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CRITICAL REVIEW

Hydrogels Based on Cellulose and Chitin: Fabrication, Properties, and Applications

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This review is focused on the fabrication, properties, and applications of hydrogels prepared from two of the most abundant biopolymers on earth, cellulose and chitin. The review emphasizes the latest developments in hydrogel preparation (including solvent systems, cross-linker types, and preparation methods, which determine the "greenness" of the process) using these biocompatible and biodegradable biopolymers. The preparation of both physical (without covalent cross-links) and chemical (with covalent cross-links) hydrogels *via* dissolution/gelation is discussed. Additionally, formation of injectable thermoset and/or pH sensitive hydrogels from aqueous solutions of derivatives (chitosan, methyl cellulose, and hydroxypropylmethyl cellulose) with or without a cross-linker are discussed. This review also compares the design parameters for different applications of various pure and composite hydrogels based on cellulose, chitin, or chitosan, including applications as controlled and targeted drug delivery systems, improved tissue engineering scaffolds, wound dressings, water purification sorbents, and others.

1. Introduction

Hydrogels are physically or chemically cross-linked three-dimensional (3D) hydrophilic polymeric networks capable of absorbing large amounts of water (or biological fluids) and swelling.[1] Any (semi-)flexible polymer is able to virtually formulate hydrogels in a variety of physical forms including slabs, membranes, beads, microgels (microspheres), and nanogels (nanoparticles), and once freeze-dried or supercritically dried, hydrogels become cryogels or aerogels, respectively.[2] Hydrogels are held together by either physical interactions (chain entanglements, van der Waals forces, hydrogen bonds, crystallite associations,[3] and/or ionic interactions[4]) or chemical cross-links (covalent bonding[5]).

Generally, hydrogels are divided into two categories, according to their natural or synthetic origin: biopolymer-based or synthetic.[6] Considering the biocompatibility, biodegradability, and tissue-mimicking consistency of biopolymer-based hydrogels, they have acquired increasing attention. It has been shown that biopolymer-based hydrogels are applied in varied fields such as hygiene (disposable diapers and feminine care products),[7] agriculture (water retention,[8] and pesticide delivery[9]), biomedical materials (drug carriers,[10] wound dressings,[11] and tissue engineering scaffolds[12]), pollutant adsorbents (heavy metal ions,[13] dyes,[14,15] and pesticides[16]), biosensors,[17] *etc.* Various natural polymers or their salts such as sodium alginate,[18] starch,[19] protein,[20] gelatin,[21] hyaluronate,[22] hemicelluloses,[23] lignin,[24] cellulose,[25] chitin,[26] and their derivatives[27,28] have been used to fabricate biopolymer-based hydrogels.

Among the biopolymers, cellulose and chitin are two of the most abundant on earth, thus having great potential in hydrogel preparation. Cellulose consists of a straight chain of β-(1→4)-linked D-glucose units, and chitin, structurally similar to cellulose, is a long-chain co-polymer of β-(1→4)-linked 2-acetamido-2-deoxy-β-D-glucose units, with acetamide groups in the C-2 position. If the degree of acetylation (%DA) of the biopolymer is lower than 50%, it is no longer called chitin, but chitosan.[29] The plentiful hydrophilic functional groups (hydroxyl- and/or amino-) in the backbones of either cellulose or chitin qualify them as promising materials for highly absorbent hydrogel systems.

In this review, we discuss cellulose and chitin hydrogels with emphasis on their fabrication, properties, and applications. Given that chemically modified cellulose and chitin polymers may result in improved processability and/or unique characteristics, hydrogels from several common derivatives of cellulose and chitin are also discussed, including methyl cellulose (MC), hydroxypropylmethyl cellulose (HPMC), sodium carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), and chitosan.

2. Dissolution of native cellulose and chitin

Most hydrogels based on native cellulose or chitin are usually prepared through a two-step process involving dissolution followed by cross-linking (*i.e.*, gelation), although culturing specific bacteria can produce hydrogels directly (discussed in the "physical hydrogels" section below). Specific solvent

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systems are required to dissolve native cellulose and chitin, which possess poor solubility characteristic due to the numerous inter- and intra-molecular hydrogen bonds between polymeric chains.

To date, only a few solvents have been used for the dissolution of native cellulose or chitin (Table 1). These include some conventional polar solvent systems such as *N*-methylmorpholine oxide (NMMO),[30] lithium chloride/dimethylacetamide (LiCl/DMAc),[31,32] paraformaldehyde/dimethylsulfoxide (PF/DMSO), triethylammonium chloride/dimethylsulfoxide (TEAC/DMSO),[33] tetrabutylammonium fluoride/dimethylsulfoxide (TBAF/DMSO),[34] lithium chloride/*N*-methyl-2-pyrolidone (LiCl/NMP),[35] and calcium chloride dihydrate/methanol ($CaCl_2$•$2H_2O$/MeOH).[26] Although the use of these polar solvents has somewhat alleviated the issues with the biopolymer's intractability, the toxicity or corrosivity of these organic components can inhibit batch production and potential applications of the resulting gels.

Table 1. Dissolution of cellulose or chitin in various solvent systems and preparation of corresponding physical hydrogels.[a]

Entry	Solvents		Matrix	Dissolution	Gelation	Ref.
S1	Polar Solvents	NMMO	Wood, cotton pulp	85 °C	7–11 wt%, cast[b]	30
S2a[c]		LiCl/DMAc	Cellulose pulp	75–90 °C (time not reported)	0.5–8 wt%, mold[b]/cast/bead[b]	33,65,66
S2b[c]					1–8 wt%, ion exchange	31
S3		PF/DMSO	Wood pulp	120 °C, 1 h	4 wt%, cast	33
S4		TEAC/DMSO	Wood pulp	90 °C (time not reported)		
S5		TBAF/DMSO	MCC	60 °C, 20 min	0.5–1 wt%, mold, coagulate	34
S6a		LiCl/DMAc	Chitin	19 °C, 12 h	1, 1.85 wt%, mold, cure[b]	67
S6b					0.3–1.5% w/v, mold/bead	32
S7		LiCl/NMP	Chitin	RT, 48 h	0.3–5% w/v, mold/bead	32,35
S8		$CaCl_2$•$2H_2O$/MeOH	Chitin	100 °C (time not reported)	1.96 wt%, coagulate, dialyze/filter	26
S9a[c]	Ionic Liquids	[C_2mim]OAc	MCC	80 °C, 3-4 h	12.5 wt%, cure	37,38
S9b[c]					5–7 wt%, bead	
S10		[C_4mim]Cl	MCC	130 °C (or microwave), 3.5 h	4.75 wt%, cast	39,40
S11		[Amim]Cl	Filter paper	70 °C, 2 h	1.5 wt%, mold, cool, coagulate	41
S12		[Amim]Br	Chitin	100 °C, 48 h	7 wt%, mold, cool	42
S13		[C_2mim]OAc	Chitin	90-95 °C, 5 h	1-3 wt%, mold, cure, coagulate	43
S14		[C_4mim]OAc	Chitin	100 °C (time not reported)	4 wt%, mold, cool, coagulate	44
S15	Deep eutectic solvents	ChCl/urea; ChBr/urea; ChCl/thiourea	Chitin	100 °C, 2 h	10 wt%, cure	48
S16	Alkali aqueous systems	Alkali	MCC, cellulose pulp	-6 °C, 2 h	3-7 wt%, cure, Sc-dry[a]	68
S17a[c]		Alkali/urea	Cellulose pulp, filter paper, tunicate cellulose	-12–-10 °C, 5–10 min; F/T (F: -5 °C, 5 h), 1 cycle	4 wt%, cure (55 °C)	54
S17b[c]					0.5-7 wt%, cast	64,69-71
S18a[c]		Alkali/thiourea	Cotton linter	-5 °C, 2–10 min; F/T (F: -8 °C, 12 h), 1 cycle	5 wt%, cast	61
S18b[c]					3-6 wt%, mold, cure	61,62,77
S19		Alkali	Chitin	F/T (F: -18 °C, 12 h), 1 cycle	2 wt%, mold, cure (60 °C)	72
S20		Alkali/urea	Chitin	F/T (F: -20 °C, 12–18 h), 1–2 cycles	2–8 wt%, cure/coagulate	75,78

[a] Choline bromide (ChBr); Choline chloride (ChCl); Dimethylacetamide (DMAc); Dimethylsulfoxide (DMSO); Freeze/thaw (F/T); Microcrystalline cellulose (MCC); Methanol (MeOH); *N*-methylmorpholine-*N*-oxide (NMMO); *N*-methyl-2-pyrolidone (NMP); Paraformaldehyde (PF); Room temperature (RT); Supercritical-drying (Sc-dry); Tetrabutylammonium fluoride (TBAF); Triethylammonium chloride (TEAC); [b] Cast: cast on a glass or ceramic plate followed by coagulation; bead: drop,[32] inject,[39] extrude,[73] or spray/atomize/nebulizer[65] into the coagulant, spay-drying[74], or ion exchange;[31] Mold: pour in a vial or a specific mold followed by curing and/or coagulation; Cure: stand at various temperatures (5–60 °C) for a certain time (minutes–weeks); [c] The "a" and "b" refer to the same dissolution process but differen gelation procedures.

Recent alternatives for cellulose and chitin dissolution and hydrogel production include ionic liquids (ILs), deep eutectic solvents (DESs), and alkali or alkali/(thio)urea aqueous systems developed since the 2000s. Various ILs used for cellulose dissolution consist of an imidazolium, pyridinium, ammonium, or phosphonium cation paired with a strongly basic, hydrogen bond accepting anion (*e.g.*, OAc^-, $HCOO^-$, $HSCH_2COO^-$, $(MeO)HPO_2^-$, $(MeO)MePO_2^-$, $(MeO)_2PO_2^-$, Cl^-, or Br^-),[36] and several of these ILs including [C_2mim][OAc],[37,38] 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl),[39,40] and 1-allyl-3-methylimidazolium chloride ([Amim]Cl)[41] have been applied in the preparation of cellulose gels. In contrast to the enormous attention captured by cellulose, not much information is yet available on chitin-dissolving ILs; typical ILs in this context are 1-allyl-3-methylimidazolium bromide ([Amim]Br),[42]

[C_2mim][OAc],[43] and 1-butyl-3-methylimidazolium acetate ([C_4mim]OAc).[44]

Deep eutectic solvents (DESs) are fluids obtained by heating two or three components that are capable of self-association through hydrogen bonding. DESs have almost identical physicochemical properties to those of ILs except that they do not entirely consist of ionic species and may be cheaper.[45,46] The classic examples are the combinations of choline chloride (mp 302 °C) with urea (mp 133 °C) or thiourea (mp 175 °C), forming a DES with a mp of 12 °C or 69 °C, respectively.[47] Although dissolution of both chitin and cellulose in DESs has been verified,[46] there is only a single report on self-assembly of chitin in such solvents (producing a soft chitin gel) and no research on cellulose gelation yet to date.[48]

Another solvent system for cellulose or chitin dissolution and gelation are the alkali/urea (or thiourea) aqueous systems developed in L. Zhang's group.[49,50] Typically, the dissolution power of alkali/urea solvent systems is in the order NaOH/thiourea > LiOH/urea > NaOH/urea >> KOH/urea aqueous solution.[49,51] In particular, the dissolution process in alkali/urea systems is very different from that in other solvents mentioned above, *i.e.*, a low temperature treatment (by precooling the solvent[52] or freezing/thawing the mixture[50]) is needed instead of stirring at room temperature (RT) or high temperatures. This may be because the dissolution of polymers in aqueous systems is an entropy-driven process (*i.e.*, the entropy of the polymers in dissociated state increases significantly compared with that in the crystalline state), whereas in other solvents it is not (*e.g.*, the entropy of the polymer chains after dissolution in IL increases very slightly or even decreases).[52,53] Although the mechanism of the dissolution of cellulose or chitin in all these solvents has not been fully determined, the widely accepted opinion is that hydrogen bond acceptors (N–O, Cl^-, OAc^-, *etc.*) and/or donors (–NH_2 in urea or thiourea) of the solvent break up the intra- and inter-molecular hydrogen bonds in the biopolymer chains upon stirring, heating, or low temperature treatment.[36,46,50,54,55]

3. Physical hydrogels

Physical hydrogels are cross-linked by physical interactions such as chain entanglements, van der Waals forces, hydrogen bonds, hydrophobic or electronic associations. For cellulose and chitin, physical hydrogels have been prepared from four major biopolymer sources: native cellulose or chitin powders (dissolved in specific solvents presented as above), from nanowhiskers (dispersed in water), from biopolymer derivatives (dissolved in water or acid), and from bacterial cellulose (BC; dissolved in specific solvents presented as above; or biosynthesized directly into gels during bacterial culture).

3.1 Hydrogel formation from native cellulose or chitin

Cellulose and chitin polymers in solution behave as random coils, semi-flexible (or semi-rigid) chains, or entangled chains, and the degree of entanglement depends on the polymer concentration.[56-60] While polymer solutions of low concentrations are completely isotropic, with increasing polymer concentration, the transition from solution to a liquid crystalline gel takes place followed by gelation into a solid gel that has an anisotropic structure.[31,37] The gel structure becomes more and more organized and stable as biopolymer concentration increases due to the higher degree of entanglements and the more hydrogen bonding interactions that exist.[37] Further, upon curing (*i.e.*, keeping the solution at various temperatures between 5–60 °C for minutes or weeks)[61-63] or coagulation (*i.e.*, immersion in certain anti-solvents such as water,[38] ethanol,[32] methanol,[26] H_2SO_4/Na_2SO_4,[64] *etc.*) in various fashions (*e.g.*, beading, molding, or casting;[30,31,34,65-74] Table 1), the physicochemical interactions between the polymer chains increases and the stability of the hydrogel enhances.

Usually, physical associations are reversible, leading to a thermo-reversible and "green" (without cross-linkers) sol-gel transition process.[75,76] However, if a) the reversible gel is coagulated in an anti-solvent, or b) the NaOH/urea (or thiourea) solvent denatures at high curing temperatures (> 60 °C, resulting in a yellow color) *via* reaction and thermal decomposition of the solvent molecules,[54,77] the solvents are washed out (in "a") or destroyed (in "b"), resulting in formation of so-called irreversible gels. Such irreversible physical gels, when vacuum- or supercritically-dried, exhibit lower degrees of crystallinity (reduced by 9–22%) than native cellulose or chitin.[32,43,78] In addition, cellulose I changes to cellulose II and β-chitin changes to α-chitin, respectively, after dissolution and gelation.[26,79]

3.1.1 Transparency. The property of "clarity" of hydrogels, or their transparency, is determined as their ability to transmit light, and is measured as light transmittance. Once formed, the transparency of hydrogels differs and depends on the curing temperature or coagulation bath used as a result of the degree of phase separation (so-called spinodal decomposition or spinodal phase separation, where one thermodynamic phase forms two coexisting phases) during the formation of hydrogels.[33,54,64,78] For hydrogels prepared in NaOH/urea aqueous systems, an increase in curing temperature causes a large decrease in transparency (*e.g.*, 85% transmittance at -10 °C, 66% transmittance at 20 °C, and nontransparent at and above 30 °C). This is caused by increased degree of phase separation and thereby enhanced hydrogel heterogeneities (*i.e.*, the number and size of the resulting polymer aggregates).[54,78]

On the other hand, when coagulative regeneration is used, the transmittance can be tuned through control of the degree of phase separation in the sample using a certain amount of coagulant (*e.g.*, water).[34] Incorporation of acetone into water as a coagulation solution increases the transparency of the hydrogels, which may be related with a "specific polymer structure" formed resulting from the balance between swelling of the gel by water and shrinking by acetone.[33] A novel method, deionization of the cellulose/LiCl/DMAc solution with ion exchange resins, has been reported for preparation of gel beads that appear colorless and transparent without a fibrous texture compared with the "water-coagulated gel," probably because

the molecular association (crystallite formation) precedes the phase separation during ion exchange.[31]

3.1.2 Strength. The strength of hydrogels is yet another well-studied characteristic. In many cases, improved strength comes with higher transparency, and similarly depends on the degree of phase separation discussed above. For example, hydrogels prepared from chitin/NaOH/urea solution through coagulation in acidic or aqueous salt solutions have smoother surfaces, more homogeneous structure, relatively smaller pore sizes, and thus improved tensile strength and transparency compared with those coagulated in water, ethanol, or acetone.[64] Tensile strength is also affected by biopolymer concentration and curing conditions, *i.e.*, higher concentration and curing treatment result in stronger hydrogels owing to the more homogenous and/or more intertwined structure.[63,78]

In addition, the mechanical strength of physical hydrogels can be improved by employing a pre-gelation process before performing coagulation as shown in the example of cellulose hydrogel beads from a NaOH/thiourea solution. In this example, hydrated cellulose membranes were packed densely with many nanospheres (200-510 nm according to the pre-gelation temperature).[61] This could be attributed to the thiourea inclusion complex aggregates (47–160 nm) in which the cellulose chains associated with NaOH hydrates as guests were encaged by NaOH and thiourea.[62,80]

3.2 Hydrogel formation from cellulose or chitin nanowhiskers

The main process for the isolation of cellulose nanowhiskers (CNWs) and chitin nanowhiskers (ChNWs) from cellulose and chitin fibers, respectively, is based on acid hydrolysis (usually sulfuric acid for CNWs and hydrochloric acid for ChNWs) of the polymer(s).[81,82] The nanoscale size (3–50 nm in width, 0.1–2 μm in length)[83,84] and electrostatic repulsions (negatively charged sulfate groups on CNWs, positively charged amino groups on ChNWs) promote a perfectly uniform dispersion of the whiskers in water. As with native cellulose and chitin, the dispersed whiskers are also able to concentrate and self-organize into nematic or solid gels above a certain concentration.[85,86]

Production of stable solid nanowhisker-based gels was achieved through further treatment of the nanowhisker aqueous suspensions, using solvent exchange,[87] ultrasonication,[88,89] dialysis (to concentrate),[90] and, most often, adjustment of pH[91] (Table 2). In ultrasonication-assisted assembly, the sonication bath provides energy with a similar order of magnitude as that of hydrogen bonds (4–50 kJ/mol),[89] allowing for the rearrangement and formation of a 3D-percolated network through hydrogen bonding. The solvent exchange method with a miscible anti-solvent (routinely acetone) results in chain rearrangement and formation of robust macroscopic gels from the nanowhisker suspension.[87] Yet another method is pH adjustment; for instance, when the pH value of the ChNW suspension in acetic acid was adjusted to 10–11, the suspension immediately turned into a freestanding hydrogel even at a concentration as low as 0.5 wt% due to the elimination of repulsive interactions between the ChNW elements under basic conditions.[91]

Additionally, cellulose and chitin nanowhiskers are used to reinforce some polymeric matrices, such as cellulose,[92] chitosan,[93] poly(vinyl acetate),[94] and poly(methyl vinyl ether-co-maleic acid) and poly(ethylene glycol)[95,96] due to the high Young's modulus (*ca.* 140 GPa) of the nanowhiskers.[97,98] The nanowhisker density (*i.e.*, content) is generally within 25% which leads to increased thermal stability, mechanical strength, and overall Young's modulus, but decreased water uptake of the polymeric gels with the increase of whisker content.[93-96] Functionalization of nanowhiskers with carboxyl or amine groups prior to their incorporation into the polymer networks results in mechanically and hydrophilically adaptive, pH-responsive nanocomposite gels.[99]

Once formed, the transparency of nanowhisker-based gels is determined theoretically by the thickness of the gels or the density of the whiskers since a single nanowhisker has a diameter less than one-tenth of the wavelength of visible light and thus does not scatter light.[90,100] For example, thin chitin nanowhisker-based gel films are transparent (transmittance = 90.2% at 600 nm);[90] and when used as reinforcement, both cellulose and chitin nanowhiskers can retain the transparency of the polymer matrix (*e.g.*, chitosan,[93] and poly(acrylic acid)[100]) to different extents depending on the whisker density.

Table 2. Preparation of physical hydrogels based on cellulose or chitin nanowhiskers.[a]

Entry	Nanowhisker	Medium	Gelation	Ref.
D1	Cellulose nanowhisker (CNW)	Water	0.73 wt%, solvent exchange	87
D2			7.4–14.8 wt%, sonicate	88
D3	Chitin nanowhisker (ChNW)	Water	3.8–10.7 wt%, sonicate	89
D4			Dialyze to 1.5 wt%	90
D5		0.05 wt% HOAc	0.05 wt%, adjust pH to 10–11	91

[a] Acetic acid (HOAc).

3.3 Hydrogel formation from cellulose or chitin derivatives

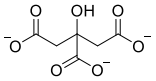
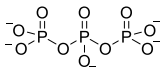
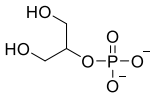
The most widely used biocompatible derivatives of cellulose and chitin are hydrophobically modified cellulose (MC and HPMC) and chitosan (deacetylated chitin), respectively. These derivatives are much easier to fabricate into hydrogels because they are water- or acid-soluble. MC and HPMC are water soluble due to the fact that hydrogen bond formation is prevented by the introduction of pendant groups; and chitosan can be dissolved in dilute acid aqueous solutions (*e.g.*, dilute acetic acid). From aqueous solutions of these derivatives, unique hydrogels such as thermoset and pH-sensitive hydrogels can be formed either with or without the addition of a physical cross-linker that can introduce hydrophobic or electrostatic associations.[101-103]

As an example of such gels, an elastic and thermo-reversible MC gel was formed when heating the MC aqueous solution above a critical temperature, which seemed dependent on MC concentration (63 °C at 0.30–2.5 wt%,[104] 42.5 °C at *ca.* 4.7 wt%,[101] 32 °C at 7.0 wt%, and 27 °C at 9.0 wt%[105]). An accepted mechanism of this gelation employs the concept of solven reorganization on heating of a MC solution, where the solvated

cage-like MC structure (originally formed through hydrogen bonds of water along MC chains) gets destroyed and thereby hydrophobic regions of MC are exposed, leading to the formation of hydrophobic aggregates.[104] The mechanism of formation of HPMC gels is thought to be similar, although solutions have slightly higher gelation temperatures (*e.g.*, 70 °C at 2 wt%) than MC solutions, indicating that the hydroxypropyl substituents inhibit the gelation.[106-108] These thermoset hydrogels have much potential as injectable drug or cell carriers *in vivo*.

Chitosan hydrogels can be obtained by coagulation in alkaline media (such as NaOH[109] and NaOH/Na_2CO_3[110] aqueous systems) to relieve the electronic repulsion of $–NH_3^+$ groups between polymeric chains. To increase the strength of chitosan hydrogels, physical ionic cross-linkers (Table 3), sodium citrate (SC)[102] and tripolyphosphate (TPP),[103,111-114] were employed, which introduced electrostatic interaction between the anion ($–COO^-$ or $P_3O10_5^-$) and cation ($–NH_3^+$) into the system and led to the formation of pH-sensitive chitosan hydrogels. In such pH sensitive chitosan hydrogels, the cross-linking density was controlled by adjusting the pH value of the ionic cross-linker solution, *e.g.*, chitosan could be completely ionically cross-linked by $P_3O_{10}^{5-}$ ions in acidic TPP solution (pH 3), whereas it was slightly ionically cross-linked in the original TPP solution (pH 8.6).[103]

Table 3. Physical cross-linkers for chitosan-based hydrogels.[a]

Type	Cross-linkers	Structure	Solvent	Gelation	Ref.
Electrostatic interaction	Sodium citrate (SC)		4% (w/v) HOAc	4% w/v, shape[b], soak[c], cure (RT, 1 h)	102
Electrostatic interaction	Tripolyphosphate (TPP)		1% (w/v or v/v) or 5% (v/v) HOAc; ultrapure H_2O	0.1–3.3% w/v, bead[d], cure (RT, 12 h)	103,111-114
Hydrophobic interaction	β-glycerophosphate (β-GP)		0.75% (v/v) HOAc; 0.1 M HCl	1.5–3% w/v, thermo-gelate	115-117

[a] Acetic acid (HOAc); Room temperature (RT), [b] Shape: gelate the chitosan solution in a certain fashion (beading, casting, or molding); [c] Soak: soak the gel in the cross-linker solution; [d] Dropping the chitosan solution of high concentrations (*e.g.*, 2% w/v) into the cross-linker solution producing beads with larger diameters, while dropping the cross-linker solution into the chitosan solution of low concentrations (*e.g.*, 0.1% w/v) producing micro or nanogels.

Another hydrophobic cross-linker, β-glycerophosphate (β-GP), was used for formation of thermoset chitosan hydrogels that featured a gelation temperature in the vicinity of 37 °C within the pH range of 6.8–7.2 (buffered by the dosage of β-GP).[115-117] The addition of β-GP increased pH and ionic strength of the chitosan solution, establishing a favorable environment to form a gel structure by both the screening of electrostatic repulsion and the enhancement of polymer–polymer hydrophobic interactions.[118] The protonation of chitosan, meanwhile, decreased strongly in the neutral chitosan/β-GP solution, especially at higher temperatures, thus leading to a minor contribution of ionic cross-linking.[118]

3.4 Hydrogel formation from bacterial cellulose (BC)

The properties of bacterial cellulose (BC) are quite different from those of plant cellulose, especially its high purity, ultrafine network structure, high hydrophilicity, and moldability during hydrogel formation (culturing without any cross-linker).[119] The species of bacteria capable of producing cellulose extracellularly is generally called *Acetobacter xylinum* (acetic acid bacteria). The culture is carried out normally in static conditions at *ca.* 28–30 °C in the culture medium containing saccharides or natural saps and juices.[120] A white BC gel pellicle generates on the surface, and its thickness increases steadily with time, reaching over 25 mm in four weeks.[120] Such BC gels help the aerobic bacterial cells hold their position close to the oxygen-rich surface and protect themselves from water loss, ultraviolet lights, enemies, heavy metal ions, *etc.*[121]

The as-biosynthesized BC gels show a slightly higher water content and ability to bind water molecules than plant cellulose gels; only 10% of the water molecules in the BC gel behave like free bulk water while the majority are more or less bound to cellulose.[122] BC gels can be easily molded into desired shapes and sizes during synthesis, *e.g.*, tubular BC gels with proper fibril orientation were created by culturing bacteria in oxygen-permeable silicone tubes with inner diameter less than 8 mm, which hold promise for use as microvessels in medical and pharmaceutical applications.[123] BC gels could also be molded into a shape with dimensions similar to cartilage tissues (*e.g.*, meniscus) as a potential implant[124] or a scaffold for chondrocyte proliferation.[125]

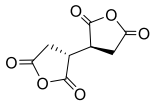
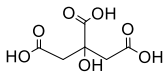
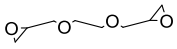
4. Chemical hydrogels

4.1 Chemical cross-linkers

To guarantee the stable structure and effective swelling of cellulose- or chitin-based hydrogels, a covalently bound 3D hydrophilic network is usually required and achieved through

the use of chemical cross-linkers during gelation, *i.e.*, small bifunctional or multifunctional molecules such as 1,2,3,4-butanetetracarboxylic dianhydride (BTCA),[126,127] succinic anhydride (SA),[128,129] citric acid (CA),[130,131] epichlorohydrin (ECH),[25,132] ethylene glycol diglycidyl ether (EGDE),[133-135] and divinyl sulfone (DVS)[136-138] (Table 4). Chemical cross-linkers form covalent bonds that link one polymer chain to another. According to the mechanism of cross-linking reactions, chemical cross-linkers for cellulose and chitin can be classified into two types: a) esterifying agents including carboxylic acids and carboxylic anhydrides; and b) etherifying agents including organochlorine, epoxide, and vinyl compounds. The first type of cross-linkers results in formation of –COOR bonds and probably a few peptide bonds (–CONH–) in chitin gels, while the second type of cross-linkers results in formation of R–O–R bonds and probably some secondary amine bonds (R–NH–R) for chitin.

Table 4. Chemical cross-linkers for cellulose or chitin hydrogels.[a]

Type	Cross-linkers	Structure	Solvent	Gelation	Ref.
Esterification	1,2,3,4-Butanetetracarboxylic dianhydride (BTCA)		LiCl/NMP	0.9–1.0 wt%, DMAP, cure (RT, 24 h), coagulate	126,127
	Succinic anhydride (SA)		LiCl/NMP; TBAF/DMSO	0.5–1.0 wt%, DMAP, cure (RT, 24 h), coagulate	128,129
	Citric acid (CA)		Water[b]	2 wt%, mold, heat (80 °C, 24 h); 0.01–0.1 wt%[c], carbodiimide, cure (RT, 24 h)	130,131
	Epichlorohydrin (ECH)		NaOH/urea	1–4 wt%, mold, heat (50–60 °C, 1–20 h)	25,132
Etherification	Ethylene glycol diglycidyl ether (EGDE)		Water[b]	3 wt%, NaOH, mold, heat (60 °C, 24 h); Bead[d] (2 wt%), NaOH, soak[e], cure (50–70 °C, 3–6 h)	133-135
	Divinyl sulfone (DVS)		Water[b]	6–9 wt%, KOH or NaOH, mold, cure (RT or 47 °C, 24 h); Shape (as emulsion)[f], NaOH, cure (55 °C, 1 h)	136-138

[a] Dimethylsulfoxide (DMSO); *N*-methyl-2-pyrolidone (NMP); Tetrabutylammonium fluoride (TBAF); [b] Cellulose derivatives (carboxymethyl cellulose (CMC), hydroxyethylcellulose (HEC), or hydroxypropyl cellulose (HPC)) or chitosan were used; [c]Nanoparticles with diameters 270–370 nm were obtained and not macrogels, due to the low concentration of the biopolymer in the solution; [d] Chitosan beads were prepared from the acid chitosan solution through injection into an alkaline coagulant; [e] Soak: soak the gel in the cross-linker solution; [f] HPC nanogels were obtained from the 0.1 wt% emulsion with dodecyltrimethylammonium bromide (DTAB) as a surfactant above the critical micelle concentration (cmc) of the surfactant.[137]

Most esterification-type cross-linking reactions of biopolymers with carboxylic anhydrides require effective nucleophilic catalysis, and typically 4-dimethylaminopyridine (DMAP) has been used; examples include using BTCA and SA as cross-linkers.[126-129] In these reactions, DMAP initially reacts with an acyl group of the anhydride, forming a positive acylpyridinium intermediate and a negative carboxyl counterion. The polysaccharide molecules are deprotonated by the latter, and then attack the acyl group in the former to form an ester (Fig. 1a).[139]

There is an alternative for the condensation route between carboxylic acid (*e.g.*, SA, CA) and biopolymer by using water-soluble carbodiimide (*e.g.*, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide, and *N,N'*-dicyclohexylcarbodiimide) as a mediation agent.[131] The mechanism potentially involves formation of a labile acyl-intermediate, capable of reacting with the biopolymer and changing itself into a nontoxic urea derivative (Fig. 1b). When changing the carboxylic acid into CMC, the cross-linking of a CMC/biopolymer composite hydrogel was achievable.[140] For etherifying cross-linkers, *i.e.*, organochlorine, epoxide, and vinyl compounds (*e.g.*, ECH, EGDE, and DVS[25,132-138]), etherification generally involves reactions in aqueous alkaline conditions (alkali-catalysis) for the deprotonation of hydroxyl groups on the biopolymer, making them highly nucleophilic and reactive with the cross-linker (Fig. 1c).

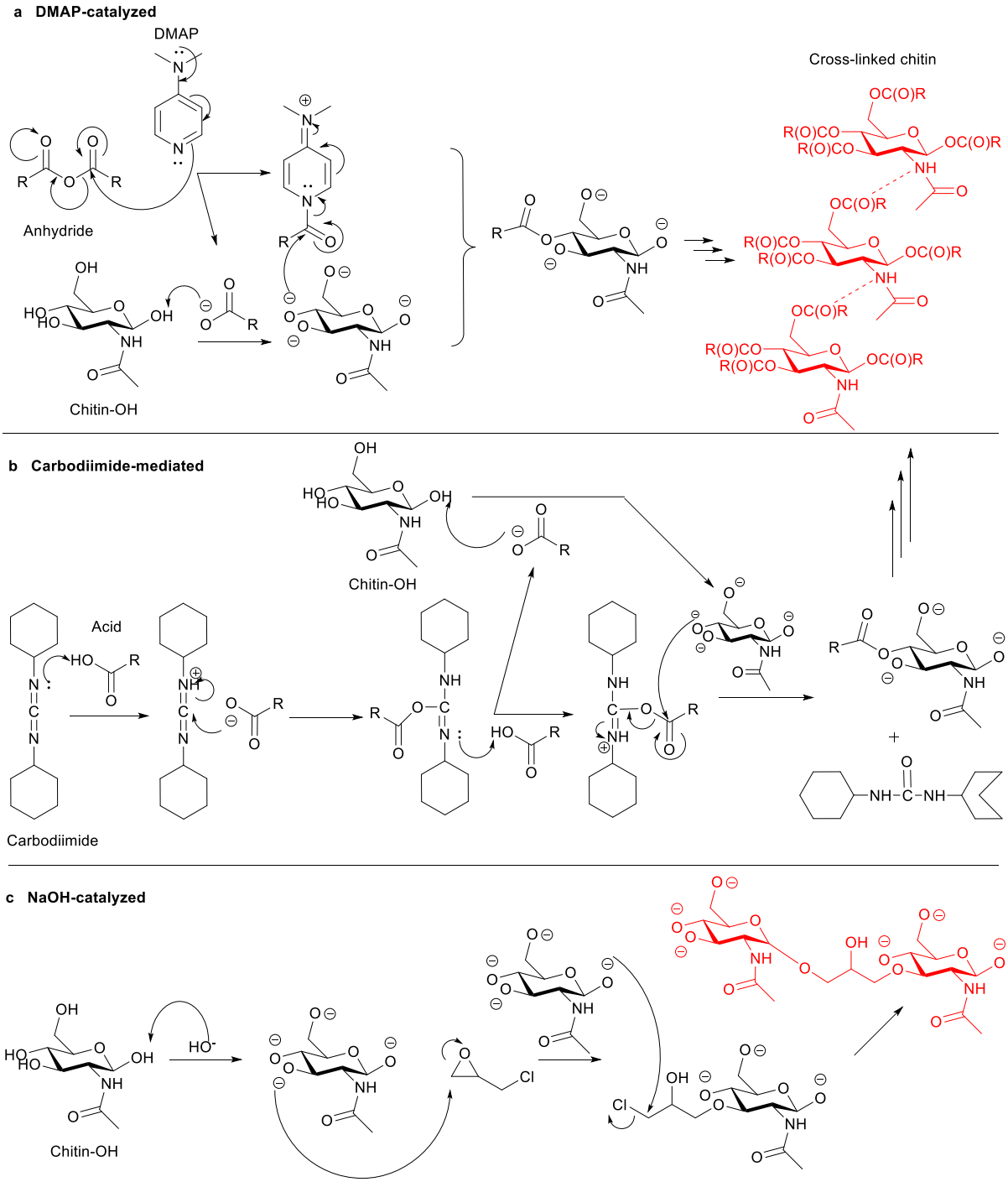


Fig. 1. Possible chitin cross-linking mechanisms of a) DMAP-catalyzed cross-linking using anhydride; b) carbodiimide-mediated cross-linking (*N,N'*-Dicyclohexylcarbodiimide is used as carbodiimide), and c) alkali-catalyzed cross-linking.

Some chemical cross-linkers are only applicable to deacetylated chitin or chitosan that has amine ($-NH_2$) groups, including glutaraldehyde (GA),[28,141,142] malondialdehyde (MDA),[143] hexamethylene-1,6-di-(aminocarboxysulfonate) (HDS),[93] and genipin (GNP).[74,144] One cross-linker molecule reacts with two amine groups in two chitosan units: GA and MDA cross-link to produce two Schiff bases (–C=N–), HDS results in peptide bonds (–CONH–), and GNP produces both a peptide bond and a tertiary amine (Table 5).

Cross-linking of chitosan gels can be performed either during or after the shaping (molding, casting, or beading) of the gel without the use of catalysts. The Schiff base can be further reduced using the weak reductant, sodium cyanoborohydride ($NaBH_3CN$), for the formation of stable secondary amines.[143] Out of all cross-linkers, genipin is naturally obtained from gardenia fruit extract and is the most "green" (10,000 times less cytotoxic than GA[145]), which endows the resulting gel with better biocompatibility and slower biodegradation rate.[74]

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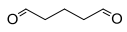
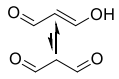
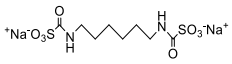
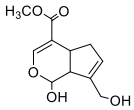
Table 5. Chemical cross-linkers for chitosan hydrogels.[a]

Type	Cross-linkers	Structure	Solvent	Gelation	Ref.
–C=N–	Glutaraldehyde (GA)		0.05 M HCl; 5% (units not reported) HOAc[b]	Bead[c] (1.5 wt%), soak[d], heat (40 °C, 72 h); 1.5 wt%, cure (RT, 24 h)	28,141,142
–C–N–	Malondialdehyde (MDA)[e]		1 M HOAc/NaOAc	3.8% w/v, cure (40 °C, 4 h), reduce ($NaBH_3CN$, 4 days)	143
–CONH–	Hexamethylene-1,6-di-(aminocarboxysulfonate) (HDS)		5 wt% HOAc	4.55 wt%, cure (60 °C, 48 h)	93
–CONH–, 	Genipin (GNP)		0.5 wt% or 2% (units not reported) HOAc	Bead[c] (1.5 wt%), soak, cure (RT, 3–16 h)	74,144

[a] Acetic acid (HOAc); Room temperature (RT), [b] NaCl (2%) can be added to improve the solution properties (viscosity, transparency, *etc.*); [c] Chitosan beads were prepared from the chitosan solution through dropping or spraying; [d] Soak: soak the gel in the cross-linker solution; [e] Malondialdehyde (MDA) was formed through the hydrolysis of 1,1,3,3-tetramethoxypropane (TMP).

4.1.1 Transparency. In general, transparency of chemical hydrogels depends not only on the degree of spinodal phase separation as for physical hydrogels, but also on the extent of cross-linking. Chemical cross-linking contributes to a highly hydrophilic 3D network with a homogeneous structure, although some cross-linkers may imbue the hydrogel with a certain color (*e.g.*, a dark-bluish color for GNP and an amber color for GA).[141,144] According to our own research,[146] the degree of swelling may also have an impact on the transparency of chemical hydrogels, *e.g.*, as-prepared chemical gels from cellulose-rich materials (CRMs; isolated with IL from wood) cross-linked with ECH before swelling in water appeared non-transparent, while after rinsing and swelling in water they became transparent or semi-transparent.

4.1.2 Pore size. The initial pore size of the hydrogels is affected by the preparation process, *e.g.*, hydroxypropylcellulose (HPC) hydrogels synthesized at temperatures above the lower critical solution temperature (LCST) were microporous, whereas those cross-linked in the single-phase regime below the LCST were nonporous since the cross-linking prior to phase separation fixed the average distance of polymer chains.[136,147] However, the measured pore sizes are affected by the drying processes. The pore sizes are generally determined by SEM after lyophilizing (*i.e.*, freeze-drying) the hydrogels, and the resulting cryogels mostly have pore sizes within the average range of 3–8 µm, which decrease with increasing biopolymer concentration or cross-linking degree.[25,132] By controlling ice crystal growth, lyophilization is able to generate various pore sizes (1–250 µm) depending on freezing conditions (temperature, freezing before or after shaping, *etc.*);[148] however, the gels tend to crack during freeze-drying and the resulting cryogels are highly brittle.[70,78]

If supercritical drying is applied as a drying technique, aerogels with pore sizes in the nanoscale (most frequently 2–50 nm[43]) are obtained since hydrogels shrink substantially during immersion in organic solvents (methanol, ethanol, or acetone) followed by supercritical drying.[68,149] The use of organic solvents to replace the water prior to supercritical drying is generally necessary, as without this step significant foaming (40–160 µm pores) during CO_2 processing is observed.[67,150] However, there is a report stating that the shrinkage of BC gels after immersing in ethanol and supercritical drying was low, and these authors were able to obtain bigger pore diameters up to 100 µm.[151]

4.1.3 Strength. The strength of chemical hydrogels is related to the biopolymer type, *e.g.*, chitin hydrogels show higher mechanical strength than chitosan hydrogels (9.5–22 *vs.* 0.07–1.6 kPa) as a result of the stronger pore walls consisting of stiffer chitin chains.[132,152] The compressive stress of hydrogels increases with increasing biopolymer concentration[132] and cross-linking density.[153] Interestingly, the modulus of chemical cellulose hydrogels rises progressively with swelling after a minimum modulus is reached at a low swelling degree, which may be explained by the high intrinsic chain stiffness (large persistence length) of the cellulose backbone.[138]

4.1.4 Water Absorbency. There seems to be a debate about the definition of "swelling ratio;" while some reports calculate it as the mass ratio of the freshly prepared hydrogel to the dry sample, more frequently, others refer to the ratio of the "rehydrated" gel to the dry sample. The former value could be at least 2–3 times higher than the latter. In this review, we will use the latter definition.

There is little research on the swelling of physical gels due to their weak structure or low swelling, so majority of the literature is related to swelling of chemical hydrogels. There are several factors that influence the water absorbency of hydrogels. First the drying procedure affects the water absorbency capacity of hydrogels. Supercritically- or freeze-dried hydrogels retain the microporosity of the gel systems and thus significantly increase the swelling properties compared with air-dried, oven-dried, or vacuum dried hydrogels, whose capillary retention decreases due to the recrystallization of the biopolymers in the gel systems. The former drying methods can produce dry gels with a swelling ratio up to 60 g/g,[25] while the latter usually lead to low swelling ratios below 3 g/g.[144] Our research shows that the molecular weight (MW) of the biopolymer plays an important role in the water uptake capacity of the resulting aerogel (*i.e.* supercritically dried hydrogel), *e.g.*, gels from chitin and CRM of higher MWs isolated with IL possessed higher absorbency than corresponding gels from commercial biopolymers of lower MWs.[146] Also, with an increase of polymer concentration, the swelling ratio of the hydrogel decreases significantly as a result of the decrease of pore sizes.[132]

The degree of cross-linking also affects swelling properties of hydrogels somewhat, although not significantly.[25,144] The introduction of electronic repulsion forces into the gel strongly increases the swelling capacity, even using common drying (*e.g.*, vacuum drying). It was reported that quaternized cellulose nanofibril nanopaper could swell in water and become a hydrogel with a maximal water absorbency up to 750 g/g.[154] Superabsorbent hydrogels with a swelling ratio up to 300–400 g/g were prepared by using SA or BTCA as the cross-linker because of the presence of grafted cross-linkers that still had carboxyl groups.[126-129] Finally, parameters of the aqueous medium, such as ionic strength,[128] pH,[127,131] and temperature,[25] may influence the water uptake of hydrogels (as discussed below).

4.2 Irradiative cross-linking

Irradiation is a useful method for the formation of covalent bonding between polymer chains. This method is advantageous because of the high purity of the hydrogel product without use of toxic cross-linkers, thus enlarging the applications in food and pharmaceutical industries. However, only a small fraction (17-30%) of gel aggregates (lumps) could be obtained by γ-ray irradiation at a dose of 20 kGy from 20 wt% biopolymer solutions (such as cellulose/IL/water, CMC and carboxymethyl chitosan (CMCts) aqueous solutions), with the assistance of generated hydroxyl radicals.[155-157]

Electron beam (EB) irradiation in vacuum seems to be able to increase the gel yield, *e.g.*, after EB irradiation, the gel fraction reached up to 55% at 20 kGy, and increased with the irradiation dose.[158,159] Further, instead of low yield and a liquid product, Petrov *et al*. obtained opaque spongy materials *via* UV irradiation from moderately frozen semi-dilute (3 wt%) aqueous polymer (*e.g.*, HPMC, HEC, and MC) solutions with (4-benzoylbenzyl)trimethylammonium chloride (BBTMAC) as a photoinitiator.[160] It was suggested that after freezing, the photoinitiator and water molecules connected to the polymer through hydrogen bonds could form a non-frozen liquid microphase in which the polymer concentration was very high, resulting in a sufficient number of chains in close enough vicinity to bind with each other during irradiation.[160] Additionally, a "radical cross-linker" (usually *N,N'*-methylenebisacrylamide (MBAAm)) could be added to the solution before irradiation to enhance the gelation efficiency.[161] It has been reported that macroradicals emerge preferentially in weakened 1 and 4 positions of cellulose as aresult of the fracture of C–H bonds upon irradiation,[162] while macroradicals of the derivatives are created in the side chains during radical cross-linking as shown in Table 6.[157,163]

Degradation of the polymer chains competes with cross-linking during irradiation, especially at high-energy doses and low polymer concentrations (10 wt%), resulting in the destruction of network structure and decrease of tensile strength.[159] Degradation could be decreased by a) using EB irradiation instead of γ-irradiation because of the much higher radical number created in the system under EB irradiation, or by b) irradiation in an oxygen-free atmosphere to avoid the generation of oxides and peroxides.[164]

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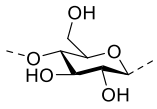
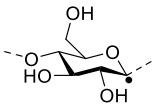
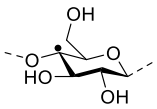
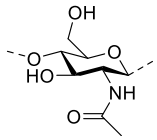
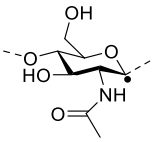
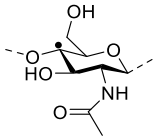
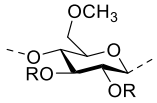
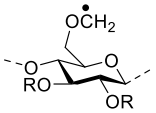
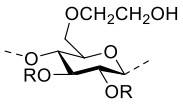
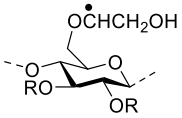
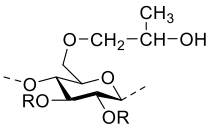
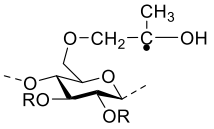
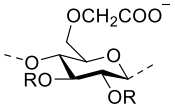
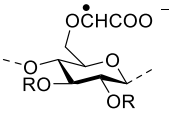
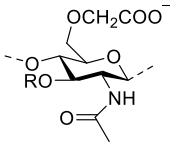
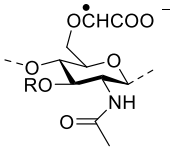
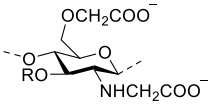
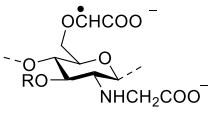
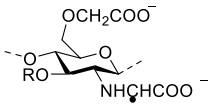
Table 6. Structure of biopolymers (cellulose, chitin, and their derivatives) and corresponding possible macroradicals during radical cross-linking.[a]

Biopolymer		Macroradical	
Cellulose			
Chitin			
Methylcellulose (MC)			
Hydroxyethyl cellulose (HEC)			
Hydroxypropylmethyl cellulose (HPMC)			
Carboxymethyl cellulose (CMC)			
Carboxymethyl chitin (CMCh)			
Carboxymethyl chitosan (CMCts)			

[a] R = H or corresponding substituent.

5. Composite hydrogels

There are few concrete and operational applications of pure hydrogels to date, such as injectable thermoset gels (mentioned above), membrane separation,[30] and encapsulation of active species,[39] although much fundamental research on their preparation has been developed. In fact, most of the pure hydrogels may not fit one specific purpose due to the lack of some feature, structure, or property. By mixing with another polymer or inorganics, novel structural materials with advantages of both components can be obtained, which

tremendously enhances the appeal of the resulting composite hydrogels in various areas. In this review, we will concentrate on two-component composite hydrogels made from cellulose, chitin, or chitosan as a matrix for various applications.

5.1 Natural polymer-based hybrid hydrogels

The preparation processes of composite hydrogels are based on those of pure hydrogels, including dissolution (or dispersion) and cross-linking. Compared to making pure hydrogels, the only extra step during formation of natural polymer-based hybrid hydrogels is the mixing of two biopolymer solutions (usually using the same solvent) before shaping into a gel with or without a cross-linker (identical to those mentioned above). The second biopolymer can also be incorporated by impregnation after obtaining the cellulose or chitin scaffold.[165] When blending with biopolymers such as CMC, sodium alginate and pectin, which have carboxyl groups on the polymer chains, the hydrogel system can be cross-linked particularly with divalent or trivalent ions, *e.g.*, Ca_2^+ and Al_3^+, owing to their chelate formation with the carboxyl groups (Fig. 2).[166,167]

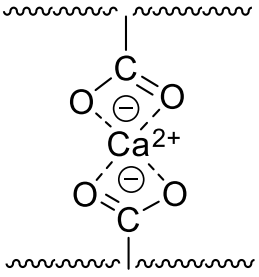


Fig. 2. Divalent metal cross-linking through chelate formation with carboxyl groups.

5.2 Biopolymer/synthetic polymer hydrogels

When mixing with synthetic polymers (*e.g.*, polyethylene glycol (PEG) and polyvinyl alcohol (PVA)), the preparation processes are identical to those of natural polymer-based hybrid hydrogels.[168-171] However, for the grafting, the monomers of the synthetic polymer are often homopolymerized in the cellulose or chitin solution with the assistance of an initiator upon heating,[172,173] irradiation (microwave,[174,175] Electron-Beam,[176,177] UV irradiation[178]) or both.[179] In some cases, grafting can take place before polymerization, *e.g.*, acrylic acid (AA) was able to link first to the biopolymer *via* esterification, acting as the active grafting sites on the chains for polymerization.[180]

There are a variety of initiators reported in the literature including potassium persulfate (PPS),[181] ammonium persulfate (APS),[182] ceric ammonium sulfate (CAS),[183] cerium ammonium nitrate (CAN),[184] benzoyl peroxide (BPO),[173] 2,2'-azobisisobutyronitrile (AIBN),[172] trihexyltetradecylphosphonium persulfate (TETDPPS),[185] and the photoinitiator 2,2-diethoxyacetophenone (DEAP).[178] As an example, sulfate ion radicals ($SO_4^{-\bullet}$) are produced from PPS upon thermal dissociation, which further react with water molecules in the solution to generate hydroxyl radicals ($OH^\bullet$). Both radicals react with monomers and cellulose and produce active sites ($C=C^\bullet$ of monomers, and $-O^\bullet$ on side chains of cellulose) for polymerization and grafting to produce a branched composite network. Meanwhile, the radical cross-linker, MBAAm, can be applied to chemically cross-link the network.

5.3 Biopolymer/inorganic hydrogels

To introduce inorganics into the hydrogel network, several approaches have been adopted: a) simply mixing the target inorganics with the biopolymer solution followed by shaping into a gel;[186-188] b) transition of the inorganic precursor into target inorganics in the biopolymer solution (or suspension) along with (or followed by) gelation;[189-191] c) *in situ* transition of the precursor in the hydrated gel or dry scaffold;[192-199] or d) using BC as a template for the ordered deposition of target inorganics during fermentation.[200] The precursors for various inorganics and the corresponding transition processes are listed in Table 7.

Table 7. Precursors for various inorganics and the corresponding transition processes.

Organics		Precursor	Transition	Ref.
Hydroxyapatite (HA)		$H_3PO_4/Ca(OH)_2$; $H_3PO_4/CaCl_2$;[a] $Ca(NO_3)_2/(NH_4)_2HPO_4$; $Ca(NO_3)_2/NH_4H_2PO_4$; $CaCl_2/Na_2HPO_4$	Precipitation reaction	196,201-205
Silver nanoparticle (Ag)		$AgNO_3$	Hydrothermal, or catalytic[b] reduction	187,192,206-209
Zinc oxide (ZnO)		$Zn(CH_2COO)_2{\cdot}2H_2O$; $Zn(NO)_2$	Catalytic[c] reduction	188,191,197,198
Silica (SiO_2)		Tetraethoxysilane (TEOS)	Hydrolysis and condensation (H/C)[d]	189,190,194,210
		Na_2SiO_3	Reaction in ethanol/water at pH 10–10.5	211
Titanium dioxide (TiO_2)		Tetrabutyl titanate ($Ti(OBu)_4$)	Hydrolysis and condensation (H/C)[e]	212
Iron Oxides	Fe_3O_4	$FeCl_3{\cdot}6H_2O/FeCl_2{\cdot}4H_2O$; $FeCl_3{\cdot}6H_2O/FeSO_2{\cdot}7H_2O$	Hydrolysis and condensation (H/C)[e]	193,199,200,213
	$CoFe_2O_4$	$FeSO_4/CoCl_2$; $FeCl_3/CoCl_2$		214,215
	Fe_2O_3	$FeCl_2$; $FeCl_3$		216-218

[a] Phosphorylation of cellulose could first be performed to enhance the transition;[202] [b] Reduction catalysts for Ag: $NaBH_4$,[206] ethylene glycol (EG),[207] polyethylene glycol (PEG),[219] ascorbic acid,[208] or sodium citrate;[187,209] [c] Reduction catalysts for ZnO: ammonium hydroxide,[197] triethanolamine (TEA),[198] or NaOH;[188,191] [d] H/C catalysts for SiO_2: ammonia,[210] heteropoly acids,[189] acetic acid,[194] or HCl;[190] [e] H/C catalysts for TiO_2 and iron oxides: ammonia,[193] NaOH,[199,212,215-218] or NaOH/KNO_3[214] upon heating. (Dilute HCl could be used to prevent hydrolysis of the precursors.[199])

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6. Applications

6.1 Drug delivery

6.1.1 Controlled release. Incorporation of a second component into the hydrogel system at different dosages will change the structure and morphology of the network, subsequently controlling their diffusion properties. CMC in the hydrogel system contributes to enhanced pore sizes due to the electronic repulsion of carboxyl groups, leading to a large swelling ratio (in this paper defined as the mass ratio of the original hydrogel to the dried one) of 1000 g/g, as well as faster release of protein drugs.[220] Another biopolymer, lignin, also leads to a more homogenous and less dense structure of the resulting composite hydrogel, and an increase in lignin content causes an increase in release rate.[221] On the other hand, the higher density and the homogeneous, smaller pores in the chitin or cellulose nanowhisker nanocomposites, allow not only a reinforcing stucture,[92,93] but also a slow release rate, thus avoiding burst release.[92] Such composite gels with composition-controlled release properties (within hours) are generally applied *in vitro* in near-neutral pH media such as 19/1 water/ethanol solution, simulated body fluid (SBF), phosphate buffer solution (PBS), or simulated intestinal fluid (SIF) as shown in Table 8.[92,220,221]

Table 8. Drug delivery hydrogel systems using cellulose, chitin, or chitosan as the matrix.[a]

Release type	Hydrogel	Cross-linker	Release medium[b]	Ref.
Controlled release by composition	Cellulose/CMC	ECH	PBS (7.4)	220
	Cellulose/lignin	ECH	19/1 water/ethanol	221
	Cellulose/CNW	N/A	SBF (7.4)	92
Thermosensitive	Cellulose/PNIPAAm	MBAAm	Water	223
	Cellulose/PNVCL	MBAAm	—	185
	Chitosan/PNIPAAm	MBAAm and GA[c]	Water	224
	Chitosan/PNVCL	N/A	— (dual responsive)	225
pH-sensitive	Chitosan/alginate	Ca^{2+} and/or TPP	SIF (6.8) and SCF (7.4)	227,228
	Chitosan/pectin	Ca^{2+} and SO_4^{2-}	PBS (7.4) containing pectinase	229,230
	Cellulose/PAAm, or PAAc	MBAAm; N/A	PBS (7.4); SIF (6.8)	175,176
Injectable	Chitosan/CMC	N/A	—	231
	Chitosan/collagen	N/A	Subcutaneous injection	232
	Chitosan/PEG	GNP; N/A	PBS (7.4)	233
Magnetic	Cellulose/Fe_3O_4	GA[c]	PBS (7.4); SA/AA (5.0)	193

[a] Carboxymethyl cellulose (CMC); Cellulose nanowhisker (CNW); Epichlorohydrin (ECH); Genipin (GNP); *N,N'*-methylenebisacrylamide (MBAAm); Polyacrylic acid (PAAc); Polyacrylamide (PAAm); Polyethylene glycol (PEG); Poly(*N*-isopropylacrylamide) (PNIPAAm); Poly (*N*-vinylcaprolactam) (PNVCL); Sodium acetate–acetic acid (SA/AA) buffer solution; Simulated body fluid (SBF); Phosphate buffer solution (PBS); Simulated colonic fluid (SCF); Simulated intestinal fluid (SIF); [b] Release medium: the most commonly used release medium for each, or the medium in which the gel shows maximal swelling; [c] Glutaraldehyde (GA) is not a common cross-linker for the cellulose matrix.

Drug release from hydrogels can also be controlled by using gel structures that can change reversibly in response to environmental stimuli. Temperature-sensitive hydrogels are probably the most commonly studied class of environmentally-sensitive polymer systems in drug delivery research.[222] The common characteristic of temperature-sensitive polymer networks is the presence of hydrophobic groups, such as methyl, ethyl, propyl groups, *etc.* As temperature increases, inter-polymer chain associations through hydrophobic interactions among hydrophobic segments strengthen, resulting in the shrinking of the hydrogel. When grafting *N*-isopropylacrylamide (NIPAAm) or *N*-vinylcaprolactam (NVCL) o cellulose or chitosan, negatively thermosensitive drug release hydrogel systems are obtained.[185,223-225] These hydrogels show a decreased swelling ratio with increasing temperature and thereby can be applied as “on–off” release devices, with “on” (swelling) at low temperature and “off” (shrinking) at high temperature.

6.1.2 Targeted release. It would be most desirable if drug release could be administered in a manner that precisely matches the physiological needs at specific sites (site-specifi targeting). The most attractive route of targeted release is

controlled by pH triggering. The pH gradient in the human gastrointestinal tract ranges from 1 to 7.5 (saliva 5–6, stomach 1–3, intestine 6.6–7.5, and colon 6.4–7.0).[226] Therefore, hydrogel systems exhibiting minimal swelling at acidic pH and maximal swelling around neutral pH can be used as potential oral drug carriers for intestine or colon-specific delivery.

While pure chitosan hydrogels (cross-linked or not) usually show a maximal swelling at low pH,[102,103,111,112] multilayer chitosan/alginate composite hydrogel beads cross-linked with Ca^{2+} and/or TPP,[227] and single-layer chitosan/alginate beads dually cross-linked with Ca^{2+} and SO_4^{2-},[228] exhibit a low drug release in simulated gastric fluid (SGF) but sustained release in simulated intestinal and colonic fluids (SIF and SCF), thus achieving intestine or colon-specific delivery. Chitosan/pectin hydrogels are also capable of colon-specific delivery because of their mucoadhesion characteristics and enzyme-dependent degradation.[229,230] In addition, polyacrylic acid (PAAc)- and polyacrylamide (PAAm)-grafted cellulose hydrogels show maximal swelling near neutral pH because of the generation of $–COO^-$ groups *via* the deprotonation of –COOH in PAAc and the hydrolysis of $–CONH_2$ in PAAm, respectively.[175,176]

Thermoset hydrogel systems, such as some pure derivative hydrogels (mentioned above), chitosan/CMC,[231] chitosan/collagen,[232] and chitosan/PEG,[233] can be injected into the body as a liquid, and form a gel *in situ* where the body temperature is above their lower critical solution temperature (LCST), offering the potential to serve as targeted drug carriers without the need for invasive surgeries. Moreover, such hydrogels usually significantly prolong the release time up to a few weeks due to the efficient encapsulation of drugs. In addition, magnetic-induced transference is potentially useful for applications in drug targeting delivery, *e.g.*, magnetite/cellulose microspheres loaded with drugs or fluorogen are hypothesized to be able to deliver to and localize in specific locations by using an external magnetic field.[193]

6.2 Tissue engineering

Tissue engineering is a most recent application of hydrogels, in which they are used as scaffolds to mimic many roles of extracellular matrixes and to engineer new tissues, *i.e.*, these scaffolds provide space and nutrients for new tissue formation, and potentially control the structure and function of the engineered tissue *in situ* or *in vitro*.[234] Currently, hydrogel scaffolds are at or near clinical uses in engineering many tissues in the body including cartilage, bone, muscle, skin, fat, artery, ligament, tendon, liver, bladder, and neurons.[12]

Hydrogel scaffolds in tissue engineering must meet a number of design criteria to function appropriately and promote new tissue formation, including processability, biodegradability (through hydrolysis[167] or enzymatic cleavage[165,205,235-237]), biocompatibility (*i.e.*, excellent cell viability/proliferation,[167,201,238,239] without inflammatory response[240]), bioactivity (*i.e.*, biomineralization),[238,241] cell adhesion ability,[165,204,205,240] *etc.* Hybridization of the matrix (cellulose or chitin) with a second component improves one or some of these properties of the scaffolds, *e.g.*, hydroxyapatite (HA) and silica enhance mechanical strength, calcification, as well as accelerate biodegradation,[237,238,242,243] while collagen and gelatin increase strength and cell attachment.[165,236,244]

The optimum pore sizes of scaffolds in tissue engineering have been shown to be 5 μm for neovascularization,[245] 20–125 μm for regeneration of adult mammalian skin,[246] and 100–350 μm for regeneration of bone.[247] However, it was later suggested that the microarchitecture plays a role in tissue regeneration, *e.g.*, bone can be regenerated in freeze-dried scaffolds with medium pore sizes as low as 16 μm (>90% porosity and concave spherical shape of the pores) *via* hematoma osteoinduction instead of osteoconduction in big pores.[248]

A selection of porous pure and composite scaffolds (dried) based on cellulose, chitin, or chitosan along with their physical properties are given in Table 9. Also, the mechanical properties of human cortical and cancellous bone are listed for comparison. While factors such as drying methods, biopolymer concentration, and cross-linking degree (mentioned above) have impacts on the pore sizes of hydrogels, pore sizes of the scaffolds can also be enhanced either by adding a "porogen" (*e.g.*, polymethylmethacrylate (PMMA)[201] and NaCl[165]) or by adding 1% surfactant to the biopolymer solution.[68]

It can be seen that the dry porous scaffolds exhibit at least one order of magnitude lower mechanical strength compared to cancellous bone and orders of magnitude lower than cortical bone. In addition, gel swelling (which will occur during cell culture) usually results in a decrease in the mechanical strength.[249] Therefore, hydrogel scaffolds are being widely used in the area of nonload bearing tissue engineering. It has been reported that chitin/HA, chitosan/alginate, and chitosan/silica can be placed into bone defects in a minimally invasive manner to promote bone regeneration.[237,243,244] The scaffolds have also been applied in other tissues, *e.g.*, the chitosan/gelatin scaffold prepared using a novel fabrication process by combining rapid prototyping, microreplication, and freeze-drying techniques possessed well-organized hepatic architectures.[236]

Some dense scaffolds (generally air-dried) match cancellous bone properties and are capable of internal fixation of bone fractures, *e.g.*, a chitosan/HA nonporous composite showed a higher bending strength and modulus of 86 MPa and 3.4 GPa respectively.[250] It is noteworthy, that Ge *et al*. found an injectable thermoset chitosan/HA/Na_2CO_3 solution, which gelated within 9 min at 37 °C, and led to angiogenesis *in vivo* when loaded with cells.[251]

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Table 9. Porous scaffold composites designed for (potential) tissue engineering and their properties.[a]

Matrix	The 2nd component	Cross-linker	Porosity (%)	Pore size (μm)	Compressive module (MPa)	Tensile Strength (MPa)	Young's modulus (MPa)[b]	Ref.
Cellulose	N/A	N/A; Kymene	71–99	0.01–10; 47.5; 100	0.20–0.24	—	8–9; 200–300	68,70,151,252,253
	Collagen	Carbodiimide technique[c]	—	15	—	84.6; 275	8.8×10^2; 9.5×10^3	239,254
	Pectin	$CaCl_2$	88	10–250	—	—	3.987	167
	HA	N/A	85–90	250–450	—	—	—	201
Chitin	N/A	N/A	82–97	$2–50\times10^{-3}$; 40–160	—	3.0–13.6	60–386; 9.32; 3.6	43,67,78,89,255
	Collagen	UV-irradiation	63–78	260–330	—	—	—	165
	Gelatin	N/A; GlcNAc	—	—	—	5–44	—	241,256
	Silica	N/A	—	—	—	—	—	238
	HA	N/A	69–78	200–400	0.27	—	0.32	204,205,237,242
Chitosan	N/A	N/A	—	1–250	—	5×10^{-3}	—	148,257
	Collagen	GA	85	37–55; 100–200	—	0.31	—	235,240
	Gelatin	GA	90–95	100	0.26	0.45–1.15	—	236,258
	Alginate	$CaCl_2$	92	100–300	0.46 (C)	—	8.16	244,259
	Silica	N/A	—	—	—	0.96	55.53	243
	HA	N/A	95	20–60	—	—	7.8–13.5	196,251,260
Cancellous Bone			—		4–12	—	100–500	261,262
Cortical bone			—		130–180	50–151	$(1.2–1.8)\times10^4$	263,264

[a] Glutaraldehyde (GA); *N*-acetyl-D-(+)-glucosamine (GlcNAc); Hydroxyapatite (HA); [b] The large difference between the modulus of the same kind of scaffold may be related to the different materials and preparation methods used; [c] Cellulose was first esterified with glycine.

6.3 Wound dressing

An ideal wound gel dressing should allow gaseous exchange, maintain the proper moisture level and constant temperature of the wound bed, remove excess exudates, protect the wound against bacteria and contamination, accelerate healing, and alleviate pain. It should also be non-toxic, non-allergenic, non-adherent, and easily removed without trauma. Currently, various forms (such as fibers, membranes, and sponges) of wound dressing products based on BC, chitin, chitosan, and their derivatives are commercially available,[11,265] of which deacetylated chitin or chitosan is a hemostat, and possesses a natural antimicrobial property due to the polycationic nature.[266] Some wound dressing gels and their outstanding features are listed in Table 10.

Since cellulose itself has no antimicrobial activity to prevent wound infection, ZnO or Ag nanoparticles (NPs) can be impregnated into the cellulose gel system to achieve antimicrobial ability.[197,206,207] The mechanisms of the bactericidal effects of ZnO and Ag NPs are different: it is assumed that water molecules can react with incorporated ZnO particles, leading to the generation of reactive oxy-radicals or hydroxyl-radicals that may cause oxidative injury inside bacterial cells,[197] while Ag NPs may penetrate inside the bacteria or attach to the surface of the bacteria disturbing permeability and respiration functions.[267] Higher concentrations of ZnO or Ag NPs are required for eukaryotes to achieve comparable toxic effects than for bacterial cells, leading to biocompatibility of the materials for human cells.[187,188] Without the antibacterial property, the BC/alginate sponge can be conceived as a temporary wound dressing material due to its appropriate cell attachment and good tear resistance properties.[268]

Wet chitin hydrogel membranes show similar water vapor transmission rate (WVTR) to that of intact skin, as well as water uptake ability and flexibility, thus are potentially capable of both transpiring substantial amounts of excess exudate and

maintaining occlusivity and wound moisture.[269,270] In addition, chitin wound dressings generally show preferred medium or weak adhesion with cells, which is caused by either the globular morphology of proliferative cells or the smaller amount of active free amino groups.[187,271] Incorporating hydrophilic PAAc into the gel system offers two advantages: controlled water sorption and cell attachment of the dressing at the wound site, which is important in the wound healing process.[180] As with cellulose dressings, the antibacterial ability of chitin dressings can be improved by hybridization with ZnO or Ag NPs.[187,188,209]

Table 10. Pure and composite gels based on cellulose, chitin, or chitosan as potential wound dressings and some of their properties.[a]

Matrix	The 2nd component	Cross-linker	Unique properties	Ref.
Cellulose	N/A	N/A	High ability to bind water (BC gels)[b]	122,265
	Ag NPs	N/A	Antibacterial	206,207
	ZnO NPs	N/A		197
	Alginate	Ca^{2+}	Good tear resistance (0.75–3, T[c]; porous)	268
Chitin	N/A	N/A	WVTR close to that of intact skin; high water uptake[b]	269,270
	PAAc	N/A	Controlled water uptake and cell attachment	180
	Ag NPs	N/A	Antibacterial, blood-clotting, weak attachment	187,209
	ZnO NPs	N/A	Antibacterial; 0.02–0.05 (T; porous)	188
Chitosan	N/A	N/A	Hemostatic, antimicrobial, WV and O_2 permeable, non-irritant (chitosan-LA), 59.87 (T; nonporous)[b]	109,110,272,273
	Gelatin	GA	Improved healing effect; antimicrobial	258,274
	Hyaluronan	N/A	Lower WVP and adhesion; antimicrobial	275
	Ag NPs	GNP	Antimicrobial; 26–29 (T; porous–porogen), 583–795 (E[c])	219,276
	ZnO NPs	N/A	Antimicrobial; 0.15 (T; porous)	277

[a] Bacterial cellulose (BC); Glutaraldehyde (GA); Genipin (GNP); Lactic acid (LA); Nanoparticles (NPs); Polyacrylic acid (PAAc); Water vapor (WV); Water vapor permeability (WVP); Water vapor transmission rate (WVTR); [b] The gel wound dressing has already been commercialized; [c] T: Tensile strength (MPa); E: Young's modulus (MPa).

In addition to the hemostatic, antimicrobial, and permeable (for both water vapor (WV) and O_2) properties, chitosan dressings are non-irritating and do not cause allergic reactions, especially the ones prepared using lactic acid (LA) as the solvent instead of acetic acid.[110,272] Incorporation of antibiotics in the wound dressings has been developed for further inhibition of wound infection.[109,273] Hybridization with gelatin can improve the healing effect because of the strong bioactivity of gelatin whose main components are collagen, a few protein amylases, and certain organic substances,[274] while hyaluronan helps weaken the water vapor permeability (WVP) and cell adhesion, which are desirable characteristics for wound dressings.[275]

The strength of wound dressings is related to the drying method and water content, which is consistent with the tissue scaffolds. In addition, nonporous or porogen-induced porous dressings that are obtained by air-drying are two orders of magnitude stronger than the porous ones obtained by freeze-drying.[188,219,268,272,276,277] Almost all hybrid composite gels meet the strength standard for wound dressings, since a low strength of 0.1 MPa is adequate for a wound dressing material.[277]

6.4 Water purification

Many liquid- and solid-phase extraction techniques have been used for the removal of toxic pollutants from water such as chemical precipitation, flocculation, flotation, coagulation, membrane filtration, ion exchange, adsorption, and electrochemical treatment.[278] Hydrogels have attracted special attention for water purification through adsorption, due to their high absorbency, porous structure, rich functional groups, and relatively low crystallinity. Incorporation of different components into the gel system endows the resulting hybrid hydrogels with abilities to remove various aquatic pollutants such as metal ions (transition or radioactive), dyes (cationic or anionic), and other ions (nitrogenous or phosphorous), *etc.* (Table 11).

It is known that dissolved pollutant ions or molecules can easily penetrate into cellulose or chitin hydrogels and establish bonds with the amine ($–NH_2$) and/or hydroxyl (–OH) groups at appropriate pH values generally through three different kinds of interactions: a) complexation (or chelation) between the lone pair electrons of N and/or O and the metal ions;[73,199,279,280] b) crystallization of the metal ions with the complexed metals as nucleation sites;[73,278] or c) electrostatic attraction (or ion exchange) between the protonated amino groups and various anions.[281,282] In addition, cross-linking has been found to decrease the adsorption capacity of the gel (although the strength or stability increases) primarily due to the decrease of functional groups, and a decrease in swelling ability of the ge also decreases sorption.[111,134,283]

Table 11. Adsorption capacities of hydrogels for removal of various pollutants from water.[a]

	Pollutant	Hydrogel (shape[b]; mass ratio)	Cross-linker	q_e[c] (mmol/g)	q_m[d] (mmol/g)	pH[e]	Ref.
Metal ions	Hg^{2+}, Cu^{2+}, Pb^{2+}	Chitin (M[b])	N/A	Hg^{2+}: 1.8; Cu^{2+}: 1.8; Pb^{2+}: 1.1	—	5	73,279
		Cellulose (M)		Hg^{2+}: 0.9; Cu^{2+}: 0.7; Pb^{2+}: 0.5	—		
		Chitin/cellulose (M; 3:1)		Hg^{2+}: 1.7; Cu^{2+}: 1.5; Pb^{2+}: 1.3	Hg^{2+}: 3.85; Cu^{2+}: 2.00; Pb^{2+}: 2.44		
	Cu^{2+}	Cellulose (B[b])	N/A	0.10	0.37	6	284
		Cellulose/collagen (B; 1:3)		0.14	1.06		
		Cellulose/chitosan (B; 1:1)	EGDE; N/A	0.44–0.65[f]	0.84	6	280
		Chitosan (B)	TPP, GA, EGDE, or N/A	0.31–1.0;[f] 1.29;[g] 2.11[h]	0.31–1.0;[f] 1.90;[g] 2.58[h]	4 or 4.5	111,134, 283
		Chitosan/alginate (B; not reported)	N/A	1.0	1.06		283
		Chitosan/PVA (B; 4:3)	N/A	—	0.75	6	300
	Hg^{2+}	Chitosan (B)	EGDE	0.91	0.91	4	293
		Chitosan/PAAm (B; not reported)		1.61	1.61		
	UO_2^{2+}	Chitosan (B)	TPP	0.67	1.0	5	112
		Chitosan/PVA IIH[i] (Bu[b] ;3:1)	EGDE	—	0.55[j]		297
	Cd^{2+}	Chitin/Fe_3O_4 (B; *ca.* 7:2)	N/A	0.933	—	> 7	199
	Pb^{2+}, Mn^{2+}, Cr^{3+}	BC/Fe_3O_4 (B; *ca.* 5:4)	N/A	Pb^{2+}: 0.25; Mn^{2+}: 0.22; Cr^{3+}: 0.21	—	*ca.* 7	200
	As^{3+}/As^{5+}	Cellulose/Fe_3O_4•NH_3 (M; *ca.* 3:7)	N/A	—	1.2	3	299
		Chitosan/TiO_2 (B; *ca.* 7:3)	N/A	—	0.047	7	289
	EB, NR, GV, RB	Chitin/SiO_2 (B; 1:14)	N/A	—	EB: 0.15; NR: 1.06; GV: 0.14; RB: 0.0062	EB: 5; NR: 6; GV: 8; RB: 4	288
Dyes	AR 37, AB 25	Chitosan (B)	EGDE; N/A	—	AR: 0.11 or 0.24;[f] AB: 0.34 or 0.63[f]	AR: < 6; AB: < 4	135
	CR	Chitosan (B)[k]	N/A	0.30	0.30	5	281
		Chitosan/CNT (B; 100:1)[k]	ECH; N/A	0.53; 0.65	0.53; 0.65	5	285-287
		Chitosan/PVA/Fe_3O_4 (B; 1:1:1)	N/A	0.67	0.67	6	213
	NO_3^-	Chitosan (B)	N/A	0.65	1.45	5	282
	NH_4^+	Chitosan/PAAc (P[b]; *ca.* 1:7)	N/A	*ca.* 0.4	7.8	6-7	290
Others	$H_2PO_4^-$	Cu(II)-loaded Chitosan	GA	0.97	0.97	5	294
	Ag^+	Chitosan IIH[i] (B)	ECH	—	1.2	5	296
	DBTS	Chitosan IIH[i] (Bu)	GA	0.09[j]	—	—[m]	295
	Phenols	Tyrosinase-loaded chitosan (M)	N/A	—	—	7	298

[a] Carbon nanotube (CNT); Epichlorohydrin (ECH); Ethylene glycol diglycidyl ether (EGDE); Glutaraldehyde (GA); Polyacrylic acid (PAAc); Polyacrylamide (PAAm); Polyvinyl alcohol (PVA); Tripolyphosphate (TPP); Anionic dyes: Acid Red 37 (AR 37), Acid Blue 25 (AB 25), Congo red (CR), Erythrosine B (EB), and Remazol Black B (RB); Positive dyes: Gentian Violet (GV), and Neutral Red (NR; protonatable); Dibenzothiophene sulfone (DBTS); [b] Bead (B); Bulk (Bu); Membrane (M); Powder (P; obtained by milling the dry gels); [c] Adsorption capacity at the pollutant concentration of 1 mmol/L; [d] Maximal monolayer adsorption capacity calculated by the Langmuir adsorption model; [e] The most suitable pH condition to achieve the most effective adsorption; [f] Depending on whether cross-linked or not; [g] The decrease of biopolymer concentration contributes to a much higher sorption; [h] Formaldehyde pre-treatment could enhance the adsorption; [i] Ion-imprinting hydrogel (IIH); [j] The lower adsorption ability of chitosan/PVA IIH may be due to the much lower uranium concentration tested in this article than in others (0.34 *vs.* 9.5 mmol/L); [k] A core–shell structure could be generated by a sodium dodecyl sulfate (SDS; as an anionic surfactant) gelation process;[285] [l] Adsorption capacity at the DBTS concentration of 4 mmol/L; [m] Adsorption was performed in an acetonitrile solution.

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The addition of a second component to the biopolymer can increase the adsorption capacity of the final material. For example, the incorporation of collagen is believed to endow cellulose gels with much better adsorption ability because of the active amino groups of collagen.[284] Zhu *et al*. used BC beads as adsorbents without removing entrapped dead bacteria cells and found that the adsorption capacity was improved because of the multiple functional groups (such as carboxyl groups, phosphoryl groups, hydroxyl groups, phosphate groups, amino groups, and amide groups) existing in the proteins, polysaccharides, and lipids of the cells, resulting in formation of coordination complexes between N, P, O, or S and metal ions.[200] Also, 0.01 wt% (relative to the chitosan matrix) carbon nanotubes (CNTs) impregnation was useful for enhancing the adsorption capacity of the composite beads due to the large specific surface area and layered hexagonal arrays of carbon atoms in CNTs.[285-287] In SiO_2 composite hydrogels, the SiO_2 skeleton has negative charge density ($Si\text{-}O^-$) above pH 3, which can interact with positively charged pollutants.[288] When TiO_2 is added to chitosan, the resulting beads have a net positive charge ($TiIV\text{–}OH_2^+$) at pH < pH_{pzc} (point of zero charge (pzc)), which can attract arsenic oxyanions (As(III): $AsO(OH)_2^-$, $AsO_2(OH)^{2-}$, AsO_3^{3-}; As(V): $AsO_2(OH)_2^-$, $AsO_3(OH)^{2-}$, AsO_4^{3-}).[289] For removal of NH_4^+ cations, a hydrogel system grafted with polyacrylic acid (PAAc) is well worth considering due to the ionic interaction between the positively charged NH_4^+ and negative adsorption sites ($–COO^-$) of the adsorbent.[290]

Research on selective removal of pollutants from contaminated water using cellulose or chitin hydrogels is scanty. Some research has focused on the adsorption of Cu^{2+}, and there is literature suggesting higher adsorption selectivity of adsorbents for Cu^{2+} over Cd^{2+}.[291] However, in most cases, neither cellulose nor chitin (or chitosan) hydrogels show selectivity for a given pollutant. In order to achieve selective adsorption, two approaches are generally followed: introducing a specific functional group in the system or utilizing ion (or molecular) imprinting techniques. Yan *et al*. modified the surface of chitosan hydrogel beads with chloroacetic acid to introduce carboxyl groups, producing a product with a higher coordination affinity for Cu^{2+} over Mg^{2+} and Pb^{2+},[292] while chitosan beads surface grafted with PAAm showed selectivity in adsorbing Hg^{2+} over Pb^{2+} due to the action of the amide groups.[293] Further, after Cu^{2+} extraction, the same chitosan beads can be used for further phosphate ($H_2PO_4^-$) adsorption from aqueous solutions, where the Cu^{2+} ions on the surface of the beads play a very important role in phosphate adsorption at pH 5.[294] (At pH < 3, most of the Cu^{2+} ions are released; while at higher pH, OH^- groups strongly competed with $H_2PO_4^-$ for the chitosan–Cu^{2+} active sites.)

The ion (or molecular) imprinting technique results in ionic (or molecular) recognition cavities (conformational memory) inside the polymeric network using the ion or molecule (generally identical to the one to be selectively adsorbed) as an imprint template during the cross-linking of polymer chains and before elution.[295-297] Although scarcely explored, a third strategy is to incorporate enzymes into the biopolymer matrix to selectively modify the target adsorbate before sorption. Phenols were selectively oxidized by the enzyme tyrosinase (immobilized within chitosan gels) into reactive *o*-quinones which reacted with nucleophilic amine functional groups present in the chitosan matrix.[298]

Adding a second component to the material can also be used to improve the properties and/or functionalities of the resulting composite hydrogels. For example, when incorporating magnetite or other iron oxides into a gel system, the resulting adsorbent can be easily attracted out of the effluent, using a magnetic field.[199,213] Nata *et al*. prepared an aminated Fe_3O_4/cellulose composite which not only could be easily collected but also demonstrated a very high adsorption ability towards metal ions because of the protonation of the introduced NH_2 on Fe_3O_4 at low pH.[299] To enhance the sorbent's mechanical strength or chemical stability, crucial in batch or column water remediation, fillers of high modulus such as SiO_2,[288] and CNTs[285-287] can be incorporated; or the biopolymer can be cross-linked with other polymers, such as the self-assembly chitosan/PVA,[213,300] or chitosan/alginate composites.[283]

Recycling of the gels and reusing them is of extreme importance for the sustainability of the process. There are several eluents proposed to desorb the ions from gels, including SC,[200] ethylene diamine tetraacetic acid (EDTA),[300] HNO_3, $AlCl_3$, $CaCl_2$, NaCl,[213,290] *etc.*, which are chelating or cation exchange agents. In addition, since most of the gels have better adsorption capacity for pollutants when the pH is within 5–7, acid (HCl)[199] or alkali (NaOH)[281,282,294] solutions can be used to strip the ions from the adsorbents. Using these methods, the desorption efficiency can reach 99%, and the gels can be reused at least 4 cycles with sometimes even higher sorption efficacy than the first time.[199,213,290]

6.5 Other applications

Hydrogels from cellulose, chitin, or chitosan are utilized widely in many other diverse fields. One of their major uses is as the supporting material for functional additives, including a) membranes containing electrolyte molecules used in a capacitor or battery (*e.g.*, cellulose/chitin containing ILs and H_2SO_4,[301,302] and chitosan/PVA containing NH_4NO_3 and ethylene

carbonate (EC)[303]); b) porous aerogels containing inorganic catalysts (*e.g.*, Ag,[192,304] TiO_2,[305,306] and SiO_2[307]) for heterogeneous catalysis; and c) hydrogels containing fluorescent quantum dots (QDs) potentially used in fluoroimmunoassays and biological labeling.[186,308] Indeed, chitosan aerogels are potential base catalysts themselves due to the amino groups.[91,309]

In addition to their role in catalysis, cellulose/SiO_2 aerogels are able to act as excellent thermal insulators while being flexible and translucent, and having high mechanical stability and processability.[210] Furthermore, pure inorganic nanomaterials, such as TiO_2,[310] SiO_2,[210] and Fe_2O_3[217] with porous networks that are useful in photocatalysis, biosensor, bioseparation, respectively, can be obtained by calcining the corresponding composite hydrogels in various forms as sacrificial templates.

There are unique polyelectrolyte hydrogels consisting of polyanionic polymers (*e.g.*, CMC, alginate, and PAAc) and/or polycationic polymers (*e.g.*, chitosan, PAAm, and polyvinylamine (PVAm)[311]), which can be used as electronic elements. Smitha *et al*. identified the chitosan/PAAc composite as an ideal proton exchange membrane in the direct methanol fuel cell, as it exhibited high proton conductivity, low methanol permeability, and adequate thermal and mechanical stability.[312] CMC/chitosan and cellulose/alginate hybrid hydrogels are potential electroactive sensors or actuators in electronic devices because they swell or shrink differentially on two electrode sides (anode and cathode) as a consequence of mobile ion transport in an electric field, causing bending towards one electrode.[313,314] To facilitate this, a plasticizer (*e.g.*, glycerol) can be added into the system to weaken the intra- and inter-molecular hydrogen bonding in the matrix and thereby improve the flexibility of the product.[314]

7. Conclusions and Perspectives

Because of their renewable, biocompatible, and biodegradable characteristics, hydrogels made from cellulose, chitin, and some of their derivatives are attracting and will continue to draw both academic and industrial attention. Considering their other advantages, such as excellent processability, high absorbency, porosity, bioactivity, abundant active groups, *etc.*, it is not surprising that these hydrogels have already found extensive applications in many areas such as drug delivery, tissue engineering, wound dressing, water purification, catalysis, electrical elements, and more. Much fundamental research has been conducted on the preparation of these hydrogels, including the development of solvent systems for native cellulose or chitin, hydrogel formation techniques, physical or chemical cross-linkers, drying methods, *etc.*, however, recent studies have mainly focused on potential applications of the hydrogels in water purification and pharmaceutical and medical systems, and less attention has been paid to other areas such as their use in the electronic and optical fields.

For future studies, more attention should be focused on 1) "green" (safe solvents, none or nontoxic cross-linkers), and/or low-energy processing for hydrogel systems; 2) injectable hydrogels forming safely within the body without the need of surgery for targeting drug release or tissue engineering; 3) pH or enzymatic triggered drug release at targeted sites; 4) hydrogel degradation in a controlled manner in tissue engineering or sustained drug release; 5) development of hydrogel functionalization as an economical way to improve efficacy, selectivity, or recycling during water purification; 6) development of new applications of hydrogel systems (*e.g.*, polyelectrolyte complex hydrogels as electrical elements); 7) development of cellulose and chitin nanowhiskers to prepare novel hydrogels with unique characteristics such as high mechanical strength and photonic properties; and 8) development of novel biopolymer isolation methods (*e.g.*, IL isolation) to produce cellulose and chitin with high molecular weights and thus unique hydrogels. Undoubtedly, hydrogels based on cellulose, chitin, and their derivatives still offer abundant promising opportunities in various industries, although significant challenges will need to be overcome before commercialization, and thus fundamental research into the nature of these systems should also continue.

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Synopsis

A review of the synthesis and applications of renewable, biocompatible, and biodegradable hydrogels made from cellulose, chitin, and some of their derivatives indicates increased attention due to their excellent processability, high absorbency, porosity, bioactivity, and abundant active groups.