cation prefers to bind neutral nitrogen- and sulfur-containing ligands, whereas the  $\text{Fe}^{3+}$  cation tends to coordinate with oxygen moieties in negatively charged ligands (e.g., carboxylate and phenolate groups).<sup>[51,107,108]</sup>  $\text{Fe}^{2+}$ -crosslinked alginate hydrogels have been demonstrated to display mesoscopic heterogeneities (i.e., turbidity) because of the monodentate association between the cation and the galacturonate unit, which is different from that of  $\text{Ca}^{2+}$ -crosslinked alginate hydrogels.<sup>[109]</sup>  $\text{Fe}^{3+}$  cation shows stronger binding to the carboxylate groups than that induced by  $\text{Fe}^{2+}$  cation. Notably, the different binding strengths between carboxylate groups and iron cations will directly affect the performances of hydrogels. In addition, the  $\text{Fe}^{2+}$  can be readily oxidized into  $\text{Fe}^{3+}$  and their reversible conversion could be achieved through electrochemical reactions. This protocol was implemented with alginate hydrogels to control the protein release. Upon electrochemical oxidation of soluble  $\text{Fe}^{2+}$ -containing alginate, the solution converted into gel state due to generation of  $\text{Fe}^{3+}$ , which showed strong complexation with alginate.<sup>[107]</sup> Furthermore, as previously mentioned that the  $\text{Fe}^{3+}$  ions could change to  $\text{Fe}^{2+}$  ions under UV light, photoresponsive ion-crosslinked alginate hydrogels have been demonstrated by using 405 nm light.<sup>[108]</sup>

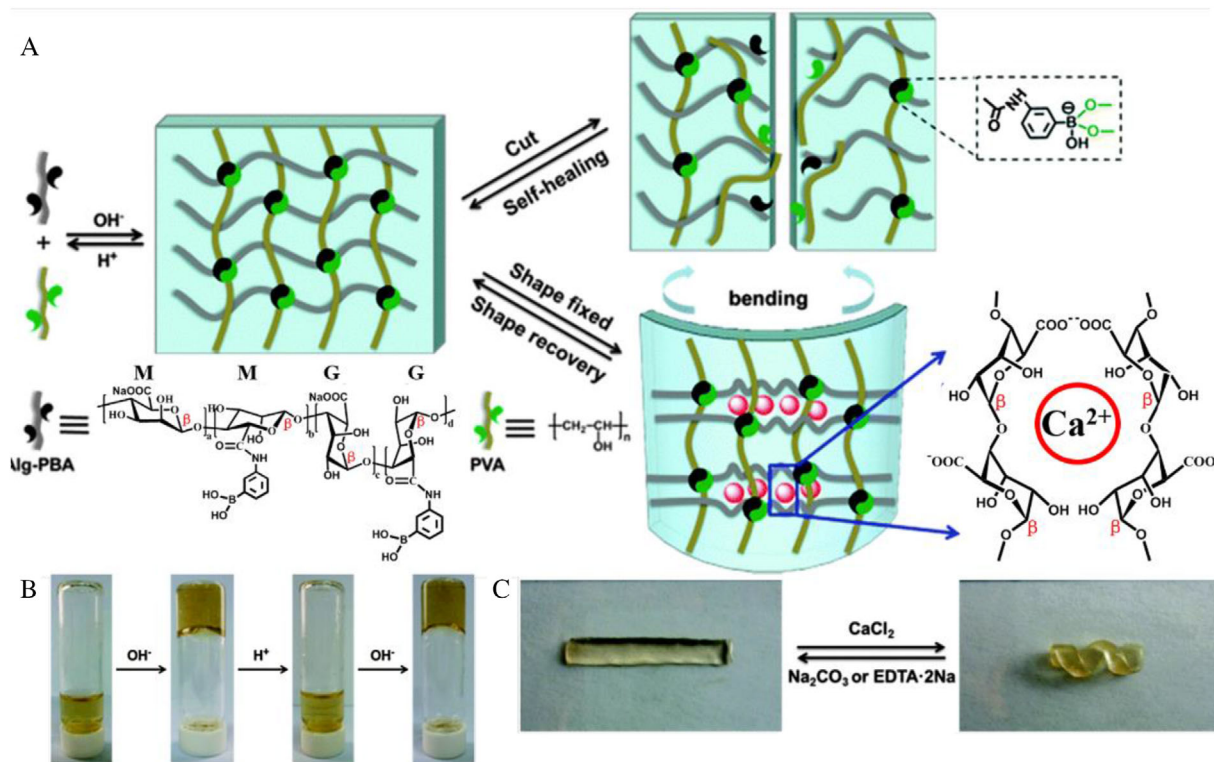
Alginate is an anionic polymer, various positively charged polymers have been utilized to crosslink alginates via electrostatic interaction instead of inorganic cations. Among the various positively charged polymers, natural biopolymers (e.g., chitosan,<sup>[110,111]</sup> cellulose,<sup>[112]</sup> and starch<sup>[113]</sup>) have been considered as promising candidates to form polyion complexes for biomedical applications.<sup>[114]</sup> Protonated chitosan is soluble in an aqueous solution under acidic conditions

( $\text{pH} < 6.3$ ), which facilitates its biodegradable character. The carboxylic groups of alginate confer its anionic character, which can form a stable ionic bond with the amine groups of chitosan.<sup>[114]</sup> It was reported that the interactions could induce the formation of hydrogels or precipitation, depending on the experimental conditions such as ionic strength, pH, concentration, and polymer ratios.<sup>[115,116]</sup> The driving force of the interpolymer complexation interactions is the electrostatic neutralization of charges. This means that polymers with low charge density should have a high concentration in the system. In addition, hydrogen bonding among the polymers (such as hydroxyl groups on chitosan and alginate) also promotes the complexation interactions.<sup>[110]</sup> Furthermore, inorganic ions have also been utilized to crosslink the hydrogels. For instance, alginate/chitosan hydrogels are fabricated via a three-step process: partial-crosslinking of alginate and chitosan with ions, freeze-drying, and pulverization of those crosslinked polymers to fabricate interpolymer complexation hydrogels with enhanced performances. It should be noted that the calcium salts and tripolyphosphate (TPP) are applied to partially crosslink the alginate and chitosan, respectively, in alginate/chitosan hydrogels.<sup>[110]</sup> The ultrafast ionic process is favorable for 3D printing.<sup>[117]</sup> However, the structural collapse and poor shape fidelity limit the extensive value of alginates in 3D printing.<sup>[118]</sup> Introducing rigid celluloses into printed hydrogels could tackle this issue and improves the printability and shape fidelity. In particular, antimicrobial alginate/cellulose hydrogels have been achieved via 3D printing with the incorporation of copper nanoparticles.<sup>[119]</sup>

Besides, synthetic polymers have also been employed as binders to fabricate composite hydrogels.<sup>[120,121]</sup> As mentioned above, PVA itself can form networks with the cyclic freezing–thawing method. The merits of the coordination of alginates with  $\text{Ca}^{2+}$  give access to prepare double-network hydrogels. For instance, PVA/alginates composite could be readily obtained via the cyclic freezing–thawing method, when the composite immersed in  $\text{CaCl}_2$  aqueous solution, the alginates formed ionic crosslinking, thus double-network composite hydrogels were achieved.<sup>[122–124]</sup> With the incorporation of salt ions in the hydrogels, they exhibited high electrical conductivity and antiseptic property.<sup>[122]</sup> When the  $\text{Fe}^{3+}$  ions were employed to crosslink the PVA/alginate hydrogels prepared by patterning, the resulting hydrogels displayed reversible macroscopic transformations. This ionic crosslink lithography approach could also achieve more complex and programmable transformations.<sup>[125]</sup>

## Chemically crosslinked alginate-based hydrogels

As mentioned in previous parts, physically crosslinked alginate-based hydrogels are attractive materials for biomedical applications. However, the reversible nature of interactions between polymer chains are sensitive to the external stimulus, and transformation from gel to sol results in deterioration of the designed structure. Many strategies have been employed to chemically crosslink the alginate chains to prepare alginate hydrogels with controllable physical properties and mechanical performances. Boronic acid could form boronate–diol interactions with 1,2- or 1,3-diols, especially, various polysaccharides are commonly used diol-containing



**FIGURE 6** (A) Schematic illustration of self-healable shape memory supramolecular hydrogel formed by Alg-PBA and PVA. (B) pH-responsiveness, and (C) shape memory effect of the supramolecular hydrogel. Adapted with permission.<sup>[102]</sup> Copyright 2014 Royal Society of Chemistry

natural polymers, boronic acid-containing hydrogels have shown important applications in many areas.<sup>[61,126]</sup> It should be noted that the affinity order of boric acid and glycol is *trans*-1,2-diol  $\ll$  1,3-diol  $<$  *cis*-1,2-diol.<sup>[127]</sup> The introduction of dynamic boronate ester bonds can endow hydrogels with many interesting performances. However, the dynamic bonds were commonly incorporated by using boronic acid or borax salt, this externally introduced component is hard to control the formation of crosslinking density.<sup>[61]</sup> Phenylboronic acid (PBA) moiety is the most used to form homogeneous crosslinked networks in hydrogels.<sup>[113]</sup> In addition, the introduced functional moieties on alginate could serve as an intrinsic part for further crosslinking, avoiding the heterogeneous issue and uncontrollable crosslinking.<sup>[102,127–129]</sup> For instance, PBA has been grafted onto sodium alginate (Alg-PBA) to prepare composite hydrogels. By mixing with PVA and  $\text{Ca}^{2+}$ , the PBA on alginate could react with PVA to form dynamic boronate–diol ester bonds, meanwhile, the  $\text{Ca}^{2+}$  could chelate with the alginate to form physical crosslinking (Figure 6).<sup>[102]</sup> The synergistic effect of boronate ester bond and metal coordination endows the composite hydrogels with self-healing properties and shape memory effect.<sup>[102]</sup> Additionally, pH also dominated the boronate–diol interactions due to the different boronic acid architectures,<sup>[130]</sup> the resulting hydrogels displayed pH- and temperature-dependent behaviors.<sup>[102,129]</sup> The hydrogels also exhibited reversible shape memory effects due to the coordination with  $\text{Ca}^{2+}$  and decomplexation induced by  $\text{Na}_2\text{CO}_3$  or EDTA treatment.<sup>[102]</sup>

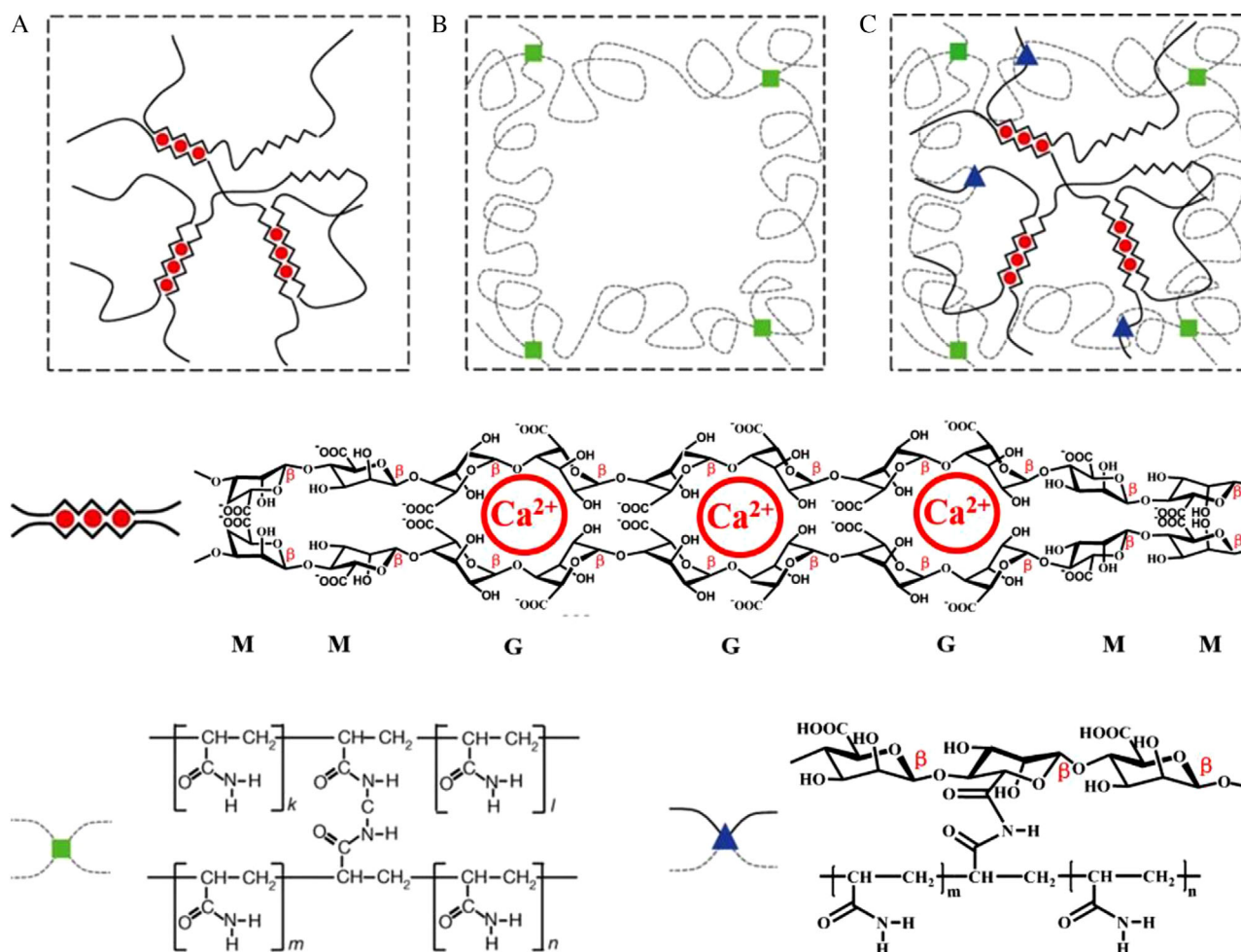
Alginate modification could also introduce various functional groups, thus giving access to crosslinking with other high efficient reactions.<sup>[96]</sup> Due to the intrinsic carboxyl acid groups on the backbone, amidation reaction is widely applied to introduce crosslinking moieties, followed by crosslinking

with high efficient click reactions. Click reactions can occur under mild reaction conditions without catalysts or initiators. This reaction represents a powerful approach for the synthesis of alginate-based hydrogel with tunable architecture and properties. For example, norbornene moiety has been grafted onto alginate to prepare hydrogels.<sup>[131–133]</sup> The norbornene moieties can experience norbornene–tetrazine<sup>[131,133]</sup> or UV-induced thiol–ene click reaction<sup>[132]</sup> to form the crosslinking network in a rapid manner. Recently, the D–A reaction was employed to prepare alginate hydrogels by reacting furan-functionalized alginate with maleimide-modified crosslinkers.<sup>[134]</sup> In addition, partially oxidized alginates could react with succinyl chitosan through Schiff-based linkages to form hydrogels.<sup>[135]</sup> Although hydrazide-modified crosslinkers have been used to crosslink cellulose for preparing hydrogels,<sup>[84]</sup> this strategy could also be employed to crosslink alginate to form hydrogels with enhanced performances.<sup>[136]</sup> Furthermore, dopamine was introduced into alginates to obtain catechol-functionalized alginate, thus the tethered catechols could undergo oxidative crosslinking to prepare mussel-inspired materials.<sup>[137,138]</sup>

## Double-network alginate-based hydrogels

The aforementioned chemical crosslinking is based on reactions with alginate, incorporating a second covalent network into the hydrogel structure is considered as a potential solution to enhance the mechanical properties by combination with ionic crosslinking of alginate network.<sup>[139–141]</sup> The easiest way to achieve a covalent network is using free radical polymerization of water-soluble monomers (e.g., AA, AM, NIPAM, and sodium styrene sulfonate) and crosslinkers





**FIGURE 7** Schematic illustration of three types of hydrogels. (A) In an alginate gel, the G blocks on different polymer chains form ionic crosslinks through  $\text{Ca}^{2+}$  (red circles). (B) In a polyacrylamide gel, the polymer chains form covalent crosslinks through MBA (green squares). (C) In an alginate-polyacrylamide hybrid gel, the two types of polymer networks are intertwined and joined by covalent crosslinks (blue triangles) between amine groups on PAM chains and carboxyl groups on alginate chains. Reproduced with permission.<sup>[139]</sup> Copyright 2012 Nature Publishing Group

(e.g., MBA). The double-network hybrid hydrogels were employed by mixing all the components together followed by photo-induced polymerization (Figure 7).<sup>[139]</sup> There are two types of crosslinked polymers in the hydrogel, that is, ionically crosslinked alginate by  $\text{Ca}^{2+}$  ions and covalently crosslinked PAM by MBA. During the stretch, the covalent network could bridge the crack and stabilize the deformation, leading to the breaking of the alginate network over a large region with high stress. Meanwhile unzipping the alginate network could dissipate energy, resulting in large strain without breaking. The synergistic effect of covalent and physical crosslinking networks endow the resulting hydrogels with high stretchability and toughness.<sup>[139]</sup> Similar to that of cellulose, surface initiation of monomers with persulfate initiator could result in crosslinked alginate hydrogels by forming covalent and physical crosslinking.<sup>[142,143]</sup>

## Chitosan-based hydrogels

Chitosan is produced from chitin that widely exists in nature. It composes of deacetylated unit (D-glucosamine) (content larger than 50%) and acetylated unit (N-acetyl-D-glucosamine), thus there are plenty of  $-\text{NH}_2$  and  $-\text{OH}$  groups along the chitosan backbone.<sup>[144]</sup> These reactive

groups can be used as crosslinking points to fabricate hydrogels. In particular, the  $-\text{NH}_2$  moieties have higher reactivity than  $-\text{OH}$  groups, and they can be readily converted into ammonium groups under suitable pH conditions (i.e.,  $\text{pH} < 6.3$ ), endowing chitosan with pH-responsive properties.<sup>[145]</sup> This characteristic also makes chitosan to be the only cationic and hydrophilic natural polymer due to the unestablished intermolecular hydrogen bonding in acidic condition. Similar to cellulose- and alginate-based hydrogels, chitosan-based hydrogels can be classified into physically crosslinked hydrogels and chemically crosslinked hydrogels based on the nature of crosslinks as well as similar chemical structures.

It has been reported that the solubility of chitosan in aqueous solution is highly dependent on the chemical structure (e.g., degree of acetylation [DA] and molecular weight).<sup>[144,146]</sup> The dominant factor is the DA of chitosan, which can influence the balance of hydrophilic and hydrophobic interaction.<sup>[147]</sup> This interpretation can be confirmed by the different morphologies of chitosan in solution or gel state. With low DA meaning that chitosan has high apparent charge density, it displays individual polymer coil state. When increasing the DA, the hydrophobicity increases simultaneously, the amphiphilic chitosan will aggregate to bead, leading to a gel state through a “continuum” of structural

analogies because of the hydrophobic interactions.<sup>[147]</sup> Concentration is also important for the formation of hydrogels. It was found that chain entanglement could occur when the initial chitosan concentration is above the critical concentration, leading to the formation of self-crosslinked hydrogels.<sup>[96]</sup>

## Physically crosslinked chitosan-based hydrogels

Chitosans can be self-crosslinked even without any organic solvent or crosslinking additives, which may be toxic for medical applications. Bulk hydrogels are formed with an increase in the pH ( $> 6.3$ ) with strong bases (e.g., NaOH or ammonium hydroxide [ $\text{NH}_4\text{OH}$ ]) because of the microcrystalline physical crosslinking induced by Van der Waals interactions and hydrogen bonds during neutralization.<sup>[148]</sup> Additionally, chitosan<sup>[16,149]</sup> or even chitin without derivatization<sup>[150,151]</sup> could dissolve in base/urea aqueous solution. High-strength hydrogels bearing nanofibrous architecture have been fabricated through the freezing–thawing process.<sup>[16,149]</sup> Recently, small-angle light scattering measurements and confocal laser scanning microscopy observations were employed to evaluate the microstructure of chitosan hydrogels during the neutralization of chitosan aqueous solutions. The microstructure is continuous and it experiences three structural transition zones from the surface to the bulk: primary membrane, oriented tubular capillaries, and micro-range porous microstructures.<sup>[152]</sup> Self-crosslinked chitosan hydrogels have been prepared via freeze–melting–neutralization method under mild conditions.<sup>[153]</sup> This process could avoid the usage of a strong base, which needs to wash out after gelation. In addition, coordination complexes between metal ions and  $-\text{OH}$  as well as  $-\text{NH}_2$  groups in the chitosan chains have been applied to prepare hydrogels, which exhibited multistimuli responsiveness (e.g., pH, chemical redox reaction, and anions) because of the reversible coordination interaction.<sup>[20,154]</sup> This gelation process is ultrafast, which could in situ form free-standing objects.<sup>[20]</sup> When hydroxyl radicals or hydrogen peroxide presented in the supramolecular hydrogels, they underwent depolymerization, leading to the release of zinc ions from the hydrogels.<sup>[155]</sup>

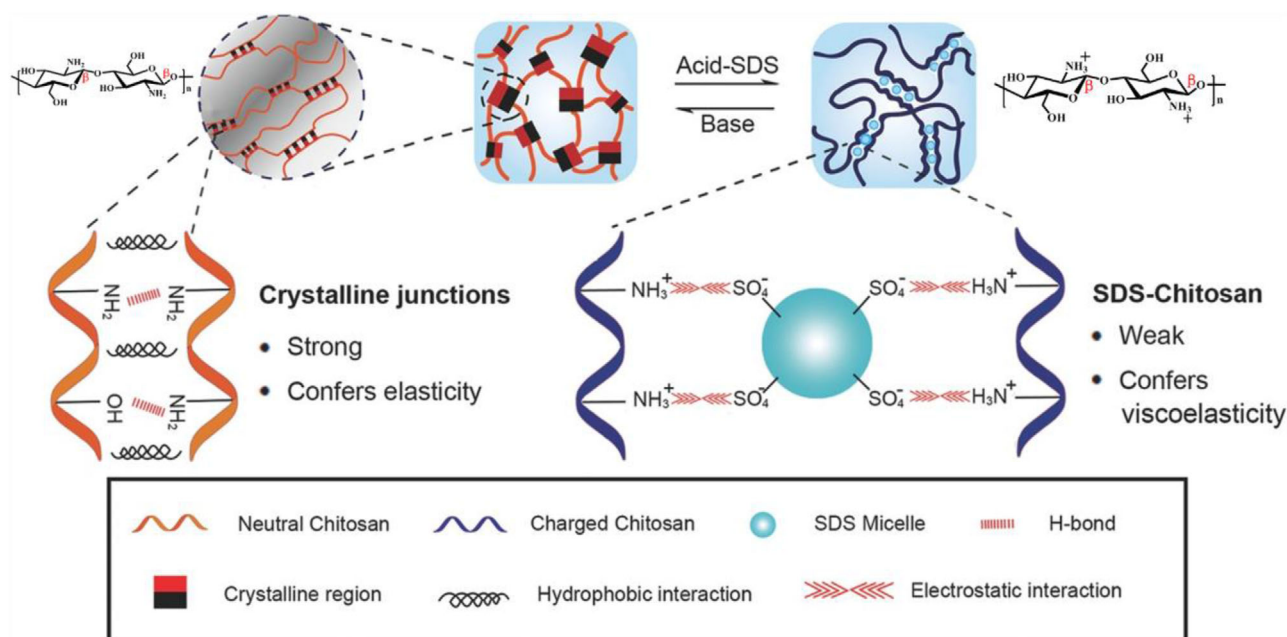
Additionally, electrostatic interaction is another technique that has been widely utilized to fabricate chitosan hydrogels. As mentioned above, the protonation of amine groups in chitosan will repel each other electrostatically to promote polymer solvation. The chitosan polycations could serve as multifunctional crosslinkers, which undergo electrostatic crosslinking with suitable oppositely charged molecules.<sup>[156]</sup> It is worth noting that concentration, anionic crosslinker types (e.g., polyelectrolytes or small molecules), as well as concentration and degree of substitution of chitosan derivatives, could affect the behavior of the gelation. TPP has already been used to crosslink alginate. However, inhomogeneous gels with anisotropic mechanical properties were usually formed arising from the quick interaction with amino groups.<sup>[157,158]</sup> To tackle this issue, it is necessary to suppress the local saturation of chitosan binding sites. The slow diffusion-based technique was employed to engineer homogeneous hydrogels by immersion in TPP–NaCl–glycerol solution.<sup>[159]</sup> In addition, other small molecules such as citric acid,<sup>[160]</sup> and gallic acid<sup>[161]</sup> have also been utilized to

crosslink chitosan. In particular, the citric acid–coordinated chitosan could convert into covalently crosslinked hydrogels facilitated by catalysts.<sup>[160]</sup>

Apart from small molecules, polyanions have also been extensively applied to crosslink chitosan. Natural polymers (e.g., CMC,<sup>[162]</sup> sodium alginate,<sup>[163]</sup> hyaluronic acid,<sup>[164]</sup> and pectin<sup>[165]</sup>) are intrinsic negative charged macromolecules. Different from low-molecular-weight crosslinkers, the properties (e.g., mechanical property, swelling behavior, and crosslinking density) could be readily manipulated by tuning the charge ratio of the added components.<sup>[96]</sup> Additionally,  $\text{Ca}^{2+}$  ions could be introduced to form a second physical crosslinking network, imparting the hydrogels with significantly better mechanical properties.<sup>[163]</sup> Furthermore, synthetic poly( $\gamma$ -glutamic acid)<sup>[166]</sup> and PAA<sup>[167]</sup> have been used to fabricate composite hydrogels through electrostatic interaction. Similarly, directly mixing native charged polymers with chitosan will also encounter the inhomogeneity issue due to the difficulty in controlling the polyanions diffusion to fabricate homogeneous hydrogels. In situ polymerization of anionic monomers as a simple and convenient way could address this problem.<sup>[167]</sup> Due to the reversible electrostatic interaction, the resultant hydrogels exhibited excellent injectable and formable properties.<sup>[168]</sup> In addition, the quick combination between the two ions, making it possible to in situ prepare hydrogels. Both these characteristics facilitated the fabrications of composite hydrogels with the 3D printing technique.<sup>[165,169]</sup> Sometimes, nanofillers (e.g., graphene oxide,<sup>[170]</sup> or polypyrrole<sup>[171]</sup>) were introduced into the system to improve the mechanical properties.

Mixtures of chitosan and negatively charged surfactants have attracted particular attentions in many fields because of the more complex self-assembly behaviors of surfactants.<sup>[146]</sup> The concentration of surfactants significantly influences the morphologies of the negative charged surfactant/polyelectrolyte mixtures.<sup>[172]</sup> Very recently, micelle-tailored mechanical properties of chitosan hydrogels were reported. Chitosan carries protonated amine at low pH, thus the resulting cationic polyelectrolyte could be crosslinked by negative-charged micelles (formed by anionic surfactant sodium dodecyl sulfate [SDS]) through electrostatic attraction (Figure 8).<sup>[22]</sup> This electrostatic crosslinking imparts the hydrogel with viscoelastic properties. Whereas the amine deprotonated at high pH, electrostatic interactions between SDS and chitosan became weak, but the emergence of crystalline network junctions resulting from hydrogen bonding and hydrophobic interaction is achieved via self-assembly.<sup>[173]</sup> These strong crystalline junctions endow hydrogel with high elasticity. The competing crosslinking mechanisms tuned by pH could be readily implemented to repeatedly reconfigure the mechanical properties of hydrogels.<sup>[22]</sup>

Other strategies on basis of hydrogen bonding or host–guest interactions for in situ preparation of physically crosslinked chitosan hydrogels have also been developed. These strategies provide controllable gelation and gel swelling behaviors. PVA could form hydrogen bonding with polysaccharide-based polymers (i.e., cellulose,<sup>[59]</sup> alginate,<sup>[122]</sup> and chitosan<sup>[174]</sup>) to prepare composite hydrogels. Therefore, PVA could also interact with chitosan through hydrogen bonding.<sup>[175]</sup> When a third component (e.g., lignin) was blended with PVA and chitosan,



**FIGURE 8** Switchable crosslinking of chitosan hydrogels. The neutral polysaccharide self-assembles to form strong noncovalent crystalline network junctions that confer elasticity. The cationic polysaccharide can be electrostatically crosslinked by SDS micelles that are healable and thus confer viscoelasticity. Reproduced with permission.<sup>[22]</sup> Copyright 2017 John Wiley & Sons Inc

mechanical properties could be significantly improved.<sup>[176]</sup> Host–guest interactions have been previously documented in the preparation of cellulose-based hydrogels with CB[8] as a crosslinker.<sup>[23,65]</sup> Recently, this strategy was extended to prepare chitosan-based nanogels.<sup>[177]</sup> Phenylalanine (Phe) was grafted onto chitosan, in which strong inclusion complexations between CB[8] and two pendant Phe moieties facilitated the formation of nanogels. The resulting gels exhibited excellent biocompatibility and selective cytotoxicity against a therapeutic target.<sup>[177]</sup>

## Chemically crosslinked chitosan-based hydrogels

Unlike physical crosslinking, the introduction of chemical crosslinking may provide good mechanical properties for chitosan hydrogel and allow the formation of chitosan hydrogels with homogeneous structure, making them promising candidates for long-term applications.<sup>[156]</sup> ECH prefers to react with hydroxyl groups and it has been used to crosslink chitosan hydrogels.<sup>[178]</sup> Additionally, other crosslinkers such as ethylene glycol diglycidyl ether<sup>[179]</sup> and genipin<sup>[180]</sup> are more easily to be attacked by active amino groups of chitosan, forming 3D network structure. Moreover, chitosan inherits plenty of amine groups in the backbone during the deacetylation process, which can highly react with aldehyde forming dynamic imine bonds via Schiff base condensation reaction at room temperature. By far, the most common crosslinkers for preparing chitosan hydrogels are formaldehyde,<sup>[181]</sup> poly(ethylene glycol) dialdehyde,<sup>[175]</sup> and glutaraldehyde<sup>[182]</sup>. Among those aldehyde crosslinkers, glutaraldehyde is the most used to crosslink chitosan to fabricate hydrogels. During the crosslinking, chitosan catalyzed the polymerization of glutaraldehyde, followed by forming Schiff's bases with amine groups in chitosan.<sup>[183]</sup> It should be noted that cellulose and alginate could be oxidized to carry

aldehyde groups, thus they have been used as crosslinkers to engineer natural hydrogels via Schiff base reaction.<sup>[184,185]</sup> In addition, chitosan can be chemically modified through reactions of its amino groups, thus other functional groups were grafted, which could undergo crosslinking reactions. For instance, thiol-functionalized chitosan could form disulfide bonds between two thiol groups to enhance the intermolecular crosslinking.<sup>[186]</sup> Apart from that, azide-,<sup>[187]</sup> furan-,<sup>[188]</sup> norbornene-functionalized chitosan<sup>[189]</sup> have been synthesized without changing the skeleton structure, which could experience rapid gelation via highly efficient click reactions (i.e., azide-alkyne, D-A, and thiol-ene reactions), respectively. Those chemical reactions could increase mechanical performances and chemical stability of the network, however, the crosslinkers prefer to react with amino groups of chitosan, which compromises the adsorption properties for wastewater treatment.<sup>[190]</sup>

The directly chemical crosslinking with small molecular crosslinkers decreases the accessibility of internal reactive sites of the chitosan beads, lowering the flexibility of chitosan hydrogel. To alleviate this effect, tremendous efforts have been made to decrease the crosslinking density, leaving other functional groups for further chemical modifications.<sup>[156]</sup> The grafting method and its procedure parameters may affect the grafting density. Grafting of water-soluble monomers on chitosan through free radical polymerization induced by potassium persulfate has been frequently employed to prepare chitosan hydrogels.<sup>[191]</sup> Similar mechanisms to those of potassium persulfate initiation,  $\text{Ce}^{4+}$ -initiated grafting on chitosan has also been employed to fabricate pH-responsive polyampholyte hydrogels.<sup>[192]</sup> In particular, radiation-induced crosslinking does not require any additives compared to other chemical crosslinking approaches, thus the final obtained hydrogels only contain polymer.<sup>[75]</sup> Moreover, radiation usually occurs in a shorter reaction time with lower cost, which is a promising method in the fabrication of materials for biomedical applications. This approach has also been



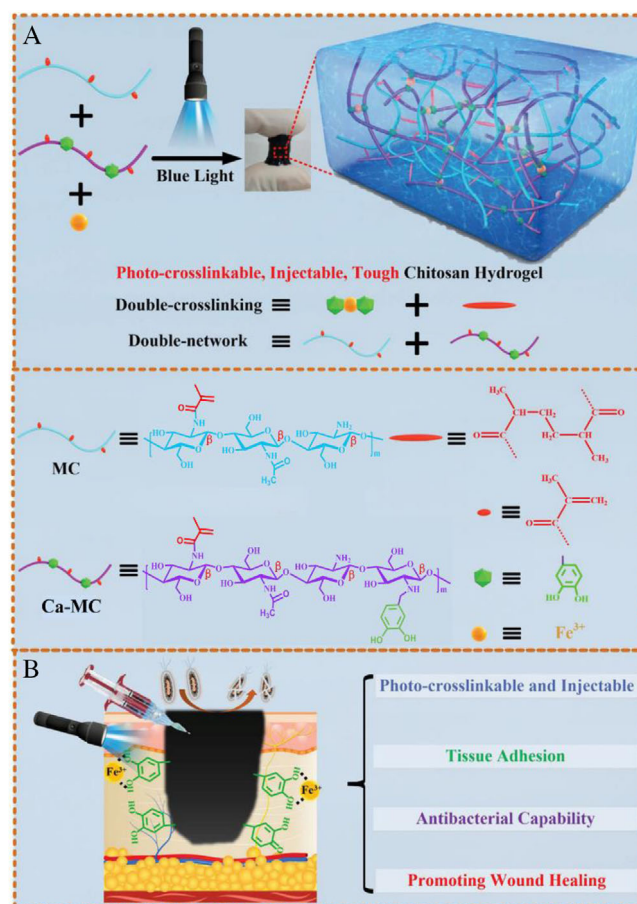
employed to develop antimicrobial chitosan-based hydrogel wound dressing containing poly(N-vinyl pyrrolidone) and lactic acid.<sup>[193]</sup>

## Double-network chitosan-based hydrogels

As mentioned above, double-network hydrogels with excellent mechanical performances have been achieved in cellulose- and alginate-based materials, in which the physical crosslinking could dissipate energy efficiently and reversibly reorganize to impart excellent fatigue resistance properties.<sup>[6]</sup> For instance, short-chain chitosan could improve the mechanical properties of PAM hydrogels that was constructed by copolymerization of AM and MBA because of the hydrogen bonding between chitosan and PAM network. When these composite hydrogels were immersed in the base solution, the microcrystalline physical crosslinks induced by deprotonation of amine groups were achieved, leading to transparent double-network hydrogels.<sup>[194]</sup> Meanwhile, treating the composite hydrogels with saline solution, the salting-out effect shielded the electrostatic repulsions, which resulted in a chain-entanglement network because of the intermolecular aggregations of hydrophobic chitosan chains, thus opaque double-network hydrogels were achieved.<sup>[194]</sup> Thereafter, force-sensitive double-network hydrogels were constructed by in situ polymerization of the PAM network and polyaniline in swelling chitosan microspheres.<sup>[195]</sup> The PAM network was interpenetrated with the stiff chitosan nanofibers, forming double-network hydrogels, and the polyaniline was bonded to the PAM network and chitosan nanofibers to form the multi-interpenetrating network structure in the chitosan microspheres. The resulting conductive hydrogels showed high sensitivity and rapid response speed for subtle pressures.<sup>[195]</sup> Very recently, catechol-functionalized methacryloyl chitosan (Ca-MC) and methacryloyl chitosan (MC) were used as components to fabricate double-network hydrogels via simultaneous crosslinking of vinyl bonds on celluloses induced by photo-initiated polymerization and catechol- $\text{Fe}^{3+}$  chelation (Figure 9).<sup>[196]</sup> The interpenetrated networks of two chitosan chains endow the hydrogels with superior mechanical performances. In addition, the hydrogels exhibited strong tissue adhesion, and antibacterial property as well as wound healing ability due to the functional groups (e.g., amino, quinone, imidazole groups). The shear strength (18.1 kPa) to porcine skin is sixfold that of clinically established Fibrin Glue.<sup>[196]</sup>

## CD-based hydrogels

CDs are a family of cyclic oligosaccharides connected by  $\alpha$ -1,4-glucosidic bonds.<sup>[197–199]</sup> They could be classified as  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD on basis of the number of  $\alpha$ -glucose units of 6, 7, and 8, respectively. CDs have many fascinating properties due to their intrinsic characteristics. The CD surfaces have plenty of hydroxyl groups, which display different reactivity because of the anisotropic steric environment. The primary hydroxyl groups with high reactivity locate at the exterior surface of the upper rim, whereas the less reactive secondary hydroxyl groups are in the lower rim.<sup>[197]</sup> This characteristic endows CDs with high selectivity for



**FIGURE 9** (A) Schematic illustration for a novel design of chitosan hydrogel formation by crosslinking two different chitosan chains via simultaneous polymerization of carbon-carbon double bonds and catechol- $\text{Fe}^{3+}$  chelation. (B) The multifunctional characteristic of photocrosslinkable ability, injectability, enhanced tissue adhesion, and antibacterial capability of chitosan hydrogels allow wound healing. Reproduced with permission.<sup>[196]</sup> Copyright 2020 John Wiley & Sons Inc

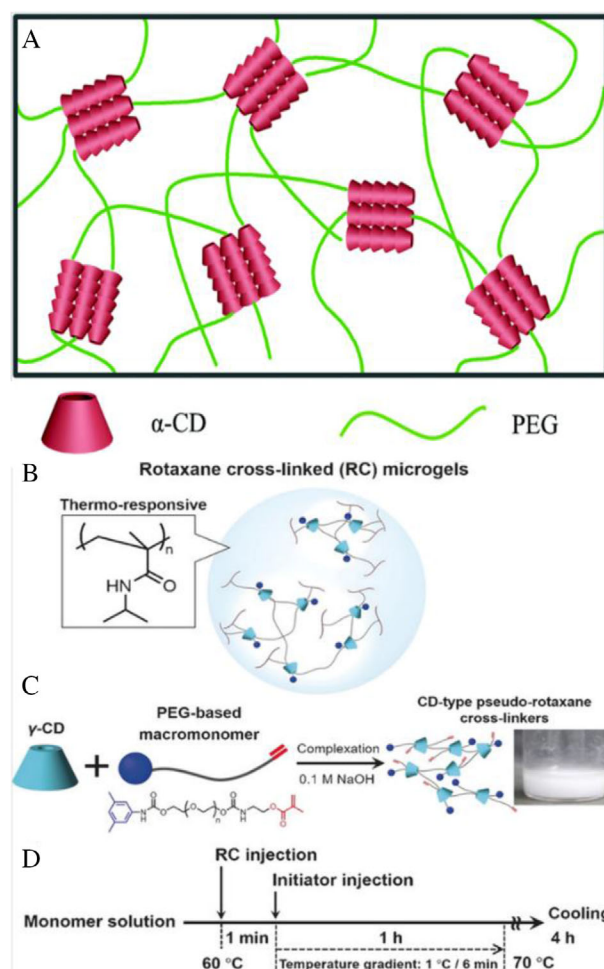
modification. For instance, multimiktoarm star copolymers composed of 14 arms of one type polymer and seven arms of another type of polymer with  $\beta$ -CD as core have been prepared via a two-step modification.<sup>[200,201]</sup> In addition, CDs have hydrophobic cavities which could serve as hosts to accommodate various guest molecules on basis of CD types,<sup>[197]</sup> or just be threaded by polymer chains.<sup>[202]</sup> Notably, the host–guest interaction is reversible and remains stable in aqueous solution. Both two characteristics are favorable for the preparation of CD-based hydrogels. Based on the intrinsic characteristics of CDs, they can be introduced into hydrogels with different manners, three types of CD-based hydrogels are fabricated till now, that is, CD-cored hydrogels, CD-threaded hydrogels, and CD-capped hydrogels.<sup>[24]</sup>

As CDs have an abundance of hydroxyl groups, which can be readily converted into initiator sites via esterification, thus they provide promising core moiety for the preparation of star-like polymers. CD-cored star-like polymers have been extensively explored with different compositions and properties.<sup>[203–207]</sup> Even though star-like polymers exhibit special topological architecture and lower hydrodynamic size in comparison with their linear counterparts,<sup>[208]</sup> they have rarely been employed for the preparation of hydrogels, which may probably due to the difficult and complicated synthetic process of star-like hydrogels.<sup>[209–211]</sup> Three-arm star-like

copolymer composed of  $\beta$ -CD center and temperature-responsive arms of poly(*N*-isopropyl acrylamide)-*b*-poly(*N*, *N*-dimethyl acrylamide) (PNIPAM-*b*-PDMA) were prepared via reversible addition-fragmentation chain transfer (RAFT) polymerization.<sup>[212]</sup> Upon thermal stimulus, free-standing hydrogels were rapidly formed at sufficiently high concentration because of the occurrence of intermicellar bridging from PDMA blocks. The hydrogels exhibited big potential in vivo drug/gene delivery.<sup>[212]</sup> Very recently, simultaneously polymerization and grafting of NIPAM and methacrylic acid as well as ethylene glycol diacrylate (EGDA) moieties on pristine  $\beta$ -CD induced by azobisisobutyronitrile were achieved, the resulting pH and thermo-responsive hydrogels exhibited noncytotoxic nature toward MG-63 cell lines.<sup>[213]</sup>

As mentioned above, CDs threaded on the polymer chains driven by inclusion complexation, forming CD-based polyrotaxane followed by end-capped with bulky molecules.<sup>[24,202]</sup> The critical point of forming polyrotaxane is the size matching of CD cavities and polymer chains. It is noteworthy that the molecular weight of the polymer chain may affect the inclusion complexation.<sup>[24]</sup> Particularly, when the  $\alpha$ -CDs of PEG-based polyrotaxane are covalently crosslinked, they form hydrogels that are topologically interlocked by figure-of-eight crosslinks.<sup>[7]</sup> Recently, amino-functionalized  $\beta$ -CD was threaded onto poly(propyleneglycol)bis(2-amionopropylether) (PPG-NH<sub>2</sub>) to obtain pseudorotaxanes, which could be crosslinked by negatively charged clay nanosheet (LAPONITEs XLG) via electrostatic forces. The resulting composite hydrogel exhibited self-healing and good adsorption properties.<sup>[214]</sup> However this crosslinking process is complicated, limiting its potential applications.

Supramolecular hydrogels based on the inclusion complexation have attracted a wide range of interests due to their fascinating properties (e.g., thixotropy and self-healing).<sup>[24]</sup> Till now, the extensively studied system is  $\alpha$ -CD-based hydrogels, because  $\alpha$ -CD has a smaller interior cavity, in which only one PEG or poly( $\epsilon$ -caprolactone) (PCL) chain can thread to form inclusion complexes, whereas poly(propylene oxide) (PPO) could not form inclusion complexation due to its large size.<sup>[24]</sup> For instance, linear PEG could penetrate the inner cavity of  $\alpha$ -CD in aqueous solutions, and the  $\alpha$ -CD moieties on the polymer chains could form channel-type crystal structure due to intermolecular hydrogen bonding among  $\alpha$ -CDs. The resulting  $\alpha$ -CD/PEG domains became hydrophobic and served as the physical crosslinking points through hydrophobic interactions, while the uncovered PEG part was hydrophilic and worked as the connecting chain, thus leading to the formation of hydrogels (Figure 10(A)).<sup>[24,215]</sup> More interestingly, adding competitive guest azobenzene (Azo) compound will replace PEG units to form complexes, leading to gel to sol transition. Whereas the system forms the gel state again under UV irradiation because trans-Azo transfers into cis-Azo and its release from the complexes, leading to the recombination of PEG<sup>24</sup> and  $\alpha$ -CDs.<sup>[216]</sup> Similarly, amphiphilic block copolymers such as poly(L-glutamic acid)-*b*-poly(ethylene oxide) (PLG-*b*-PEO),<sup>[217]</sup> and PEO-*b*-PPO-*b*-PEO (Pluronic F127),<sup>[218]</sup> could form hydrogels through the synergy of inclusion complexation between  $\alpha$ -CD and PEO blocks as well as aggregation of hydrophobic blocks. In addition, PEO-grafted poly(organophosphazenes)



**FIGURE 10** (A) Schematic illustration of the formation of supramolecular hydrogel based on  $\alpha$ -CD and PEG. Adapted with permission.<sup>[24]</sup> Copyright 2018 Royal Society of Chemistry. (B) Schematic illustration of (B) rotaxane-crosslinked (RC) microgels, (C) a cyclodextrin-based pseudorotaxane crosslinker, and (D) the procedure for the modified precipitation polymerization for RC microgels. Adapted with permission.<sup>[220]</sup> Copyright 2017 John Wiley & Sons Inc

could also form hydrogel with  $\alpha$ -CD in aqueous solution due to inclusion complexation.<sup>[219]</sup> It should be noted that  $\beta$ -CD could not form inclusion complexation with PEG, but also with PCL or PPO, whereas  $\gamma$ -CD could thread two PEG or PCL chains simultaneously.<sup>[24]</sup> For example, two PEG-based terminal bulky macromonomers could penetrate  $\gamma$ -CD, then they could copolymerize with NIPAM monomer, forming rotaxane-crosslinked (RC) microgels.<sup>[220]</sup> The microgels exhibited thermo- and pH-responsive volume transitions because of the thermos-responsive PNIPAM block and mechanical cross-linking points that arising from changeable rotaxane networks (Figure 10(B)).<sup>[220]</sup>

The CD moieties can be introduced in polymer chain ends or as pendant functional groups in monomers, leading to the preparation of CD-capped polymers. When a second component was employed to crosslink the CD-capped polymers, CD-containing hydrogels could be readily achieved. On the basis of this consideration, host-guest interaction is extensively exploited to prepare supramolecular hydrogels. The driving forces for this interaction are hydrophobic and van der Waals interactions between the interior cavity of CDs and hydrophobic guest. Notably, the binding constant of

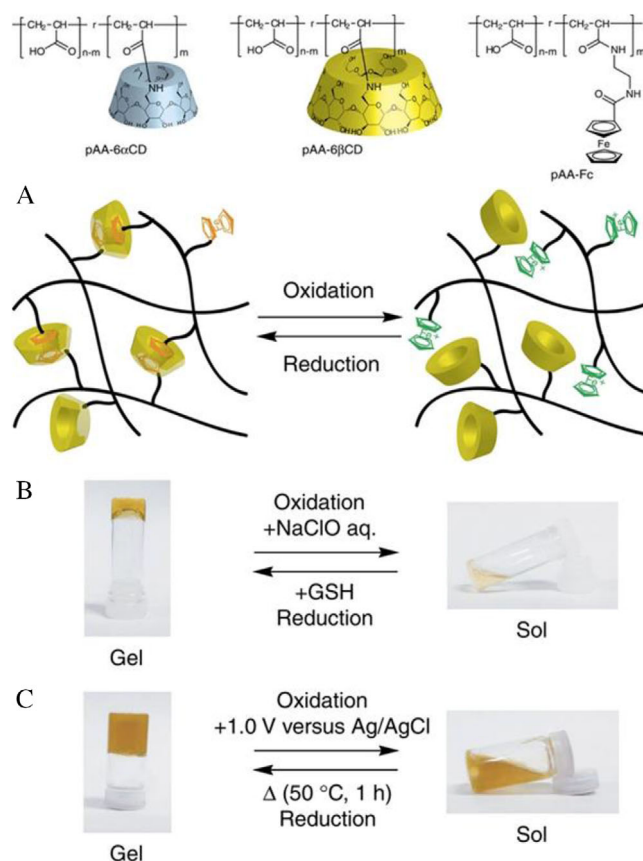


host–guest complexes is highly dependent on the size matching of guest molecules and CD cavity, as well as environmental conditions.<sup>[221]</sup> In addition, with the structural tunability of host–guest complexes by the external environment, the binding abilities of the host–guest pairs will be changed simultaneously, leading to dissociation of the complexes, thus endows the complexes with stimuli-responsive properties. Among the three types of CDs,  $\beta$ -CD is the most widely studied due to its suitable interior cavity to most guest molecules and its low cost.<sup>[222]</sup> The frequently used guest molecules, such as adamantane (Ad), azobenzene (Azo), ferrocene (Fc), and cholic acid, could form host–guest pairs with  $\beta$ -CD in aqueous solution.

As the primary hydroxyl groups could be selectively transformed into the mono-amino-substituted CD, then, the acrylamido-CD monomer could be achieved through amidation reaction.<sup>[223]</sup> It should be noted that multivinyl bonds can be attached on CDs, thus they can serve as multifunctional crosslinkers for chemical crosslinking.<sup>[224]</sup> Therefore, these pendent CD groups have been incorporated into the polymer chain as molecular recognition moieties for host–guest interactions. Similarly, guest moieties have also been introduced into different polymer architecture through post- or premodification. Mixing these two different polymers, they could in situ form hydrogels through host–guest interaction.<sup>[197]</sup> As mentioned above, external stimuli (e.g., pH, light, redox, and temperature) could induce the dissociation of host–guest complexes, leading to the formation of stimuli-responsive hydrogels that could be used for biomedical applications.<sup>[24]</sup>

Acrylamide-based hydrogels bearing CD moieties are the most widely studied system, which could be prepared via free radical polymerization. For instance, host hydrogels were synthesized by copolymerization of AM, CD-functionalized acrylamide and crosslinker in one pot. Guest hydrogels consist of different guest moieties (e.g., Ad, *n*-butyl (*n*-Bu), and *t*-butyl (*t*-Bu)) were prepared similarly.<sup>[225]</sup> All the hydrogels are labeled with different colors. When these hydrogels were mixed and shaken in a dish,  $\beta$ -CD-gels prefer to bind with Ad-gels and *t*-Bu-gels due to the specific host–guest recognition, whereas  $\alpha$ -CD-gels preferentially adhere with *n*-Bu-gels. Particularly, the firmly adhered hydrogels from  $\beta$ -CD-gels and Ad-gels are strong enough to stand up without broken because of the higher binding affinity between  $\beta$ -CD and Ad moieties.<sup>[225]</sup> This method has been extended to synthesize stimuli-responsive hydrogels. For example, Azo moiety was introduced into the hydrogels to prepare Azo-gels, they could assemble with  $\beta$ -CD-gels, photoirradiation with 365 nm light led to the dissociation of assembled hydrogels,<sup>[226]</sup> or macroscopic deformations in both size and shape of hydrogels.<sup>[227,228]</sup> In another case, ferrocene-based hydrogels (Fc-gels) mixed with  $\beta$ -CD-gels, aggregation between them was observed. However, when it oxidized into ferrocenium cation ( $\text{Fc}^+$ ) with ceric ammonium nitrate, the resulting  $\text{Fc}^+$ -gel could not adhere with  $\beta$ -CD-gels, but react with poly(sodium styrenesulfonate)-containing gels as a result of the electrostatic interactions.<sup>[229]</sup> However, covalent crosslinking was incorporated in this type of hydrogels, they display limited self-healing properties.

Notably, the CD-containing polymers can serve as multifunctional crosslinkers, they can coordinate with guest-containing polymers to form supramolecular hydrogels. This reversible host–guest interaction endows hydrogels with



**FIGURE 11** (A) Chemical structures of the host polymers and the guest polymer, and schematic illustration of sol–gel transition. (B) Sol–gel transition experiment using chemical reagents. (C) Sol–gel transition experiment using electrochemical reactions. Electrochemical oxidation (+1.0 V versus Ag/AgCl) transformed the hydrogel into the sol, whereas reduction recovered the gel. Adapted with permission.<sup>[230]</sup> Copyright 2011 Nature Publishing Group

self-healing properties.<sup>[221]</sup> Tremendous efforts have been devoted to developing self-healing hydrogels. For example, amino-CDs and aminoethylamide Fc were partially grafted onto linear PAA through amidation reaction, leading to the formation of host polymers (PAA-CDs) and guest polymer (PAA-Fc), respectively (Figure 11).<sup>[230]</sup> Mixing these two polymers (PAA-6 $\beta$ CD/PAA-Fc) in buffer solution, hydrogels were formed immediately because of the host–guest interactions between  $\beta$ -CD and Fc as well as the multipoint crosslinks in the polymers, and they exhibited excellent self-healing properties.<sup>[230]</sup> Whereas PAA-6 $\alpha$ CD could not form gelation with PAA-Fc because of the mismatching of  $\alpha$ -CD and Fc moieties. As the Fc could be oxidized into  $\text{Fc}^+$ , the resulting hydrogels exhibited sol–gel transition under chemical reagents (i.e., NaClO for oxidation and glutathione [GSH] for reduction), or electrochemical reactions (Figures 11(B) and 11(C)).<sup>[230]</sup>

However, the mixture of CD-containing host polymer and Azo-containing guest polymer could not form hydrogels, this may ascribe to the low content of host and guest moieties as well as flexible PAA chain.<sup>[231]</sup> Nonetheless, when using rigid curdlan to substitute the PAA chain, and CDs were attached to all repeating units in the polymer chain, it could form hydrogel with the same Azo-containing guest polymer.<sup>[232]</sup> Similarly, cholic acid- and  $\beta$ -CD-containing polymers could also form hydrogels with equimolar host



and guest moieties,<sup>[233]</sup> and it exhibited CO<sub>2</sub> responsiveness resulting from the competitive guest molecule (i.e., benzimidazole).<sup>[234]</sup> Besides the commonly applied guest molecules, the isopropyl group in NIPAM could serve as the guest component to complex with  $\beta$ -CD through host–guest interaction.<sup>[235]</sup> In addition, the introduction of conductive CNT or graphene could endow hydrogels with near-infrared (NIR) light-responsive property because of the transformation from NIR light to heat.<sup>[235,236]</sup> Furthermore, CDs can be crosslinked by ECH in alkaline media to form polycyclodextrins,<sup>[237–239]</sup> or dimer,<sup>[240]</sup> which can act as multifunctional crosslinkers, when mixing with guest-containing polymers, supramolecular hydrogels are readily obtained through host–guest interactions.

## APPLICATIONS OF POLYSACCHARIDE-BASED HYDROGELS

### Self-healing hydrogels

Hydrogels with controlled structure and mechanical performances have attracted tremendous interests in the field of self-healing materials.<sup>[241]</sup> With the self-healable properties, polysaccharide-based hydrogels should be capable of reconstructing their structure and functionality from damage, which could facilitate the optimization of integrated functions of hydrogels with good safety, reliability, and durability.<sup>[242]</sup> Self-healing hydrogels could be divided into external stimulus self-healing and autonomous self-healing depending on the healing behaviors. The former strategy needs stimuli such as heat, UV light, and other self-healing agents to trigger the healing process. While the later one is based on the dynamic covalent bonds or noncovalent interactions (e.g., hydrogen bonding, ionic interaction, host–guest interactions, and hydrophobic interactions) to repeatable self-heal the materials.<sup>[243]</sup> The noncovalent bonds not only serve as recombination moieties for self-healing but also act as sacrificial bonds to increase the toughness. Polysaccharides (i.e., cellulose, alginate, and chitosan) have abundant hydroxyl groups on backbones, which could form hydrogen bonding with other polymer such as PVA to form self-healing composite hydrogels.<sup>[62,63,124]</sup> When TA was employed to modify the CNCs, mussel-inspired hydrogels with high mechanical self-healing properties via extensive multihydrogen bonding were achieved.<sup>[63]</sup>

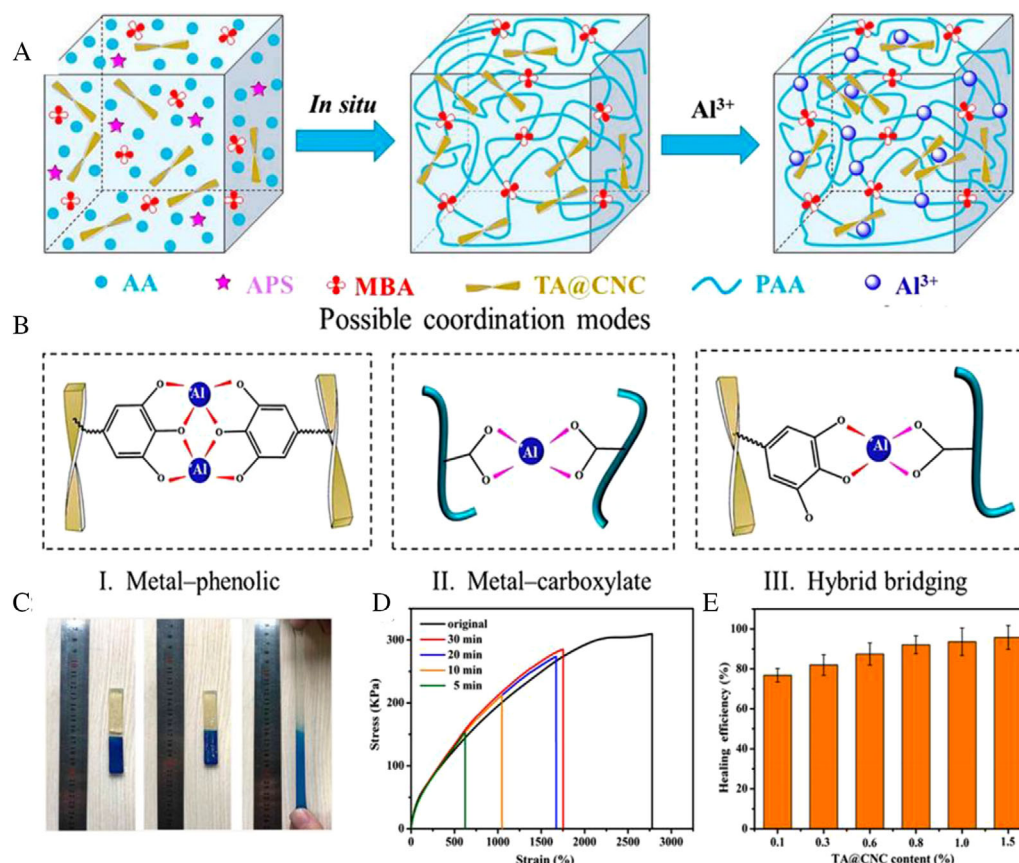
Moreover, dynamic boronate ester bonds between PVA and TA@CNC synergistically combining with hydrogen bonding has also been utilized to mimic biological tissues with fast self-healing properties.<sup>[64]</sup> Ionic coordination is also extensively used to synthesize self-healing hydrogels especially the presence of acid groups on polysaccharides or their derivatives. Strong, tough, and self-healable hydrogels were fabricated by incorporating CMC into PAA-Fe<sup>3+</sup> hydrogels followed by simply immersion in NaCl solution to form more ionic interactions because of the salting-out effect.<sup>[244]</sup> Host–guest interaction shows specific recognition between motifs, this could facilitate the selectivity and recombination, leading to a fast self-healing process. For instance, supramolecular hydrogels based on three-component recognition by CB[8] binding were fabricated, in which the modified PVA bridges the CNC-grafts together in the present of CB[8]

via host–guest interaction. The hydrogels exhibited rapid self-healing even upon aging for several months.<sup>[23]</sup> CD-based host–guest interactions (e.g., CD-Ad,<sup>[245]</sup> CD-Fc,<sup>[230]</sup> CD-cholic acid,<sup>[233]</sup> and CD-Azo<sup>[237]</sup> pairs) have also been used to prepare self-healing hydrogels with healing efficiency higher than 90%. Moreover, self-healing hydrogels based on dynamic covalent chemistry (e.g., D-A reaction,<sup>[88,134,246]</sup> boronate ester bonds,<sup>[59,64,102,128]</sup> disulfide moieties,<sup>[84,186]</sup> and imine bonds<sup>[184,185,247]</sup>) have also been extensively exploited to produce self-healing hydrogels due to the easy modification of polysaccharides.

Among these contributions, self-healing time is more valued than whether hydrogel is fully healed. It is difficult to simultaneously achieve both high mechanical properties and fast self-healing behavior. One possible approach to address this issue is by introducing multiple self-healing mechanisms to balance the effect of sacrificing mechanical properties on increasing self-healing efficiency. Recently, a tough, self-healing hydrogel was constructed by using TA-coated cellulose nanocrystals (TA@CNCs) and metal ions in PAA covalent polymer network (Figure 12).<sup>[62]</sup> The possible synergistic multiple interactions composed of metal–phenolic coordination between TA@CNCs, metal–carboxylate coordination between PAA chains, as well as hybrid bridging between TA@CNCs and PAA chains contribute to the high mechanical property (a strain of 2900%) and autonomous fast self-healing property with high efficiency (>95%).<sup>[62]</sup> In general, it is crucial to have a deep understanding of the self-healing mechanisms to have better control of the performances, which is important for further potential applications.<sup>[241]</sup>

### Sensors

Hydrogels could alter their volume significantly in response to certain alterations or stimuli. This behavior can transform into different output signals including chemical, physical, and electrical properties, which makes them promising candidates for sensors (such as pH sensors, chemical sensors, strain sensors, and pressure sensors).<sup>[3]</sup> The sensitivity of the sensor is dominated by the quantity changes from input to output. For a good sensor, it should be sensitive to objective property and insensitive to other performance.<sup>[3]</sup> When proper functional groups or conductive fillers were introduced into the polymer networks, the hydrogels will exhibit stimuli-responsive ability.<sup>[9,26]</sup> It is noteworthy that noncovalent interactions are weak and dynamic, thus they are sensitive to external environments, resulting in the fabrication of stimuli-responsive sensors. Polysaccharide-based hydrogels crosslinked by noncovalent interactions have been studied for preparing self-healing materials, therefore those hydrogels should also inherit the merits of noncovalent interactions for stimuli-responsiveness.<sup>[26]</sup> For instance, the stability of hydrogen bonding and ionic interactions significantly depends on the pH and temperature of the system. Under low pH conditions,<sup>[18,22]</sup> or low temperature,<sup>[19]</sup> the hydrogen bonding dominates the breaking and reconstruction of the percolating network in hydrogels, leading to the reversible sol–gel transformation. It was reported that pH values could also affect the formation of ionic interactions,<sup>[20]</sup> and imine bonds,<sup>[84]</sup> resulting in pH-responsive hydrogels. Moreover,

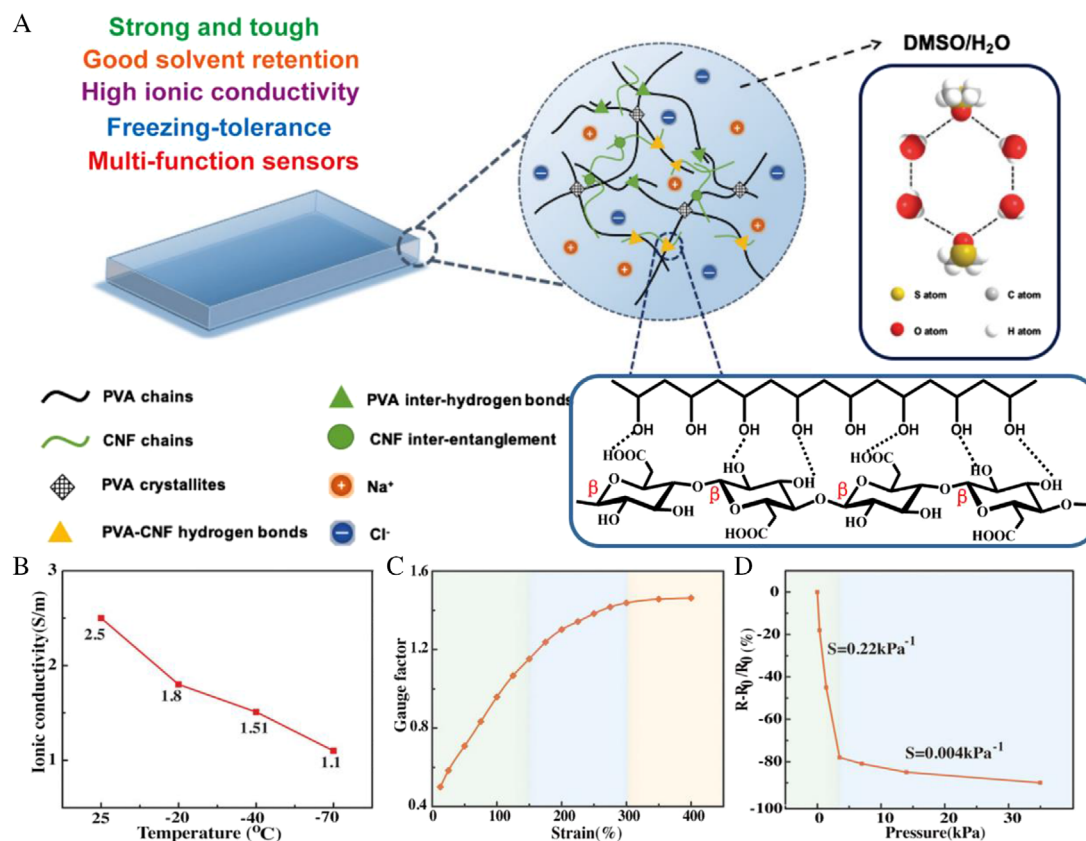


**FIGURE 12** (A) Schematic illustration of ionic gel synthetic process. (B) Possible coordination modes among TA@CNC, PAA, and  $Al^{3+}$  ions. (C) The ionic gel is cut into two pieces and recombined. Then the fractured gel can self-heal automatically into a complete gel and sustain stretching without failure after 30 min healing. (D) Typical stress-strain curves of the original and self-healed TA@CNC-0.8 ionic gels with different healing time. (E) Healing efficiency of ionic gels as a function of TA@CNC content after 30 min healing. Adapted with permission.<sup>[62]</sup> Copyright 2018 American Chemical Society

reduction and oxidation could induce the decomposition and regeneration of disulfide bonds with DTT and  $H_2O_2$ , thus resulting in redox-responsive hydrogel sensors with the reversible sol-gel transition.<sup>[84]</sup> Additionally, reversible electrochemical switching of the stiffness of redox-responsive hydrogels based on host-guest reactions has also been reported, in which the electrochemical oxidation triggered the formation of hydrophilic  $Fc^+$  moieties, leading to its decomplexation from the CD cavity.<sup>[229,230]</sup>  $CO_2$ -switchable self-healing hydrogels exhibited reversible sol-gel transition due to the dynamic host-guest complexation, which can be used for biochemical and biomedical gas sensor.<sup>[234]</sup> Furthermore, photoresponsive hydrogels based on photoisomerization of Azo moiety<sup>[216,232,248]</sup> or photoreduction of  $Fe^{3+}$  to  $Fe^{2+}$ ,<sup>[51,101,108]</sup> have also been employed to fabricate light sensors. The reversible transformation of *trans*-Azo to *cis*-Azo led to the formation and deterioration of CD-Azo host-guest complexes, whereas the photoreduction process is irreversible due to the release of  $CO_2$ . Stimuli-responsive hydrogels could be used to test environment changes, however most of them are based on transformation of stiffness, in which the mechanical properties would also be affected.

Flexible electronics mimicking the function of skins have been significantly developed for various applications.<sup>[249]</sup> Strain- and pressure-sensors are usually based on the change of electrical resistance on conductive hydrogels. The conductive hydrogels could be divided into electron-conductive and ion-conductive hydrogels.<sup>[9]</sup> Electron-conductive hydrogels are constructed by introducing conductive materials (e.g.,

carbon nanotube,<sup>[250]</sup> graphene,<sup>[251]</sup> metals,<sup>[252]</sup> and conductive polymers<sup>[195,253]</sup>) into the polymer networks. Their conductivity mainly results from the movable electrons through tunneling effect and contact effect, and it is weakly dependent on water content.<sup>[9]</sup> Nonetheless, the conductive materials are usually hydrophobic and it is difficult to homogeneously disperse in hydrogels. Whereas for the ion-conductive hydrogels, its conductive mechanism originates from the movement of ions in the networks, and their conductivity significantly depends on the water content.<sup>[254–257]</sup> It should be noted that polysaccharides are intrinsic polyelectrolytes (i.e., alginate<sup>[256]</sup> and CMC<sup>[254,257]</sup>), the resulting hydrogels exhibited good ionic conductivity without the addition of salt. However, ion-conductive hydrogels show lower sensitivity with gauge factor  $\sim 1$ –3 induced by geometrical changes than that of electron-conductive hydrogels during stretching.<sup>[9]</sup> For instance, cellulose/PVA composite hydrogel exhibited a linear relationship of relative resistance variation as a function of strain, with a gauge factor of 1.04 and a low-pressure detection limit of 14.7 Pa.<sup>[57]</sup> When conductive silver nano-materials were introduced through *in situ* reduction of  $Ag^+$  by reductive phenolic hydroxyls in TA@CNC/PVA hydrogels, the resulting hydrogels showed a higher gauge factor and relatively broad sensible range of strain (up to 400%).<sup>[252]</sup> However, the conventional hydrogels could freeze at subzero temperature, thus suppressing the ion movements in the network. In addition, ionic conductivity is also highly dependent on the mechanical properties. High strength will restrict the ion mobilities because of the tight network structure, leading



**FIGURE 13** (A) Schematic illustration of PVA-CNF organohydrogels formed in DMSO/H<sub>2</sub>O binary mixture. (B) Ionic conductivity of PVC-1%-CNF organohydrogels at 25, -20, -40, and -70°C. (C) The increase of the Gauge factor as a function of tensile strain. (D) Relative resistance change and pressure sensitivity of PVA-1%-CNF organohydrogel-based sensors at varying pressure. Adapted with permission.<sup>[257]</sup> Copyright 2020 John Wiley & Sons Inc

to low ionic conductivity. Very recently, ionic conducting hydrogel with high ionic conductivity and mechanical properties were fabricated via the sol-gel transition of PVA and CNFs in dimethyl sulfoxide (DMSO)-water binary mixture (Figure 13).<sup>[257]</sup> The composite organohydrogels exhibited stress of 2.1 MPa and strain of 400% with CNF content of 4 wt% arising from the synergistic effect (e.g., PVA hydrogen bonds, PVA-CNF hydrogen bonds, PVA crystalline domain crosslinking points, and CNF interentanglement) caused by DMSO/H<sub>2</sub>O solvent and reinforcing effect of CNFs. The conductivity of hydrogels could reach up to 1.1 S·m<sup>-1</sup> at -70°C resulting from the high dielectric constant of DMSO, and it remained transparent and flexible withstanding cyclic twisting, bending, and folding. Furthermore, the composite hydrogels displayed high sensitivity toward both tensile and compressive deformation and they could detect full-range human body movement with high stability and durability.<sup>[257]</sup>

## Energy storage and conversion

Hydrogels have been widely used in the field of energy storage and conversions such as batteries and supercapacitors.<sup>[258]</sup> Generally, energy storage devices are composed of electrodes and electrolytes, in which hydrogel can provide ionic conductivity, electrochemical activity, and flexibility due to its crosslinked 3D networks with interior spaces filled with aqueous electrolytes and high stability.<sup>[259]</sup> In addition, multiple functional groups (e.g., carboxyl acid groups) in hydrogels provides the capability to coordinate

with cations as anchoring points, thus achieving higher ionic conductivity for the electrolyte.<sup>[258]</sup> As for hydrogels for electrodes or binders in batteries, electronic conductivity is the main parameter to transport the ions involved in electrochemical reactions. Solid-state cellulose hydrogel electrolytes were fabricated by dissolving cellulose in concentrated ZnCl<sub>2</sub> solution, followed by in situ crosslinking with Ca<sup>2+</sup> ions,<sup>[19]</sup> and it exhibited high ionic conductivity of 74.9 mS·cm<sup>-1</sup>. The resulting zinc-ion hybrid supercapacitors displayed a high capacity of 193 mA·h·g<sup>-1</sup> and excellent stable cycle performance with 94.7% capacity retention.<sup>[259]</sup> To further improve the mechanical performances and stability of hydrogel electrolyte. Flexible and self-healable electro-conductive hydrogels were fabricated on the basis of PVA-borax (PVAB) and carbon nanotube-cellulose nanofiber (CNT-CNF) hybrid hydrogel that combines the conductivity of CNTs and template function of CNFs.<sup>[250]</sup> The obtained supercapacitor demonstrated better capacitance retention of ~98.2% for 10 damaging/self-healing cycles and ~95% for 1000 cycles under various deformation.<sup>[250]</sup> In addition, double-network hydrogels have also been used to fabricate cellulose-based electrolyte with high mechanical robustness even in the strong alkaline electrolytes (6 M KOH).<sup>[260]</sup> The -OH ions attached on sodium polyacrylate and cellulose chains via hydrogen bonding could facilitate the ion transport between the polymer chains, leading to the enhancement of conductivity. The obtained flexible zinc-air battery exhibited a high power density of 210.5 mW·cm<sup>-2</sup> upon being stretched to 800%.<sup>[260]</sup> Recently, carboxylated chitosan hydrogel film was used as gel polymer electrolyte



for supercapacitors, which exhibited high flexibility, high electrolyte absorption capacity, and high ionic conductivity because of the hydrophilic groups of carboxylated chitosan and its high compatibility with HCl electrolyte.<sup>[261]</sup> Mixing problems often existed in electrodes, which contained many inorganic materials such as carbon nanomaterials. Agglomerations of nanoparticles decreased the surface area and the conductivity path.<sup>[4]</sup> It should be noted that hydrogels could be used as templates for inorganic frameworks. For example, hierarchical oxygen-enriched porous carbon materials were synthesized by carbonizing the biopolymer composite consisting of sodium alginate and bacterial cellulose, as well as KOH activation at different temperature. The resulting supercapacitors exhibited excellent cycling stability with 93.8% capacitance retention after 10,000 cycles as a result of the synergistic effect of rich oxygen content and porous structure.<sup>[262]</sup>

## Biological applications

Polysaccharide-based hydrogels derived from renewable resources, have been extensively researched in the field of biomedical applications such as drug delivery, wound dressing, tissue engineering, and bioimaging, due to its intriguing properties (e.g., excellent biocompatibility, nontoxicity, degradability, and promotion of collagen deposition).<sup>[25,263]</sup> The properties of swelling behavior and pH sensitivity play a crucial role in hydrogel-based drug delivery systems. The drugs preloaded in the assembled network could be controllably released under external stimuli, and the release rate is highly dependent on the disassembling rate of the network.<sup>[123]</sup> It is worth noting that physical crosslinking usually results in fast release and uncontrollable delivery. For instance, CDs/PEG hydrogels show fast release kinetics due to the hydrophilic nature of PEG, which is not suitable for long-term drug release.<sup>[24]</sup> Introducing chemical crosslinking is an important strategy to regulate drug delivery and improve loading efficiency. Cellulose-based hydrogels crosslinked by dynamic imine bonds were fabricated, and drug-containing PEO-b-PDPA copolymer micelles were embedded in the hydrogels. The double encapsulations by micelle and polymer network suppress the leakage of drugs during the injection. Under low pH conditions, the micelle and network were disassembled, inducing the drug delivery.<sup>[264]</sup> Wound healing is a natural characteristic of skins to fix damaged tissues, and this phenomenon contains four important processes (i.e., coagulation, inflammatory, cell proliferation, and collagen fiber regeneration).<sup>[265]</sup> Polysaccharide-based hydrogels have the potential to provide an appropriate pH environment, humidity, oxygen pressure, and prevent microbial invasion. Novel platforms composed of TPP-crosslinked chitosan and  $\text{Ca}^{2+}$ -crosslinked alginate interpolymer complexes were developed to simulated wound fluid and whole blood. The resulting hydrogels exhibited enhanced water uptake, controlled degradation, improved cytocompatibility, and good mechanical properties, making them promising candidates for wound dressing.<sup>[110]</sup> Polymer hydrogels have some similarities with the soft tissues of the human body, such as 30%–80% water content, various mechanical properties.<sup>[25]</sup> However, some hydrogels cannot meet the high qualities of the soft tissues (including toughness, mechanical

strength, and so on). Thus, structure design and uniformity of hydrogels are important parameters in determining their applications. Injectable hydrogels based on dihydrazide-modified cellulose (CHO-CMC) and aldehyde-modified dextran via hydrazine crosslinks are reported.<sup>[85]</sup> Compared with unmodified CNC, CHO-CNCs could fill in cavities in any shape without preprocessing, and showed more elasticity and stability, resulting in a potential candidate for bone tissue engineering.<sup>[85]</sup> The swelling issue of hydrogels can damage the surrounding tissues in the body,<sup>[266]</sup> the incorporation of pentenyl groups in chitosan can address this problem. During the crosslinking with UV irradiation, the formed hydrophobic chains generate a strong hydrophobic effect to extrude the excess water in the hydrogel. The hydrogel also exhibits controllable temperature and pH responses and excellent biological compatibility for minimally invasive tissue engineering.<sup>[267]</sup> Moreover, introducing catechol moieties that are easily oxidized to catecholquinone could enhance the adhesive properties with tissues.<sup>[138,196]</sup> Recently, 3D printing has been employed to prepare polysaccharide-based hydrogel scaffolds with excellent mechanical properties, which show good biomimetic mineralization of hydroxyapatite for further bone tissue engineering applications.<sup>[268,269]</sup> Fluorescent hydrogels have also attracted tremendous interests due to their significant potential in bioimaging. Generally, luminescent materials (e.g., rare elements,<sup>[270,271]</sup> quantum dot,<sup>[272]</sup> and organic fluorescent dyes<sup>[273]</sup>) were introduced into hydrogel networks through chemical covalent grafting or physical mixing. All-biomass fluorescent hydrogels were fabricated by in situ crosslinking of alginate or CNFs with the presence of biomass carbon dots. The carbon dots not only increase the mechanical properties due to hydrogen bonding but also endow the hydrogels with good fluorescent characters.<sup>[272]</sup> Nonetheless, most of the physically crosslinked fluorescents lead to weak mechanical properties and suffer from the leakage during the process. Covalently fixing of fluorescents in hydrogels could address those issues.<sup>[270,273]</sup> Recently, 3-(trimethoxysilyl)propyl methacrylate (MPS)-functionalized rare element nanoparticles serving as crosslinkers were copolymerized with monomers to covalently anchor on polymer network to form double-network polysaccharide-based hydrogels, which showed strong surface adhesion, full-color fluorescence.<sup>[270]</sup> Furthermore, fluorescent hydrogels with a strong afterglow could be detected both under the skin and in the stomach, making them a promising candidate for bioimaging.<sup>[271]</sup>

## CONCLUSIONS AND OUTLOOK

The review presents the recent progresses in the design and synthesis of a series of polysaccharide-based (i.e., cellulose, alginate, chitosan, and CDs) hydrogels as well as their potential applications in self-healing hydrogels, sensors, energy storage and conversion, as well as biomedical fields over the past decade. Cellulose, chitosan, and alginate containing diverse functional groups have 1D structures, while CDs possess inherent cavity structure, which could coordinate with different guest molecules. Due to their intrinsic chemical structures and functional moieties on the backbone, discrete crosslinking routes are introduced to craft

polysaccharide-based hydrogels via physical crosslinking (e.g., hydrogen bonding, host–guest interaction, hydrophobic interactions, and ionic interaction), (dynamic) covalent crosslinking, or double-network crosslinking. In addition, the characteristics of chitosan, cellulose, and alginate could be readily altered via chemical modifications (e.g., oxidation and esterification), rendering them with more chemical structure controllability for further crosslinking. Polysaccharide-based hydrogels with physical crosslinking or dynamic covalent crosslinking manifest many intriguing properties (e.g., self-healing and stimuli–response) due to the reversible bonds, making them more promising for self-healing materials and sensors. The intrinsic polyelectrolyte nature of polysaccharide-based hydrogels imparts them with good conductivity, showing great potential in supercapacitors and batteries. Furthermore, polysaccharide-based hydrogels exhibit great potential for biological applications because of their peculiar features (i.e., biocompatibility, biodegradability, and nontoxicity) in conjunction with the unique characteristics of hydrogels.

Despite many impressive advances of polysaccharide-based hydrogels over the last decade, some challenges remain to be addressed. First, mechanical properties are the key parameters for hydrogels. Most polysaccharide-based hydrogels have low strength and/or toughness ascribed to the single-network structure. In contrast, double-network hydrogels have demonstrated excellent mechanical performance due to the synergistic effect of chemical and physical crosslinking. Moreover, introducing multiple noncovalent interactions in a physically crosslinked network will further improve mechanical performance. In addition, other strategies still require to be explored for improving mechanical properties. Second, other stimuli-responsive hydrogels with controllable and reversible features need to be developed. The release rate of drug delivery is highly dependent on where it works, thus it is significantly important to control the drug release in targeted sites and improve the long-term stability of drug release in some situations. Moreover, the sensitivity and work range of strain- or pressure sensors with high self-healing efficiency need to be enhanced to monitor more human movements. Third, the ionic conductivity of polysaccharide-based hydrogels depends on the ion concentrations and strengths. It is crucial to exploit alkaline-tolerant highly stretchable electrolytes for batteries and supercapacitors. Additionally, the ionic conductivity and mechanical properties of conventional polysaccharide-based hydrogels will deteriorate under subzero conditions, thus antifreezing, sensitive hydrogel sensors with outstanding mechanical properties in cold weather are highly desirable. Fourth, it is still of key importance to evaluate the biocompatibility and biodegradability of polysaccharide-based hydrogels in vitro and in vivo for biological applications because polysaccharides display different biodegradation behaviors in various conditions. Fifth, there are many functional groups on polysaccharides, it is easy to obtain polysaccharide-based bottlebrush polymers with densely grafted side chains for preparing hydrogels that have weak entanglement. This modification can introduce different architectures (linear, comb-like, and brush-like structures) to tune the properties of hydrogels. Moreover, the polysaccharide-based bottlebrush hydrogels will show faster ion transfer in energy storage and conversion because of the absence of entanglement in the

systems. Finally, polysaccharide-based hydrogels have shown excellent tissue adhesion, introducing antibacterial agents (e.g., TiO<sub>2</sub> nanoparticles and quaternary amine) in the hydrogels will yield antibacterial hydrogels with adhesive property, which can be used for surface modification of the public facilities and will show great potentials in the public health. Therefore, polysaccharide-based hydrogels will continue to be an active field for fundamental and applied researches.

## DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

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## ORCID

Zhiqun Lin  <https://orcid.org/0000-0003-3158-9340>

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## AUTHOR BIOGRAPHIES



**Zili Li** was born in Anhui, China. He received his BS degree in materials science and engineering from Zhengzhou University, and PhD degree in chemistry from University of Science and Technology of China in 2017. Now he is doing postdoctoral research in Prof. Zhiqun Lin's

group at Georgia Institute of Technology. His current research focuses on the synthesis of self-healing soft matters, 2D polymers, and polymer/inorganic nanocrystal composites for electrocatalysis and plasmonics.



**Zhiqun Lin** is a Professor in the School of Materials Science and Engineering at the Georgia Institute of Technology. He received his PhD degree in Polymer Science and Engineering from the University of Massachusetts, Amherst in 2002. His research interests include

block copolymers, polymer-based nanocomposites, polymer blends, conjugated polymers, functional nanocrystals, hierarchically structured and assembled materials, surface and interfacial properties, solar cells, batteries, photocatalysis, and electrocatalysis.

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