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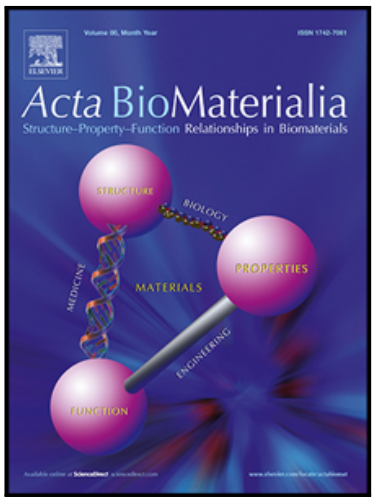

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Engineering nanocomposite hydrogels using dynamic bonds

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Graphical Abstract

Abstract

Nanocomposite (NC) hydrogels are promising biomaterials that possess versatile properties and functions for biomedical applications such as drug delivery, biosensor development, imaging, and tissue engineering. Different strategies and chemistries have been utilized to define the structure and properties of NC hydrogels. In this review, we discuss NC hydrogels synthesized using dynamic bonds, including dynamic covalent bonds (e.g., Schiff base and boronate ester bond) and non-covalent bonds (e.g., hydrogen bonds and metal-ligand coordination). Dynamic bonds can reversibly break and reform to provide self-healing properties to NC hydrogels as well as be influenced by external factors to allow NC hydrogels with stimulus-responsiveness. The presence of dynamic bonds in NC hydrogels can occur at the polymer-polymer or polymer-particle interfaces, which also determines whether the particles act as fillers or crosslinkers in hydrogels. Several representative examples of NC hydrogels fabricated using dynamic bonds are discussed here, focusing on their design, preparation, properties, applications, and future prospects.

Keywords

nanocomposite hydrogels, dynamic bonds, self-healing, stimuli-responsiveness

1. Introduction

Hydrogels are three-dimensional crosslinked polymeric networks with high water absorption capacity that show great potential in biomedical applications such as drug delivery [1], antibacterial applications [2], tissue engineering [3], biosensor development [4], and cell imaging [5]. There has been growing interest in the development of hydrogels with tailorable

physicochemical and mechanical properties, multi-functionality, stimulus-responsiveness, and self-healing behavior. Such versatile hydrogels exhibit tunable properties and mechanical responses under dynamic loading. However, traditional hydrogels with a single non-reversible covalently crosslinked network are usually brittle, show low response to external stimuli, cannot be remolded, and lack the ability to self-heal when the crosslinked network is broken [3]. Traditional hydrogels formed by covalent bond might release heat during the crosslinking process and shrink due to polymerization (such as thiol-ene reaction [6], copper(I)-catalyzed azide and alkyne cycloadditions (CuAAC) [7]). In addition, traditional hydrogels usually have poor mechanical properties due to their uneven network structure and lack of energy dissipation mechanisms, further limiting their applications in biomedical science and tissue engineering [8]. To address these challenges, researchers have applied different strategies to fabricate strong and tough hydrogels. For example, multiple crosslinking chemistries (e.g., covalent and non-covalent bonds) have been utilized in the syntheses of double-network (DN) hydrogels [9], triple network (TN) hydrogels [10], nanocomposite (NC) hydrogels [11], and NC double-network (ncDN) hydrogels [12].

NC hydrogels are tough hydrogels in which nanoparticles (NPs) are incorporated into the matrix to reinforce the polymeric network [13, 14]. The structures of NC hydrogels possess different sizes and morphology. As an example, Tong *et al.* synthesized tunable networks of graphene hydrogels (GDH), where GDH-1 (close-cell GDH) and GDH-2 (open-pore GDH) were achieved *via* different connection paths between covalent bonding [15]. The connection paths were adjusted with optimization of the polymer concentration as well as the temperature during the reaction. As the temperature increased, open-pore GDH with increased pore size was observed due to the ring-opening reaction. In addition, smaller the size of NPs provided better thermal stability and electrical conductivity of NC hydrogels.

The major advantages of NC hydrogels compared to traditional hydrogels are that the NPs can significantly enhance the mechanical properties, provide desirable functions to the hydrogels, as well as allow the modulation of the properties and features of hydrogels by the application of “smart” stimuli. The unique properties of NPs also allow NC hydrogels to form innovative functional materials with unique characteristics (e.g., fluorescence [16], conductivity [17], magnetic responsiveness [18], and antibacterial properties [19]) for specific applications. For instance, biocompatible gold NPs allow NC hydrogels to be used for drug delivery [20], silver NPs with antibacterial properties can be used in wound dressing [21, 22], carbon-based nanomaterials with good conductivity have been widely used in sensors and actuators [23, 24]; hydroxyapatite provides good biological activity and improved mechanical properties of artificial bones for bone tissue engineering applications [25, 26]; the magnetic response of iron oxide NPs can be used to heat NC hydrogels permitting controlled drug release [27, 28]. Particularly, with rational choices of components and crosslinking mechanisms, NC hydrogels can be used for immune regulation for *in vivo* immunological applications. As an example, chitosan has been demonstrated to possess immune-stimulating property and mediate the activation of antigen-presenting cells [29]. Therefore, chitosan and its derivatives can be used as adjuvants for the development of prophylactic vaccination and vaccine pellets [30]. On the other hand, magnesium ions are required for integrin

binding and cell attachment to modulate the phenotypic polarization of macrophages [31], where the macrophages are key immune cells that regulate the immune system, disease progression, and wound healing [32]. Thus, magnesium ions have been applied in biomedical implants to induce host macrophages to modulate host responses with alternative polarization (M2) [33, 34]. As bisphosphonate groups are able to chelate with magnesium ions through coordination bond formation [35], NC hydrogels contained bisphosphonate groups are promising materials to manipulate the immune system *in vivo* [36]. A recent example of using NC hydrogels for immune-regulation is that Fan *et al.* synthesized an injectable adhesive hydrogel as a photothermal-derived antigen reservoir for enhanced anti-tumor immune [37]. This hydrogel was based on a thermosensitive nanogel containing catechol groups and was loaded with MnO_2 NPs. After intratumor injection, the concentrated nanogel dispersion was transformed into a viscous hydrogel. The photothermal effect of MnO_2 NPs induced immunogenic cell death and released a large amount of autologous tumor-derived protein antigens under near-infrared radiation, showing an ideal immunostimulatory substance that avoided the problem of tumor heterogeneity.

NC hydrogels are typically prepared using two major strategies based on whether NPs are physically embedded in the matrix or chemically bonded to the polymeric network (**Scheme 1**) [38, 39]. To physically incorporate NPs in the hydrogel network, NPs can either act as fillers in hydrogels without any chemical interaction with the polymeric network [40-42] or be introduced into the network by blending or *in situ* NP formation (**Scheme 1a** and **1b**) [43-45]. On the other hand, surface-functionalized NPs can behave as gelators to chemically crosslink the polymeric network of hydrogels (**Scheme 1c**) [46]. Nevertheless, some favorable features of biomaterials (e.g., self-healing, stimulus-responsiveness, shear-thinning, and viscoelasticity) are still missing in NC hydrogels fabricated using covalent crosslinking [47-49].

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Scheme 1. NPs are used as fillers in NC hydrogels: (a) NPs exist in the NC hydrogels by blending method or (b) *in situ* NP formation. NPs are used as crosslinkers in NC hydrogels: (c) surface-functionalized NPs exist in the NC hydrogels by grafting method.

NC hydrogels fabricated using dynamic bonds have been demonstrated to exhibit unique characteristics and dynamic features compared to traditional NC hydrogels. Given the utility of dynamic bonds at the material interface (especially at the NP-polymer interface), the interface stress relaxation and the mechanical properties of NC hydrogels can be significantly improved [57, 58]. Dynamic bonds include dynamic covalent bonds (e.g., Schiff base, disulfide bonds, boronate ester bonds, and Diels-Alder reaction) and non-covalent bonds (e.g., hydrogen bonds, coordination bonds. hydrophobic interactions, host-guest interactions, and electrostatic interactions) (**Scheme 2**). Dynamic bonds present in hydrogels can be used as sacrificial bonds to effectively dissipate energy, thereby enhancing the mechanical properties of the hydrogels [50]. The rupture and reconstruction

of reversible dynamic bonds not only provide the hydrogels with high strength but also impart the hydrogels with recoverability and self-healing properties, facilitating their advanced applications in different fields [51]. The inherent advantages and disadvantages of dynamic bonds contribute to the properties of NC hydrogels as well as determine the subsequent applications. (**Table 1)** For example, hydrogels fabricated using a dynamic Schiff base linkage are pH-responsive and generally decompose in a weakly acidic environment [52, 53], making them potential drug carriers for cancer treatment [54, 55] and wound healing [56, 57]. A summary of the NC hydrogels fabricated using dynamic bonds is shown in **Table 2**.

There are several comprehensive reviews about the formation of hydrogels with dynamic bonds to perform favorable properties (e.g., self-healing and stimuli-responsiveness) for a wide range of applications. In this review, we provide an overview of the preparation and properties of NC hydrogels fabricated with dynamic bonds and highlight a few of their recent applications. We categorize the examples by the locations of the dynamic bonds in NC hydrogels: polymer-polymer interface, polymer-particle interface, and both of the polymer-polymer and polymer-particle interfaces.

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Scheme 2. Dynamic covalent bonds and non-covalent bonds are dynamic bonds used in the fabrication of NC hydrogels.

Table 1

Comparison of the advantages and disadvantages of different types of dynamic bonds presented in NC hydrogels

pes of dynamic nds	**Advantages**	**Disadvantages**	**Applications**	**Reference**
ronate ester bond	Nonspecific chemical bonding *In situ* formation	Bond can't be formed under extreme pH conditions	Detection of glucose	[58, 59]
ls-Alder ction	One-step reaction Thermally reversible reaction	Requires high temperature and a long time to reform the bonds	Treatment of heat therapy	[60]

ulfide bond	Room temperature interaction	Controlled by oxidizing agents and reducing agents Produce reaction by-products	Controlled and targeted drug and gene delivery	[51, 61]
iff base	Excellent mechanical strength	Amadori rearrangement	Cancer treatment Controlled drug release	[62] [63-65]
drogen bond	Nontoxic chemical bonding	Poor mechanical strength	Detection of drug release Antibacterial activity	[66, 67] [68]
drophobic raction	Widely formed in every water-containing system	Poor bonding strength	Drug release	[69]
st-guest raction	Convenient to adjust the molecular properties of the guest species through a wide range of stimuli	Specific in some cases. Binding to each other temporarily	Complement of patient-specific stem	[70]
ctrostatic raction	Rapid bond formation	Need positive and negative reactive groups	Wound healing	[71]
ordination bond	Different applications with different kinds of metal ions	Metal ions remaining in the human body	Bone tissue reproduction Printable drug release	[72] [73]

Table 2

Summary of NC hydrogels fabricated with dynamic bonds.

Nanoparticle	Polymer	Dynamic bond	The location of the dynamic bond	Application	Reference
Gold nanoparticles	Poly(NIPAAm[a]-*co*-APBA[b]-*co*-AAm[c]) and PVA[d]	Boronate ester bond	Polymer-Polymer	Remotely healable cell capture and release systems, and cytocompatible soft fillers of biological cavities	[74]
Cerium oxide nanoparticles	PVA[d] and chitosan	Hydrogen bond	Polymer-Polymer	Antibacterial and wound healing	[43]
Iron oxide nanoparticles	Chitosan and 4-formylbenzoic acid functional polyethylene glycol	Schiff base	Polymer-Polymer	Cancer treatment and tissue regeneration	[75]
BPEI[e] conjugated graphene	BPEI[e] and aldehyde-modified biopolymers of chondroitin sulfate multialdehyde	Schiff base	Polymer-Polymer	Postoperative breast cancer recurrence	[76]
Iron oxide nanoparticles	GC[f] and OHA[g]	Schiff base	Polymer-Polymer	3D printing	[77]
Iron oxide nanoparticles	PLGA[h]-MPEG[i] and PFOB[j]@MPEG[i] (guest)	Host-guest	Polymer-Polymer	Tumor treatment	[44]

	(crosslink agent: α-CD[k] (host))				
Aldehyde modified Carbon dot	PEI[l]	Schiff base	Polymer-NP		[78]
Amine modified Carbon dot	Oxidation dextran	Schiff base	Polymer-NP	Antibacterial activity	[79]
Amine modified silica nanoparticles	FBEMA[m] and P(MPC-*co*-FBEMA)[n]	Schiff base	Polymer-NP	Controlled Drug Delivery (*in vitro*)	[64]
2-Furyl-(undecenyl)-11-triethoxysilane or 3-maleimidopropyltriethoxysilane modified silica nanoparticles	Poly (butyl methacrylates) and poly-siloxanes	Diels-Alder	Polymer-NP		[80]
Maleimide- containing gold nanoparticles	Furan functional chitosan	Diels-Alder	Polymer-NP	Drug delivery	[81]
Thiol surface-functionalized mesoporous silica nanoparticles	$(PEGSH)_4$[q]	Disulfide	Polymer-NP		[82]
Iron oxide nanoparticles	mPEG-COOH[o], 4cPEG-OH[p]	Coordination	Polymer-NP		[83]
Bioactive glass (100 nm nanoparticles agglomerated in 10 μm clusters)	$(PEGSH)_4$[q] (crosslink agent: $HAuCl_4$)	Coordination	Polymer-NP	bone generation	[84]
Gold nanoparticles	PNIPAm[a] and *N*,*N*-bis(acryloyl)cystamine	Coordination	Polymer-NP	Temperature responsiveness and drug delivery	[85]
Magnesium silicate nanoparticles	Bisphosphonate functionalized hyaluronic acid	Coordination	Polymer-NP	Drug delivery	[86]

Acrylated bisphosphonate magnesium nanoparticles	Bisphosphonate functionalized hyaluronic acid	Coordination	Polymer-NP	Regulates the differentiation of encapsulated stem cells	[87]
Gold nanoparticle (guest)	Au(I): 6-thioguanosine (host)	Host-guest	Polymer-NP	Biomolecule recognition, nanotechnology, drug delivery	[88]
Zirconium hydroxide	Copolymerization of 2-acrylamido-2-methyl propane sulfonic acid and acrylamide	Hydrogen bond	Polymer-NP	Healable artificial cartilage and tissue engineering	[89]
Zirconium hydroxide	Copolymerization of acrylic acid and *N*,*N*-dimethylacrylamide	Hydrogen bond	Polymer-NP	Electro-responsiveness	[90]
Acetalated-*β*-cyclodextrin (~200 nm) and graphene oxide	PVA[d]	Hydrogen bond	Polymer-NP	Drug delivery	[91]
Silicate nanoplatelets [zeta potential of -39 mV]	Gelatin [zeta potential of 10 mV]	Electrostatic interaction	Polymer-NP	Hemorrhage	[92]
Nanoparticle can be composed of either poly(styrene) or poly(ethylene glycol)-*block*-poly(lactic acid) (PEG-*b*-PLA)	HOMC[r] derivatives	Hydrophobic interaction	Polymer-NP	Drug delivery	[93]
Tannic acid modified cellulose	PVA[d]	Boronate	Polymer-Poly	Tissue substitute	[94]

nanocrystal	(crosslink agent: borax)	ester bond	mer		
		Hydrogen bond	Polymer-NP		
$MnFe_2O_4$ nanoparticles	PVA[d]	Boronate ester bond	Polymer-Polymer	Conductive bulk	[95]
Nanofibrillated cellulose	(crosslink agent: borax)	Hydrogen bond	Polymer-NP		
Iron oxide nanoparticles	Difuran functionalized diphosphonic acid-terminated PEO[s] and trismaleimide	Diels-Alder	Polymer-Polymer	Drug delivery	[96]
		Coordination	Polymer-NP		
Gold nanoparticles	Thiol functionalized hyaluronic acid, thiol functionalized gelatin, and PEG[i]	Disulfide bond	Polymer-Polymer	Bioprinting	[51]
		Coordination	Polymer-NP		
Silver nanoparticles	PVA[d] and chitosan	Hydrogen bond	Polymer-Polymer	Antibacterial activity	[45]
			Polymer-NP		
Amine modified silica nanoparticles	Unmodified and oxidized alginate, gellan gum	Schiff base	Polymer-Polymer	3D printing (*in vitro* and *in vivo*)	[97]
		Coordination	Polymer-NP		
PBA-rGO[t]	TEG-CS[u] and PDA[v]	Schiff base	Polymer-Polymer	Antibacterial activity	[98]
		Boronate	Polymer-NP		

		ester bond				
Multiwall carbon nanotubes	Am[c], AEAM[w] and F127[x]	Hydrogen bond Schiff base Ionic interaction	Polymer-Polymer Polymer-NP	Soft sensors	electronic	[99]

[a] *N*-isopropylacrylamide

[b] 3-(acrylamido)phenylboronic acid

[c] Acrylamide

[d] Poly(vinyl alcohol)

[e] Branched polyethylenimine

[f] Glycol chitosan

[g] Oxidized hyaluronate

[h] Poly(lactic-co-glycolic acid)

[i] Poly(ethylene glycol)

[j] Perfluorooctyl bromide

[k] α-cyclodextrin

[l] Polyethylenimine

[m] 4-formylbenzoate ethyl methacrylate

[n]Poly(2-methacryloyloxyethyl phosphorylcholine-*co*-4-formylbenzoate ethyl methacrylate)

[o] Linear monofunctionalized polyethylene glycol carboxylic acid

[p] 4-arm catechol-terminated polyethylene glycol

[q] 4-arm poly(ethylene glycol) tetrathiol

[r] Hydroxypropylmethylcellulose

[s] poly(ethylene oxide)

[t] Phenylboronic acid modified reduced graphene oxide

[u] Triethylene glycol-grafted chitosan

[v] Polydextran aldehyde

[w]2-aminoethyl acrylamide hydrochloride

[x]Triblock copolymer of poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)

2. Dynamic bonds at the polymer-polymer interface

Hydrogels constructed using dynamic bonds are an emerging field with several advantages over traditional static hydrogels [100], and the incorporation of NPs in the dynamic hydrogels can further improve their properties as well as functions. Directly incorporating bare NPs into hydrogels through physical blending or *in situ* NP formation is a simple and straightforward strategy to prepare NC hydrogels. In particular, the physical embedding method allows easy scale-up of the preparation of NC hydrogels. In this section, dynamic bonds (e.g., imine bonds, hydrogen bonds, and host-guest complexation) used to crosslink the polymers in the NC hydrogels are discussed.

2.1 NC hydrogel preparation using blending method for NP incorporation

Hydrogels prepared using dynamic imine bonds have been widely demonstrated due to the relatively easy functionalization of the polymers with amine and aldehyde groups. Ko *et al.* developed self-healing ferrogels using glycol chitosan (GC), oxidized hyaluronate (OHA), and superparamagnetic iron oxide NPs (SPIONs) [77] (**Fig. 1**). The GC/OHA/SPION ferrogels were formed by simply blending all the materials, where GC and OHA were crosslinked through imine bonds. The ferrogels can be produced in various structural shapes (i.e., grid shape and chessboard shape) through extrusion-based 3D printing. The presence of SPIONs in NC hydrogels allows these printed structures to respond to magnetic fields, showing potential applications in 4D printing.

Hydrogen bonding is a popular non-covalent interaction utilized in the formation of dynamic hydrogels [101]. Kalantari *et al.* used chitosan, poly (vinyl alcohol) (PVA), and cerium oxide NPs (CeO_2 NPs) to prepare NC hydrogels [43]. Chitosan and PVA were used to form hydrogels through hydrogen bond formation, and the chitosan/PVA hydrogels were dehydrated before the adding of CeO_2 NP solutions. The chitosan/PVA/CeO_2 hydrogels presented enhanced cell compatibility and survival rate, as well as effective antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), showing great potential for wound dressing applications.

Wu *et al.* synthesized injectable magnetic hydrogels blended with iron oxide NPs (Fe_3O_4 NPs), where Fe_3O_4 NPs were used as magnetic resonance contrast agents to ensure the accurate injection of a magnetic hydrogel nanozyme (MHZ) [44]. The crosslinked network of the MHZ was formed by the self-assembly of PEGylated Fe_3O_4 NPs and α-cyclodextrin (α-CD) through

crystalline host-guest inclusion complexation. The hydrogels provided a combination of hyperthermia and catalytic therapy to tumor cells by creating a high temperature of 42°C and toxic reactive oxygen species (ROS).

2.2 NC hydrogels preparation using in situ NP formation for NP incorporation

Agnihotri *et al.* fabricated antimicrobial NC hydrogels with dynamic bonds using a chitosan-PVA network along with *in situ* formed silver NPs (AgNPs) [45] (**Fig. 2**). Three dynamic interactions in the chitosan-PVA network included hydrogen bonds between chitosan and PVA, hydrogen bonds between glutaraldehyde and PVA, and imine bonds between glutaraldehyde and chitosan. The hydroxyl groups of polymers are ideal sites for anchoring silver ions, helping to stabilize and immobilize AgNPs during the subsequent in situ NP formation. Hence, the hydrogel acted as a carrier during the reaction and subsequently served as a matrix for the immobilization of the synthesized AgNPs. As silver ions tend to interact non-covalently with the hydrogel network, in situ NP formation leads to the formation of a uniform distribution of AgNPs in the hydrogels. Hydrogels were used against *Escherichia coli. (E. coli),* showing that the AgNP-immobilized hydrogels presented superior antibacterial efficacy compared to that of pure hydrogels at all sampling times: the growth of *E. coli* in the AgNP-immobilized hydrogels was reduced by 83.5%, while that in the pure hydrogels was reduced by 24.4% after incubation for 12 h (**Fig. 2b**) [45].

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Fig. 2. (a) Schematic representation of *in situ* synthesis of AgNPs inside the chemically crosslinked chitosan/PVA hydrogels. (b) Antibacterial test of chitosan-PVA hydrogels and AgNPs-loaded chitosan-PVA hydrogels. Reproduced with permission [45].

Gholamali *et al.* fabricated oxidized starch/CuO NC hydrogels for drug delivery application. Pure oxidized starch hydrogels were first prepared *via* crosslinking oxidized starch with hydrogen bonds between polymer chains, while CuO NPs were directly formed in the swollen hydrogel after the oxidation of the Cu (I) ions (**Fig. 3**) [102]. Studies on drug release showed that CuO NPs prolonged the drug release from the hydrogel, which was due to the longer path was required for the migration of the drugs from the NC hydrogels to the medium as well as the adhesive interaction between the drugs and CuO NPs. The drug release time using oxidized starch/CuO NC hydrogels was longer (> 20%) than the time using hydrogels without CuO.

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Fig. 3. (a) Schematic illustration of the *in situ* formation of CuO NPs in the oxidized starch hydrogel network. Drug release behavior of oxidized starch NC hydrogels containing different concentrations of CuO NPs at (b) pH 2.1 and (c) pH 7.4. Reproduced with permission [102].

Yang *et al.* fabricated silica nanoparticle (SNP)-poly(acrylic acid) (PAA) NC hydrogels by the *in situ* grafting of SNP to reinforce the network [103]. Highly flexible NC hydrogels were prepared by using SNPs as fillers and hydrophilic PAA was grafted on the SNP surface through radical polymerization. SNPs were collected by adjacent polymer chains and uniformly dispersed in the PAA matrix. The mechanical properties of the SNP-PAA NC hydrogels were tunable by adjusting the concentration and size of SNPs, where the mechanical strength and toughness of the SNP-PAA hydrogels were improved with the higher proportion of SNPs as well as the smaller particle size.

3. Dynamic bonds at the polymer–particle interface

Incorporating NPs into the hydrogel network through physical blending or *in situ* NP formation is an easy and effective strategy for NC hydrogel preparation. However, the polymer–particle interface cannot be further regulated using bare NPs, and the NPs might be unevenly distributed in the network [38]. Therefore, surface-functionalized NPs are more favorable to provide the possibility of modulating the polymer–particle interface as well as achieving homogeneous particle dispersion [104, 105]. Most importantly, the chemical interactions between polymers and NPs also significantly improve the stability, toughness, and mechanical properties of NC hydrogels [106].

3.1 Dynamic covalent bonds at the polymer–particle interface

Surface-functionalized NPs have been demonstrated to effectively interact with polymers through dynamic covalent bonds to significantly improve the mechanical properties of materials [107, 108]. The interface region of nanocomposites acts as a stress concentrator and becomes the main site of composite failure. Here we provided several examples focusing on the NC hydrogels with dynamic covalent bonds at the polymer-particle interface.

Wu *et al.* utilized amine-functionalized silica NPs as gelators to crosslink aldehyde-containing copolymers synthesized by the free-radical polymerization of 2-methacryloyloxyethyl phosphorylcholine (MPC) and 4-formylbenzoate ethyl methacrylate (FBEMA) (**Fig. 4a**) [64]. The silica NPs played multiple roles in the hydrogel network such as enhancing the mechanical strength of hydrogels and providing drug delivery platforms. The loss modulus of hydrogels can be modulated in a dose-dependent manner, and the elastic property of the hydrogels was almost doubled by slightly increasing the percentage concentration of NPs from 10% to 13% (**Fig. 4b**). The mechanical strength, degradation, and drug delivery behavior of hydrogels were considerably changed by a

slight change in pH at values of 6.4, 6.6, 6.8, and 7.4, indicating its promise as a drug delivery system that can be triggered by local acidosis in tumors and wounds.

Yang *et al.* fabricated NC hydrogels using amine-functionalized carbon dots and oxidized dextran through the formation of imine bonds [79]. Carbon dots synthesized using ε-poly-L-lysine not only contain abundant primary amines on the surface that react with oxidized dextran but also impart extraordinary antibacterial properties to the NC hydrogels (**Fig. 4c**) [27, 109]. Additionally, carbon dots can be released from the network through reversible imine bonds to improve the bactericidal action. NC hydrogels with different ratios of carbon dots and polymers (i.e., 1:3, 1:2, 1:1, and 2:1) exhibited excellent antibacterial activity with notable inhibition zones, where the NC hydrogels killed nearly 100% of *Staphylococcus aureus* (*S. aureus*) after a short contact time at 37°C (**Fig. 4d**). Zengin *et al.* developed the thiol surface-functionalized mesoporous silica nanoparticles and the hydrophilic polymer polyethylene glycol through the dynamic thiol-disulfide bond covalent interaction to form a NC hydrogel [82]. NC hydrogels can significantly improve the mechanical strength of the material. The storage modulus of the hydrogel containing nan particles and that of the polymer alone are 32 ± 5 kPa and 1.3 ± 0.3 kPa, respectively.

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Fig. 4. (a) Schematic diagram of the network formation of P(MPC-*co*-FBEMA) hydrogels using amine-functionalized silica nanoparticles as crosslinking agents. The hydrogels presented an excellent drug release profile in a pH-responsive manner. (b) Rheological properties of P(MPC-*co*-FBEMA) hydrogels prepared from constant polymer content and different loadings of silica nanoparticles. Reproduced with permission [64]. (c) Preparation of the NC hydrogels using amine-modified carbon dots and oxidized dextran. (d) Photograph of the inhibition zones of the NC hydrogels with different ratios of carbon dots and polymers (i.e. 1:3, 1:2, 1:1, and 2:1). Reproduced with permission [79].

3.2 Non-covalent interactions at the polymer–particle interface

Most traditional hydrogels exhibit low mechanical properties and weak toughness due to the lack of energy dissipation as well as the inherent structural heterogeneity within the hydrogel network [104]. Jiang *et al.* fabricated NC hydrogels using zirconium hydroxide ($Zr(OH)_4$) NPs as multifunctional crosslinkers to interact with the copolymers of 2-acrylamido-2-methyl propane sulfonic acid (AMPS) and acrylamide (AM) using hydrogen bonds (**Fig. 5a**) [89]. The NC hydrogels exhibited excellent mechanical properties (tensile strength ~404.3 kPa and compression strength ~36.6 MPa) and self-healing efficiency (~86%) (**Fig. 5b**). The $Zr(OH)_4$ NP-crosslinked NC hydrogels can be further optimized to afford high mechanical strength (tensile strength ~2

MPa and Young's modulus ~1.2 MPa) and fast electrical response by using the monomer of acrylic acid to provide stronger interactions with $Zr(OH)_4$ NPs [90].

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Fig. 5. (a) Schematic illustration of the NC hydrogels using $Zr(OH)_4$ NPs as crosslinkers along with the *in situ* free-radical copolymerization of 2-acrylamido-2-methyl propane sulfonic acid (AMPS) and acrylamide and (AM). (b) The NC hydrogel was stretched about four times compared to its original length and was compressed and rapidly recovered to its original shape. Reproduced with permission [89].

Metal-ligand coordination is a well-known chemical interaction that can be applied to hydrogel formation [110-112]. The metal-ligand crosslinks in hydrogels provide hydrogels with several desirable mechanical properties such as enhanced toughness, self-healing capabilities, stimulus-responsiveness, and high energy dissipation efficiency. Li *et al.* used Fe_3O_4 NPs and catechol-modified polymers to prepare NC hydrogels through catechol-iron coordination, wherein the mono-functionalized polyethylene glycol carboxylic acid (mPEG-COOH)-modified Fe_3O_4 NPs acted as crosslinking agents (**Fig. 6a**) [83]. The reversible catechol-iron bonds in NC hydrogels imparted the hydrogels with stimulus-responsive and self-healing abilities (**Fig. 6b**). In addition, the NC hydrogels responded to a magnetic field owing to the presence of magnetic Fe_3O_4 NPs (**Fig. 6c**).

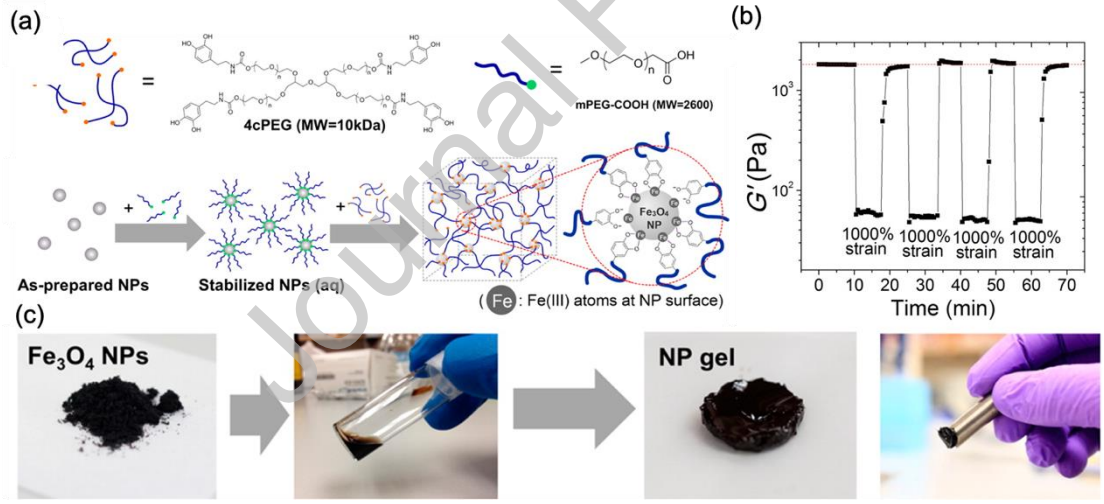


Fig. 6. (a) Schematic illustration of the mPEG-COOH modified iron oxide NPs and catechol-polymers used to form the NC hydrogels *via* catechol-iron coordination. (b) Oscillation strain test in NC hydrogels between 1% to 1000% strain. (c) Demonstration of the magnetic attraction of NC hydrogels. Reproduced with permission [83].

Another popular metal-ligand coordination used in NC hydrogels is the coordination bonding between magnesium ions and bisphosphonate ligands [111]. Particularly, magnesium ions play several important roles in biochemical processes, such as they can significantly enhance the adhesion and diffusion of osteoblast and also promote the mineralization process [113, 114]. Ossipov *et al.* utilized magnesium silicate nanoparticles ($MgSiO_3$ NPs) to crosslink bisphosphonate-functionalized hyaluronic acid through the magnesium-bisphosphonate interaction [86]. In addition, $MgSiO_3$ NPs with porous and hollow-like structures were used as drug carriers with a loading efficiency of ~80%. Zhang *et al.* synthesized bisphosphonate-grafted hyaluronic acid (HA-BP) and mixed it with acrylated bisphosphonate (Ac-BP) and magnesium chloride (**Fig. 7a**) [87], where Ac-BP-Mg NPs were formed *in situ* and used as crosslinkers for HA-BP. The HA-BP-Mg NC hydrogels presented excellent self-healing behavior and injectability (**Fig. 7b–c**), and the injected hydrogels showed no significant toxicity to the human mesenchymal stem cells (hMSCs) (**Fig. 7d**). In addition, the acrylic groups in the introduced structure can be further polymerized under UV irradiation, enhancing the mechanical properties of the NC hydrogels and also preventing cell diffusion and osteogenesis.

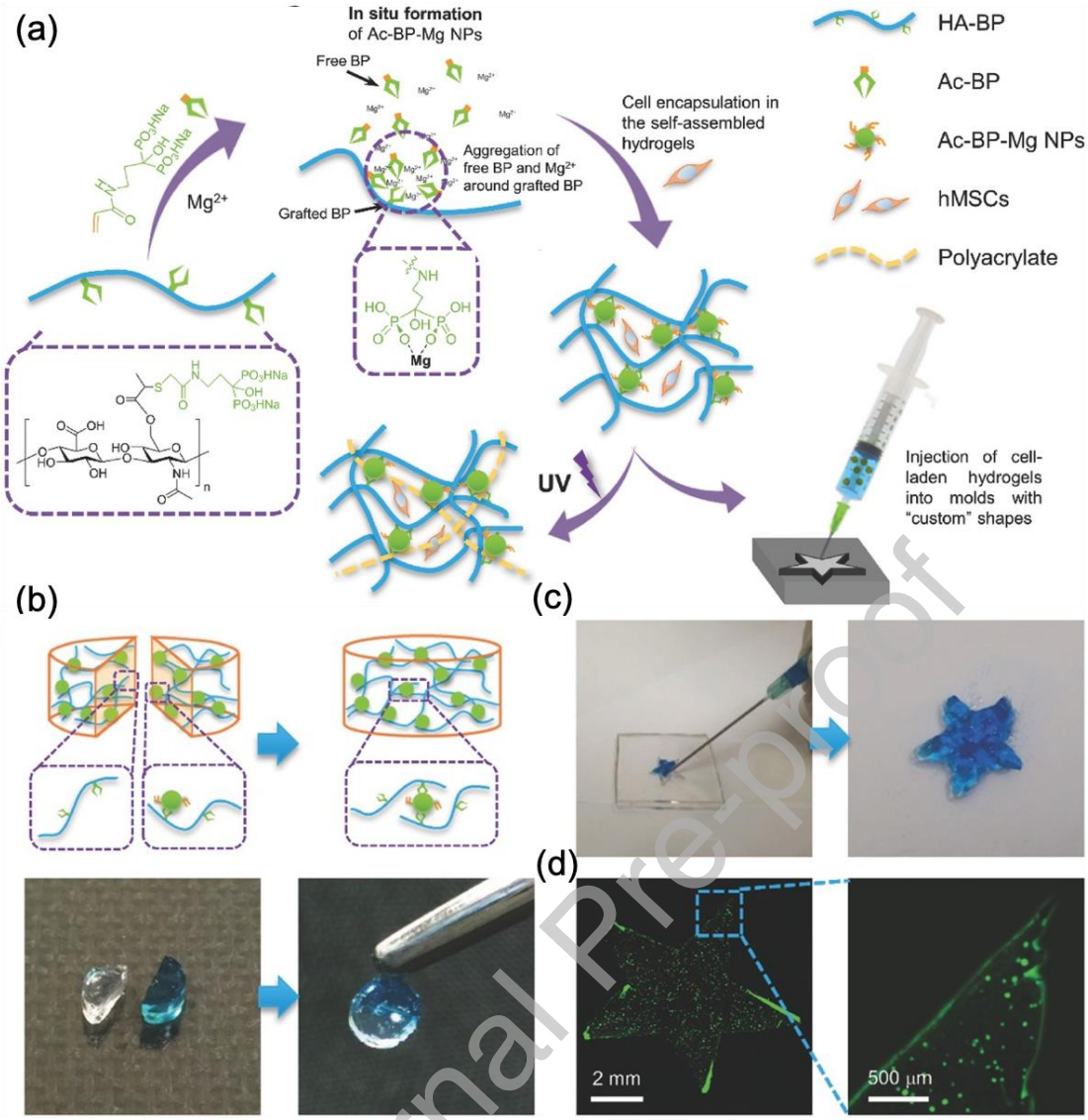
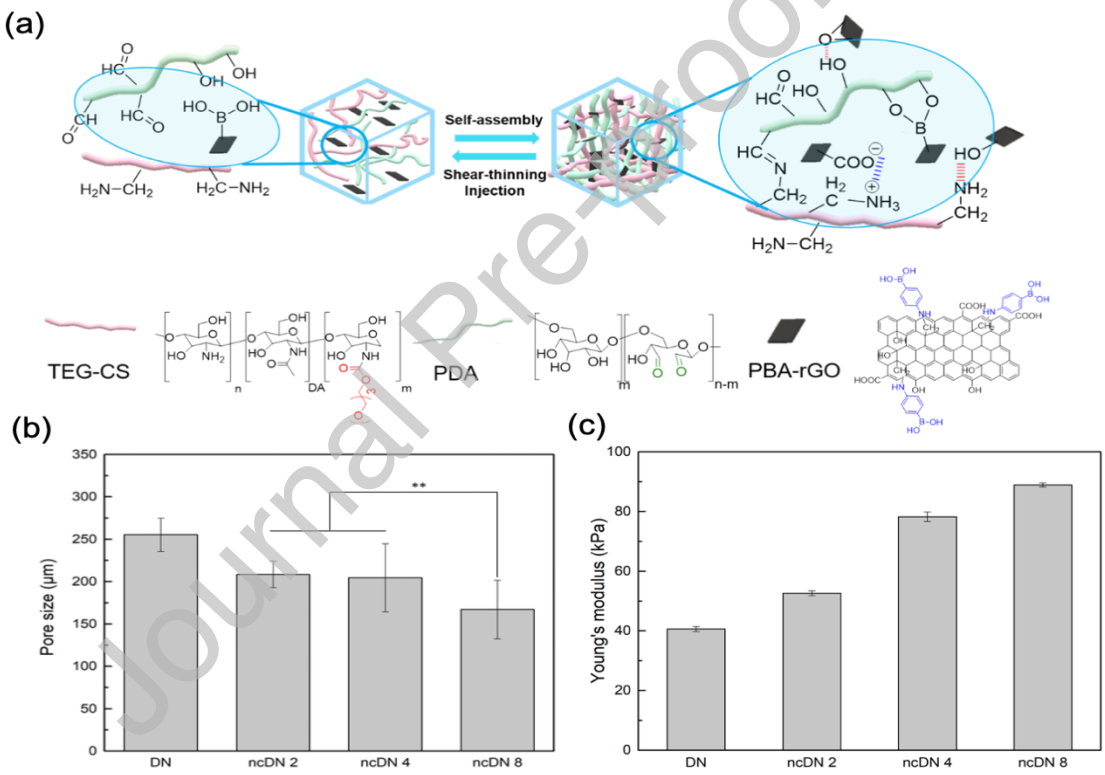


Fig. 7. (a) Schematic illustration of the fabrication of the self- assembled bisphosphonate- grafted hyaluronic acid-magnesium (HA- BP- Mg) NC hydrogels. (b) Schematic illustration and a demonstration of the self-healing behavior of HA- BP- Mg NC hydrogels. (c) A demonstration of the injectability and moldability of HA- BP- Mg NC hydrogels. (d) Live/dead staining of the hMSCs encapsulated in the HA- BP- Mg NC hydrogels after being injected into a star- shaped mold. Reproduced with permission [87].

4. Dynamic bonds at both the polymer–polymer and polymer–particle interfaces

Tsai *et al.* developed a new type of double-network NC (ncDN) hydrogels using multiple crosslinking chemistries and surface-functionalized nanomaterials that exhibit dynamic interactions at both polymer–polymer and polymer–particle interfaces (**Fig. 8a**) [98]. In the ncDN hydrogel design, tri(ethylene glycol)-grafted chitosan (TEG-CS) and polydextran aldehyde (PDA) were crosslinked through imine bond formation between the amine groups on TEG-CS and the aldehyde groups on PDA. In addition, phenylboronic acid-functionalized reduced graphene oxide (PBA-rGO) was used as a multivalent gelator to provide electrostatic interactions and hydrogen bonds with TEG-CS, while generating borate ester bonds and hydrogen bonds with PDA. These dynamic bonds were rapidly formed in the ncDN hydrogels (~10 s) and acted as reversible crosslinks in the network, providing the hydrogels with shear-thinning and self-healing properties. In particular, the properties of the ncDN hydrogels can be fine-tuned by varying the amount of PBA-rGO. For example, with the increase in the content of PBA-rGO, the crosslinked network became denser and the Young's moduli of the hydrogels increased (**Fig. 8b–c**). The ncDN hydrogels retained good cell viability (over 90%) and exhibited antibacterial activity against *E. coli* and *Staphylococcus aureus (S. aureus)*, presenting great potential for biomedical



applications.

Fig. 8. (a) Schematic illustration of the ncDN hydrogels constructed with TEG-CS, PDA, and PBA-rGO through the formation of electrostatic interaction (blue dashed line), hydrogen bonds (red dashed line), imine bonds, and boronate eater bonds. (b) The pore size and (c) Young's modulus of the ncDN hydrogels. Reproduced with permission [98].

Lee *et al.* fabricated NC hydrogels through the reversible imine bonds between oxidized alginate (OxA) and amine-functionalized silica nanoparticles (SiNPs) as well as the physical crosslinking of gellan gum [97]. There was a fivefold increase of yield stress in the NC hydrogels with NP content of 2 wt%, and the printability and structural fidelity of NC hydrogels were also improved. In addition, the NC hydrogel-printed structures can be further stabilized through calcium ion crosslinking without any biotoxicity to mice **(Fig. 9a)**. Wu *et al.* prepared NC hydrogels using one-pot polymerization of acrylamide (AM) and 2-aminoethyl acrylamide hydrochloride (AEAM) in the presence of multiwall carbon nanotubes (MWCNT), aldehyde-modified F127 (triblock copolymer PEO_{100}-PPO_{65}-PEO_{100}, F127-CHO), and LiCl [99]. **(Fig. 10a)** AM played a major role in the formation of the polymeric network through the multiple intermolecular hydrogen bonds. Through the polymerization, AM also introduced the amine-containing monomer AEAM to generate ionic interactions and Schiff base bonds with MWCNT and F127-CHO, respectively. These multiple interactions considerably improved the mechanical strength of the NC hydrogels. Particularly, the integration of dynamic Schiff base bonds with nanofiller reinforcement and micellar crosslinking provided hydrogels with a combination of excellent elasticity and superb self-healing properties. **(Fig. 10b)**

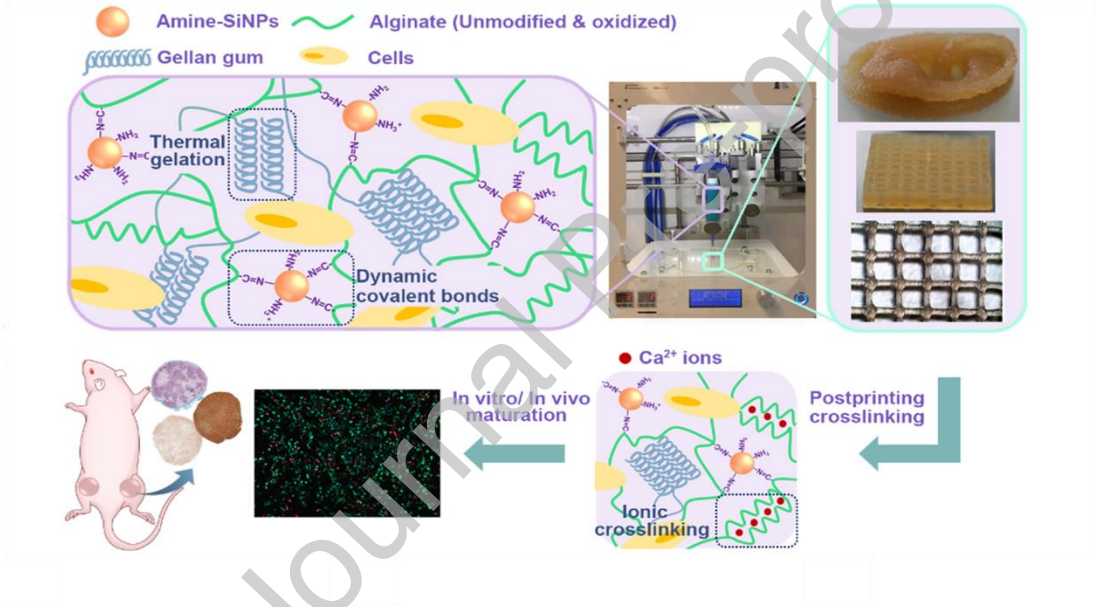


Fig. 9. Schematic presentation of the NC hydrogels based on dynamic covalent imine bonds between SiNPs and oxidized alginate. The NC hydrogels were used as biocompatible bioinks for bioprinting. Reproduced with permission [97].

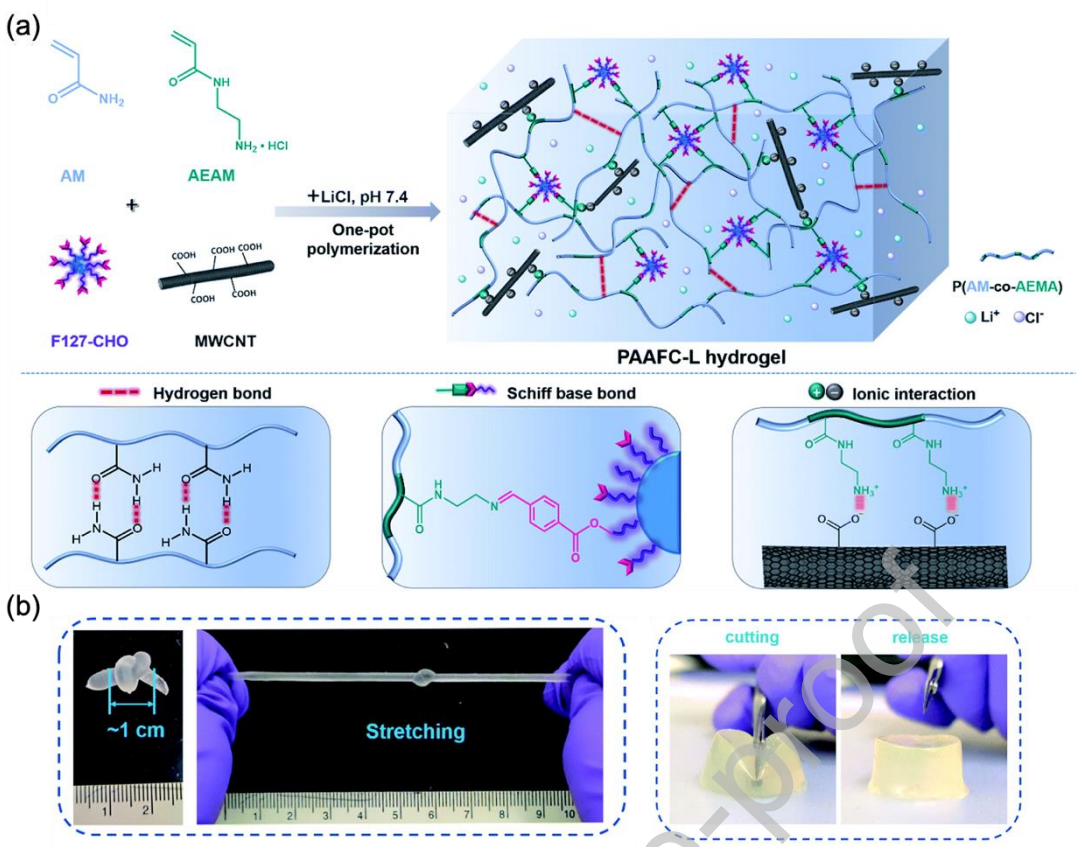


Fig. 10. (a) Schematic illustration of the NC hydrogels constructed with AM-*co*-AEMA copolymer, F127-CHO, and MWCNT through the formation of hydrogen bonds, Schiff base bond, and ionic interactions [99]. (b) Photographs showing a NC hydrogel knot being stretched 10 times compared to its original length, and withstood cutting, and recovered instantly after release with no visible scar left. Reproduced with permission [99].

5. Conclusions and future prospects

Engineering NC hydrogels using dynamic bonds is a rapidly emerging field that provides significant advantages over traditional NC hydrogels. The unique properties and performance of dynamic NC hydrogels such as self-healing, shear-thinning, stress relaxation, stretchability, multi-functionality, and stimulus-responsiveness permit their use in several advanced applications, including controlled and sustained drug delivery, 3D printing, and tissue engineering.

The NC hydrogels with dynamic bonds have performed several desirable properties in current research, however, some concerns and challenges remain.

- The dynamic bonds used in NC hydrogels are currently limited to the Schiff base, hydrogen bonding, and metal-ligand coordination, which decrease the diversity of the dynamic crosslinking network of NC hydrogels. Thus, the development of next-generation NC hydrogels fabricated using various other types of dynamic bonds is needed.
- The development of NC hydrogels should take advantage of the reversible dynamic bonding properties combined with clinical medicine (such as pH response of imine bond can achieve goals for acidic tumor-targeted therapy), with the intrinsic qualities of nanoparticles and polymer (such as silver nanoparticles and chitosan for antibacterial effect and magnesium nanoparticles enhance the adhesion and diffusion of osteoblast and promote the mineralization process) to achieve a more significant effect.
- Computational modeling may be a useful tool to investigate the structure-property relationship at the polymer–particle interface, thus providing a platform for the potential improvement of the performance of dynamic NC hydrogels.
- Metal-based NPs have been demonstrated to crosslink polymers using surface ions (e.g., bisphosphonate/magnesium ion and catechol/iron ion). However, a systematic investigation on the influence of metal ion crosslinking or metal-based nanoparticle crosslinking on the structural, chemical, and physical properties of NC hydrogels is lacking.
- The dispersibility of NPs in hydrogels is also critical, as poor NP dispersion can negatively impact the mechanical properties and structural stability of NC hydrogels.
- A series of innovations in the fields of polymer chemistry, micro- and nano-manufacturing technologies, and biomolecular engineering have broken the limits of designing NC hydrogel networks with customized functions. However, very limited research has focused on the use of NPs to make hydrogel structures through emerging techniques.
- Dynamic bonds provide self-healing and stimulus-responsive properties to NC hydrogels, they may also decrease their mechanical robustness and sustainability. Thus, the thoughtful design and choice of dynamic bonds are required to optimize the physicochemical and mechanical properties of dynamic NC hydrogels for specific applications.
- Controlling the reversible crosslinking chemistry of polymers and NPs, designing tunable structures and properties of hydrogels, and integrating the unique functionality of NPs for biomedical applications are the directions of future research.
- NC hydrogels, especially the NC hydrogels crosslinked using NPs, should be evaluated for their long-term stability in the body. The release of NPs or polymers into systemic organs during degradation must be explored at every step.

- The *in vivo* biocompatibility, biodegradation, biodistribution, clearance rate, and the degree of organ accumulation of NC hydrogels should be considered and investigated systematically when the NC hydrogels are integrated into clinical settings for practical biomedical applications.

Taken together, the rational design of biomedical NC hydrogels requires the control of chemical and physical properties as well as the consideration of biological-related variables. Designing NC hydrogels with strong mechanical strength, long-term biocompatibility, and controllable biodegradability will encounter many challenges for their biomedical applications.

Statement of Significance

This review provides an overview of the current progress in NC hydrogel development using dynamic bonds, summarizing the material design, fabrication approaches, unique performance, and promising biomedical applications. The presence of both nanoparticles and dynamic bonds in hydrogels shows a combined or synergistic effect to provide hydrogels with dynamic features, definable properties, multi-functionality, and stimulus-responsiveness for advanced applications. We believe that this review will be of interest to the hydrogel community and inspire researchers to develop next-generation hydrogels.

Declaration of Competing Interest

The authors declare no competing financial interest.

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