Review

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Nanocomposite Hydrogels and Their Applications in Drug Delivery and Tissue Engineering

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Traditional hydrogels usually possess inferior mechanical properties as well as lacking multi-functionalities. Nano-sized particles/fillers, both inorganic and organic materials, have unique chemical, physical, and biological functions, and have been extensively studied as biomaterials or bio-functional materials. Nanocomposite hydrogels, which combine the advantages of both nano-fillers and hydrogel matrices, may result in improved mechanical and biological properties and find their potential applications in biomedical field. This paper reviews recent developments in the synthesis, preparation, and characterization of nanocomposite hydrogels; their biomedical applications, such as drug delivery matrices and tissue engineering scaffolding materials are also summarized.

KEYWORDS: *Nanocomposite Hydrogel, Drug Delivery, Tissue Engineering.*

CONTENTS

INTRODUCTION

Owing to their porous network structure, swelling/deswelling behavior, and mechanical properties, which provide physical support for cell adhesion and proliferation as well as excellent biocompatibility, hydrogels have been extensively studied in biomedical applications including tissue engineering and drug delivery.[1] There is an increasing demand for hydrogel with enhanced mechanical properties, multi-responsiveness, as well as multi-functionalities with the rapid development of biomedicine. However, the inferior mechanical properties and limited functionality of hydrogel have hindered its wide applications, for example, as load-bearing materials.

Various strategies have been explored to improve the performance of hydrogels, among which is the incorporation of nanoparticles in the hydrogel matrix to fabricate nanocomposite hydrogels (NC gels).[2, 3] Nanoparticles, including inorganic nanoparticles (such as clay, hydroxyapatite, graphene, and metallic nanoparticles) and organic/polymeric nanoparticles, can be used as fillers to reinforce the hydrogel matrix and bring the hydrogel new functionalities as well.[4] Herein, we review the recent research advances in NC gels defined by the type of nanoparticles, with a focus on inorganic NC gels such as clay NC gels, metallic NC gels, carbon nanotube/graphene NC gels, hydroxyapatite NC gels, and magnetic NC gels (Fig. 1). The application of the NC gels in biomedical field, such as delivery of bioactive molecule and tissue engineering scaffolds are also summarized.

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NANOCOMPOSITE HYDROGEL

Clay Nanocomposite Hydrogel

Various kinds of clay, such as montmorillonite (MMT), laponite, and attapulgite have been utilized as the nanofiller in NC gels.[5] Clay NC gels with enhanced mechanical properties,[6] tunable cell adhesion,[7] good biocompatibility, and biodegradability,[8] could be prepared via physical or chemical crosslinking.

Haraguchi et al. first reported the synthesis of clay NC hydrogels using poly(*N*-isopropyl acrylamide) (PNIPAm) as the hydrogel matrix,[9] which exhibited good optical transparency, rapid temperature-sensitive de-swelling, and excellent mechanical performance with elongation at break exceeding 1000%.[9–12] An unique organic/inorganic network structure was proposed for the clay NC gel (Fig. 2), exfoliated clay sheets are uniformly dispersed

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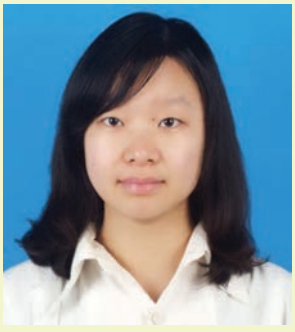

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Chao Zhang earned his B.S. degree in Applied Chemistry (1998), M.S. degree in Polymer Chemistry (2002), and Ph.D. degree in Polymer Chemistry (2005) from Wuhan University, China. He had been working as postdoctoral fellow at the University of Wisconsin-Milwaukee and the University of California, San Diego from 2006 to 2010. In 2010, Dr. Zhang became an Associate Professor of Biomedical Engineering in the School of Engineering at the Sun Yat-sen University, China. His current research interests include the nano-sized drug carriers, contrast agents for medical imaging, and tissue engineering etc.

in an aqueous medium, and a number of flexible polymer chains are attached to neighboring clay sheets through non-covalent interaction, thus clay sheets can act as "cross-linker" in the gel. The PNIPAm/clay NC gels showed a quite uniform network structure even with high content of clay (25 mol%).[9,10] In addition, this NC gel possesses self-healing capability through autonomous reconstruction of crosslinks across a damaged interface.[11] By simply mixing small amount of clay (2–3 wt%) and organic components (sodium polyacrylate and a dendritic macromolecule, less than 0.4 wt%) in water, NC gel could also form via the physical interaction between clay and hydrogel matrix, transparent hydrogel with high mechanical strength and rapid self-healing properties was observed.[12]

The physical properties of NC gels can be controlled by altering the content of clay.[13] NC gels with low and high clay content showed structural difference on elongation. In NC gels with low content of clay, the clay platelets may be aligned perpendicular to the stretch direction; while the clay platelets may be orientated parallel to the stretch direction in NC gels with high content of clay (> 10 mol%), resulting in much-improved mechanical properties.[10]

However, due to the clay–clay interactions, gelation of clay suspensions may occur at high clay content,[14] resulting in poorer mechanical properties than the theoretical values of the NC gels. Inspired by the well-ordered brick-and-motar microstructure of nacre, Wang et al. prepared PNIPAm/clay NC gels with layered structure combining simple vacuum-filtration self-assembly and *in situ* free-radical polymerization, which exhibited greatly improved mechanical and optical properties even at high clay content (25 wt%).[15] The layered NC gels showed unique tensile properties compared with normal NC gels, with highest deformation of 1200% and modulus of 43.2 MPa.

Clay NC gels based on different kinds of gel matrices have been investigated. Natural polymers, i.e., alginate and methyl cellulose, have been used for the preparation of clay NC gels.[16,17] Using biocompatible or bio-absorbable hydrogel matrix, such as polyethylene glycol (PEG),[8]

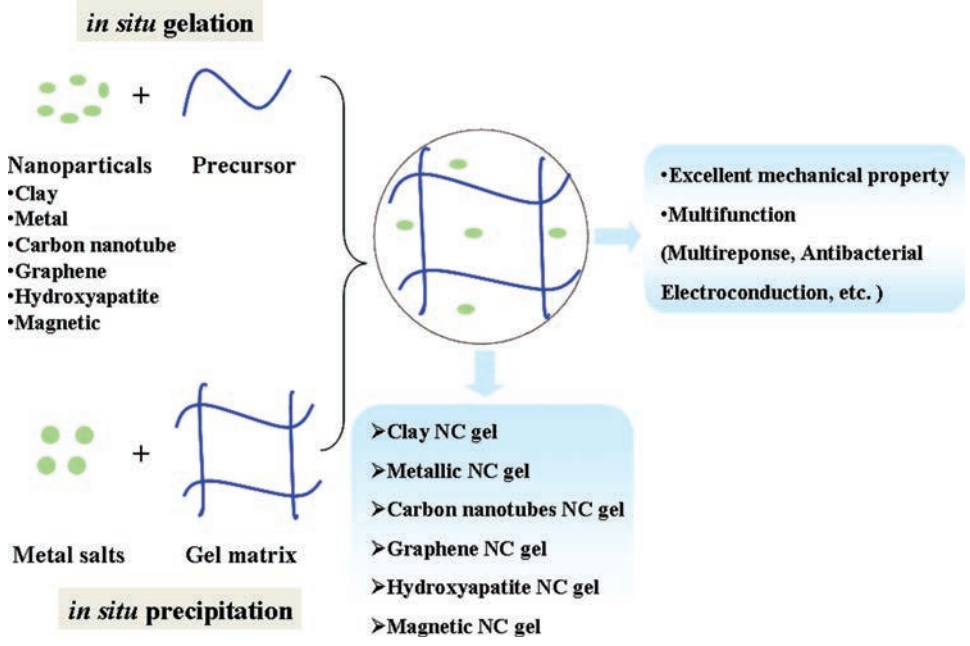

Figure 1. **Preparation and type of nanocomposite hydrogel.**

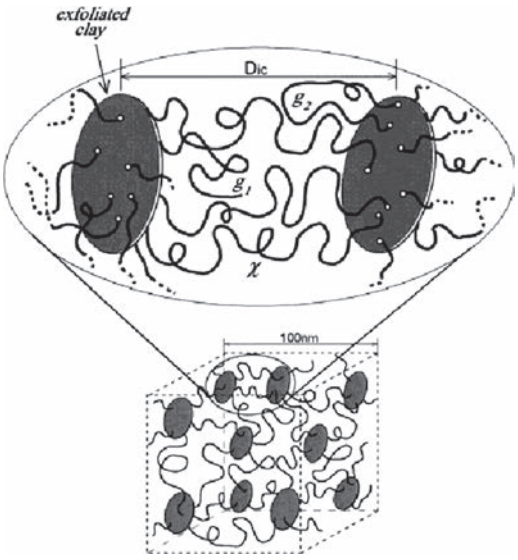

Figure 2. Schematic representation of the structural model with organic/inorganic networks in the NC gel. Reprinted with permission from [9], K. Haraguchi, et al., Mechanism of forming organic/inorganic network structures during *in-situ* free-radical polymerization in PNIPA-clay nanocomposite hydrogels. *Macromolecules* 38, 3482 (2005). © 2005, ACS Publications.

poly(ethylene oxide)-*block*-poly(propylene oxide)-*block*-poly(ethylene oxide),[18] and poly(trimethylene carbonate)-*block*-PEG-*block*-poly(trimethylene carbonate),[19] NC gels with good biocompatibility and enhanced mechanical properties can be fabricated without sacrificing their biocompatibility. In addition, the incorporated clay nanoparticles might also act as drug reservoirs,[20,21] which released drug in stomach and intestine with reduced/no burst release in initial period.[22]

Metallic Nanocomposite Hydrogel

Different kinds of metal nanoparticles, such as gold (Au)[23] and silver (Ag) nanoparticles,[24] have been used as nanofiller in the NC gels; those metallic nanoparticles would afford the NC gels with unique properties including excellent antibacterial activity, optical properties, and electric conductivity.[25]

Different methods have been developed for the synthesis of NC gels with metallic nanoparticles. One of the commonly used methods is the *in situ* polymerization, in which the metallic nanoparticles are mixed with the precursor and then polymerization of precursor is carried out to form gel.[24] The metal nanoparticles can be modified with organic surfactant to obtain homogenous dispersion in precursor sulution.[26] The other way to prepare metallic NC gels is the *in situ* generation of metallic nanoparticles in the hydrogel matrix.[27,28] In this method, hydrogel acts as template for the nucleation and growth of nanoparticles (Fig. 3).[27] Usually, hydrogel is swelled in the metal salts (i. e. $KAuCl_4$) solution, and modulates the formation of colloidal metal nanoparticles (i.e., Au) after the addition of a reductant (i.e., sodium borohydride).[27] Induced by light, the reduction of metal salts to nanoparticles and polymerization of the precursor can occur simultaneously. By utilizing this method, biosensor based on PEG NC gels containing gold nanoparticles and glucose oxidase enzyme were fabricated in one pot.[29] The reduction of metal salts and the polymerization of precursor can also been carried out in one-pot through γ-radiation technique.[30]

Carbon Nanotubes and Graphene Nanocomposite Hydrogel

Carbon nanotubes (CNTs) have attracted great interest since they were first reported in 1991.[31] Due to its chemical/thermal stability, excellent mechanical properties, and electric properties, CNTs can dramatically enhance the mechanical properties of the hydrogels,[32] as well as introduce multi-responsiveness to the hydrogels.[33] Covalent or non-covalent binding of CNTs to the hydrogel matrix has been utilized in the fabrication of NC gels.[34,35] One of the most challenging tasks is to disperse pristine CNTs in the hydrogel matrix homogenously, and functionalization of CNTs via covalently grafting or non-covalent attachment of a polymer chain or molecule can help to resolve this problem.

Homenick et al. prepared a collagen NC gel with poly(ethyleneimine) (PEI) grafted sing-walled carbon nanotube (SWNT), which resulted in a dramatic enhancement of the Young's modulus of the NC gels even at relative low crosslink densities, as compared with that of gels from pristine SWNT.[34] Modification of CNTs through $\pi-\pi$ interaction can also be harnessed to enhance the dispersion of CNTs in hydrogel matrix, for example, water soluble hybrids of SWNT and pyrene modified β-cyclodextrin (Py-β-CD) can be prepared by simply mixing Py-β-CD and SWNT (Fig. 4), and this hybrid may be used as nano-filler in the preparation of supramolecular NC gels via the host-guest interaction.[35]

Graphene can be considered as a single atomic layer of carbon atomic obtained from graphite or as an unfolded single-walled carbon nanotube.[36] Due to their high superficial area, good electrochemical properties, and excellent mechanical properties, graphene and graphene oxide (GO) have been used for the preparation of NC gels with high strength and stimuli-responsive properties. However, graphene is easy to reaggregate, and is difficult to form NC gels with homogenously dispersed graphene. Using frontal polymerization technique, Alzari successfully prepared graphene NC gels.[37] Unlike graphene, GO is characterized by abundant hydrophilic oxygenated functional groups, which facilitate its dispersion in aqeous and exfoliation into monolayer sheets,[38] NC gel can be readily prepared via covalent or non-covalent crosslinking between GO and hydrogel matrix. For example, mixing GO and poly(vinyl alcohol) (PVA) in solution followed by violently shaking would result in a physical NC gel, in which PVA act as the physical cross-linking agent. This GO

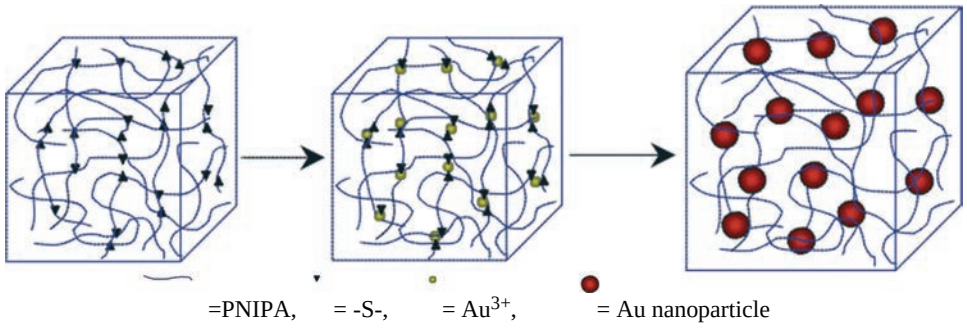

Figure 3. **The preparation of NC gels using hydrogel as nanoreactor. Reprinted with permission from [24], G. R. Bardajee, et al., A novel and green biomaterial based silver nanocomposite hydrogel: Synthesis, characterization and antibacterial effect. *J. Inorg. Biochem.* 117, 367 (2012). © 2012, Elsevier.**

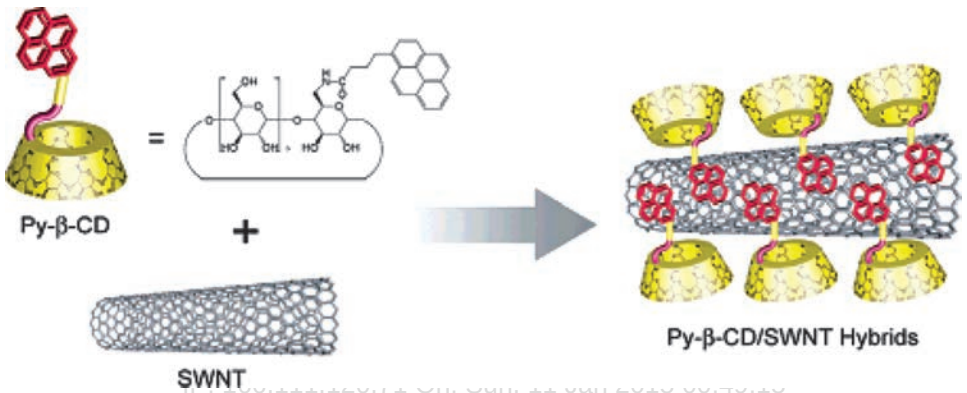

Figure 4. **Preparation of water-solube SWNT via $\pi-\pi$ interaction. Reprinted with permission from [32]. H. Liu, et al., Dual-stimuli sensitive composites based on multi-walled carbon nanotubes and poly(*N*,*N*-diethylacrylamide-co-acrylic acid) hydrogels. *React. Funct. Polym.* 70, 294 (2010). © 2010, ACS Publications.**

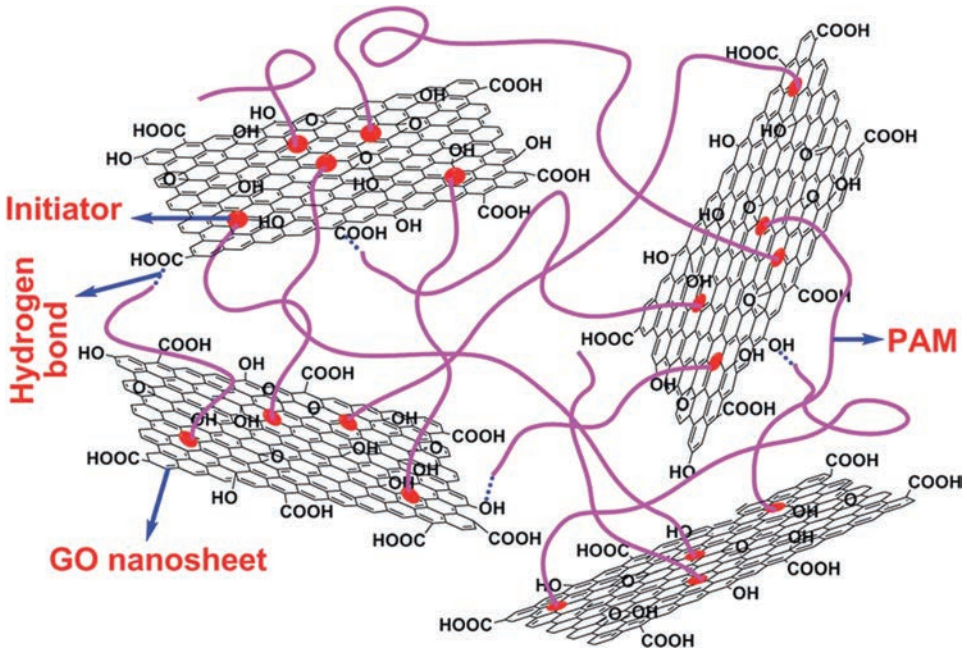

Figure 5. **A schematic network of PAM/GO nanocomposite hydrogel. Reprinted with permission from [39], H. Bai, et al., A pH-sensitive graphene oxide composite hydrogel. *Chem. Commun.* 46, 2376 (2010). © 2010, RSC Publishing.**

NC gel may undergo pH-induced sol–gel transition and could be used for selective drug release under physiological condition.[39]

Incorporation of GO into the hydrogel will produce gels with excellent mechanical properties.[40–43] Poly(acrylic acid) (PAA)/GO NC gel were prepared using *N*,*N*-methylenebisacrylamide (BIS) as the crosslinker, in which the poly(acrylic acid) chains were crosslinked with BIS surrounding GO.[40] The NC gel showed excellent mechanical properties with an elongation at break of 300%. Highly stretchable polyacrylamide (PAAm)/GO NC gels was prepared through *in situ* free-radical polymerization of acrylamide in the aqueous solution of GO. PAAm chains were combined densely with GO nanosheets through strong non-covalent interactions including hydrogen bonding, ionic bonding, and physical adsorption (Fig. 5). Due to the large distance between GO nanosheets and the flexibility of PAAm chains, NC gel with elongation at break over 3000% could be obtained with the concentration of GO in the hydrogel matrix was as low as 0.0079 wt%.[41] In addition to its role of nano-filler, GO can also act as both initiator and cross-linking center of hydrogel, producing NC gels with extremely high elongations (5300%), and excellent resilience.[42]

GO may also bring novel properties to the hydrogel. PNIPAm/GO NC gel was prepared by *in situ* polymerization of NIPAm monomer under γ-irradiation in the presence of GO. The NC gels showed excellent controlled photothermal properties owing to the high optical absorbance of GO in the near-infrared range.[43]

Hydroxyapatite Nanocomposite Hydrogel

Hydroxyapatite (HAp) owns the biomimetic microstructure similar to the inorganic component of mammalian bone tissue and was proved to have excellent osteoconductivity. NC gel from HAp would be expected to have improved bioactivity, biocompatibility as well as mechanical properties.[44,45] In tissue engineering, *in situ* gellable or injectable hydrogels have shown advantages in surgery via minimally invasive techniques. By mixing HAp with PEG-polycaprolactone-PEG (PEG-PCL-PEG) amphiphilic block copolymer, an injectable thermal responsive NC gels was prepared. The mixture underwent sol–gel phase transition and was stable in the gel state at 37 °C. The phase transition temperature could be tuned by adjusting the concentration of HAp, which may be attributed to the interaction between the PEG-PCL-PEG and HAp.[46] The interaction between the hydrogel matrix and HAp can also be utilized to improve the mechanical properties of the NC gels. Gaharwar et al. reported a highly extensible and tough PEG/HAp NC gel. As a result of the interaction between PEG and HAp, the NC gels showed ten-fold increase in toughness, eight-fold increase in fracture stress, and three-fold increase in tensile modulus compared with the pure PEG hydrogel.[47]

Biomimetic *in situ* mineralization through the nucleation of HAp in the hydrogel results in high affinity integration of HAp with the hydrogel matrix.[48,49] The nucleation and formation of mineralized HAp bundles can be mediated and controlled by hydrogel matrix (i.e., PVA). For example, during PVA mediated nucleation of HAp, the thickness of mineralized bundles increased and the size of HAp decreased with increasing the concentration of PVA.[49]

Magnetic Nanocomposite Hydrogel

By incorporating magnetic nanoparticles (i.e., iron oxide) into the hydrogel matrix, NC gel with remote-controlled magnetic responsive properties can be obtained.[50] In general, magnetic nanoparticles, i.e., γ-Fe_2O_3, Fe_3O_4, and $CoFe_2O_4$, can be introduced into the hydrogel matrix via *in situ* gelation and *in situ* precipitation methods.

In the *in situ* gelation, the magnetic nanoparticles are dispersed in the precursor solution before the gel forms.[51–53] By using this method, NC gels with uniform magnetic nanoparticle size can be obtained. However,

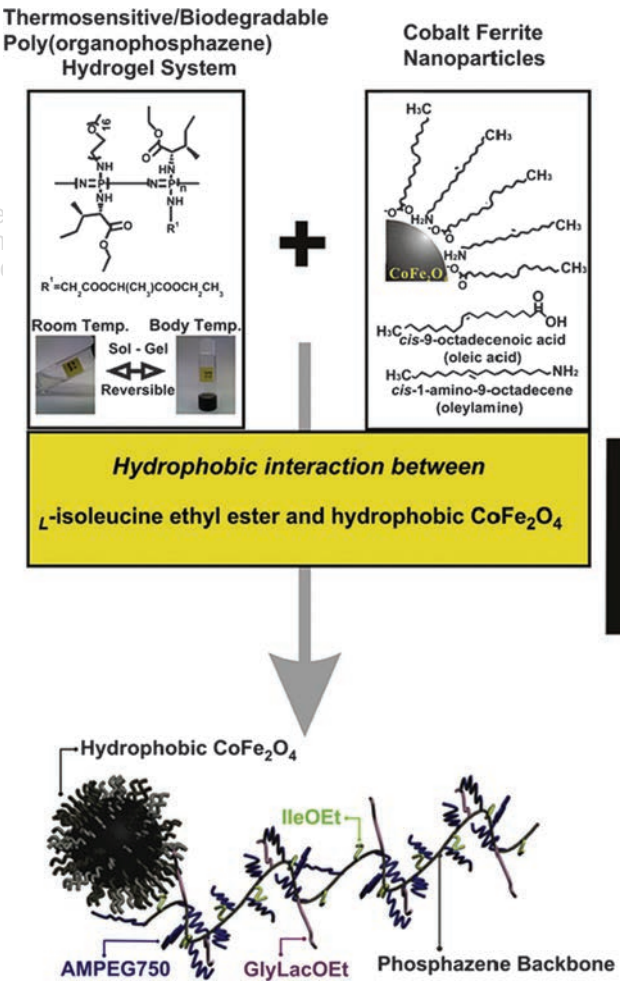

Figure 6. Synthesis of the thermosensitive/magnetic poly(organophosphazene) hydrogel. Reprinted with permission from [50], Y. H. Li, et al., Magnetic hydrogels and their potential biomedical applications. *Adv. Funct. Mater.* 23, 660 (2013). © 2013, Wiley.

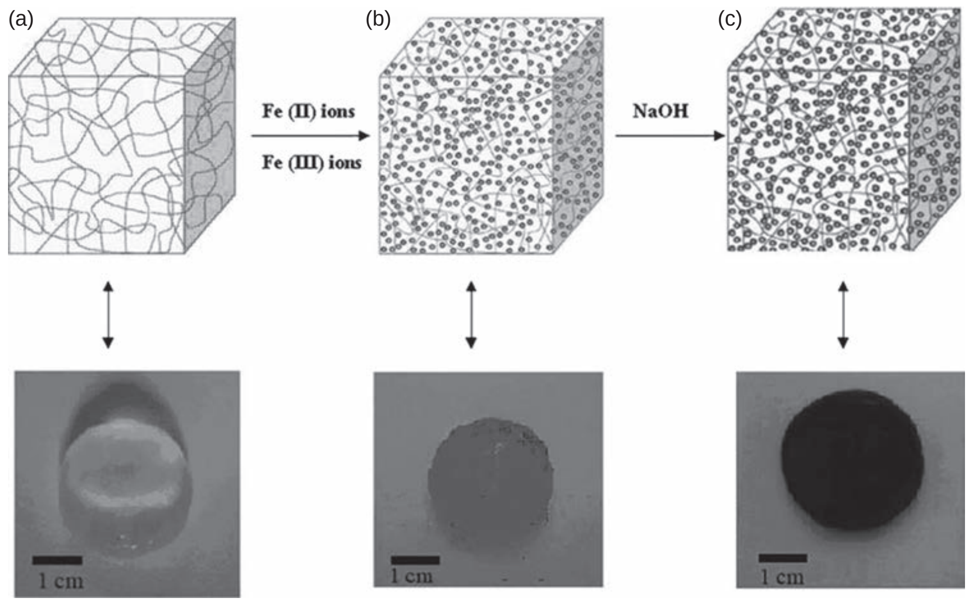

Figure 7. **The formation process of magnetic hybridized hydrogel (a) before the loading with iron ions; (b) after the loading with iron ions; (c) subsequent reduction reaction with sodium hydroxide. Reprinted with permission from [51], A. R. Frimpong, et al., Synthesis and temperature response analysis of magnetic-hydrogel nanocomposites. *J. Biomed. Mater. Res., Part A.* 80A, 1 (2006). © 2006, Wiley.**

modification of the nanoparticle is neccesary to achieve uniform distribution since the the magnetic nanoparticles are easy to aggregate Kim et al. reported a $CoFe_2O_4$/poly (organophosphazene) NC gel, in which $CoFe_2O_4$ nanoparticle with hydrophobic surface was bound to the hydrogel matrix via hydrophobic interaction between the surfaces of the nanoparticle and the hydrophobic *L*-isoleucine ethyl esters group on the polymer (Fig. 6).[53] The NC gel showed excellent thermosensitivity, reversible sol–gel phase transition, and injectability; the gel was injected into a rat brain using stereotactic surgery for long-term magnetic resonance imaging.

In the *in situ* precipitation process, the magnetic nanoparticles are formed via chemical reaction of the precursor salts inside the hydrogel matrix.[54–56] For example, Liang et al. synthesized a polysaccharide-based magnetic NC gel by reduction of iron(II) chloride and iron(III) chloride (Fig. 7).[54] The iron ion can easily bind to the hydrogel matrix due to its electrostatic interaction with the anionic groups on chitosan chain, and thus an uniform distribution of the magnetic nanoparticles could be achieved.

Various magnetic NC gels based on different hydrogel matrix have been prepared. Owing to their magnetic responsive properties, those magnetic NC gels have wide potential applications in biomedical field, including controlled drug release and tissue engineering.

APPLICATION OF NANOCOMPOSITE HYDROGELS

As a new generation of materials, NC gels combine the advantages of both hydrogel and nano-fillers. The mechanical, electrical, magnetic, and optical properties of nano-fillers in addition to the excellent biocompatibility of hydrogels would endow the NC gel with extraordinary functionalities, which may find their great potential in biomedical practice.

Drug Delivery

NC gels could be an appropriate carrier to load and transport biochemical factors. Physical properties of the NC gels such as swelling ratio, mesh size, and diffusion coefficient, which may affect the release behavior of those biochemical factors from the hydrogel matrix, can be fine-tuned by controlling the chemical structure of the hydrogel network. In the local delivery of drug, NC gels can serve as reservoir of drug molecules based on the interaction between drug molecule and nano-filler or hydrogel matrix. Stimuli-responsive NC gels hold great potential in drug release, from which drug can be intelligently released under external stimuli, such as electric field, magnetic field, temperature and pH etc.

Liu et al. investigated release behavior of vitamin B-12 from a NC gel composed of chitosan and MMT under electro-stimulation.[56] MMT, as inorganic filler, was incorporated into the chitosan matrix to enhance the anti-fatigue property and corresponding long-term sustainable release kinetics; thus overcome the deterioration of the responsiveness and reversibility of chitosan upon repeated on-off electro-stimulation switching operations. With a lower MMT concentration (1 wt.%), vitamin B-12 exhibited a pseudo-zero-order release from the NC gel, and the release mechanism switched from diffusion-controlled mode to

swelling-controlled mode when NC gel was subjected to electro-stimulation.

Lee et al. investigated NC gel composed of poly[acrylic acid-co-poly(ethylene glycol) methyl ether acrylate] (PAA-co-PEGMEA) and hydrotalcite (HT).[57] Vitamin B-2, vitamin B-12, crystal violet, and phenol red were selected as model drugs; it was found that the release of the four different model drugs from the NC gels increased with the increase of the HT content.

Hawkins et al. utilized Pluronic® F-127, an extensively studied polymer that underwent sol–gel phase transition in aqueous upon temperature, as the matrix to incorporate iron oxide nanoparticles and drug molecule.[58] The nanocomposite sol–gel can be easily injected percutaneously into a patient where the system will automatically gel upon reaching physiological temperatures (Fig. 8(A)). When a magnetic field is applied, the nanoparticle will heat the system to temperature near or above the gel-to-solution transition, thereby causes the dissolution of the gel and consequently the burst release of loaded drug (Fig. 8(B)); when magnetic field is removed, the sample will return to physiological temperatures, and the gel state will be re-formed (Fig. 8(C)); the remaining drug could be released by applying the magnetic field (Fig. 8(D)). Remote pulsatile control of drug delivery can be achieved through the actuation of nanocomposite sol–gel block copolymers in an alternating magnetic field (Fig. 8(E)).

Using NC gel as a tool, targeted drug delivery under external magnetic field for treating cancers or other complex diseases have been reported. Iron oxide particles (Fe_3O_4 and γ-Fe_2O_3) are most commonly used in fabrication of magnetic stimuli-responsive NC gels. Bajpai et al. investigated a simple *in situ* approach to prepare magnetic NC gels with superparamagnetic nanoparticles (Fe_3O_4) homogeneously dispersed in a poly(methyl methacrylate) (PMMA) grafted polyvinyl alcohol (PVA) hydrogel matrix.[59] Antibiotic drug ciprofloxacin (CFx) was loaded in this superparamagnetic NC gel, and magnetic-sensitive drug release was achieved by application of varying magnetic field, the released amount of CFx was found to decrease at higher strength of magnetic field.

Incorporating Fe_3O_4 nanoparticles into PNIPAm hydrogel can achieve intelligent release of encapsulated drug under alternating magnetic field. Upon the application of the pulse of the alternating magnetic field, the NC gel would be heated up by the magnetic particles and collapse, which may raise the release rate of incorporated drug. However, when the pulse of the alternating magnetic field is turned off, the gels can recover from the collapse and the release rate of incorporated drug will be reduced. This NC gel may be applied to stepwise, on-demand release of drug.[60]

Prolonged and sustained release is highly desirable in the case of long-term administration of drug. Jiang et al.[61] incorporated linear PAAm to PNIPAm/clay hydrogel; the incorporation of PAAm can effectively change the lower critical solution temperature (LCST) of the PNIPAm/clay hydrogel, which decreases from 32.8 °C to 27.9 °C with the concentration of PAAm increasing from 0 to 50%. Release of bovine serum albumin (BSA) could be prolonged upon the addition of PAAm at 20 °C and 37 °C, respectively. A special domain consisted of linear PAAm and clay platelets was proposed and considered to entrap residual BSA both in the swollen and collapsed hydrogel matrix and be responsible the retard release of BSA.

Popescu et al. fabricated a pH-responsive hydrogel/liposome nanocomposite for controlled delivery of hydrophilic drug.[62] Poly(2-vinyl pyridine)-*block*-poly(acrylic acid)-*block*-poly(*n*-butylmethacrylate) (P_2VP_{25}-PAA_{576}-$PnBMA_{36}$) ABC terpolymer, which underwent pH-induced sol–gel transition above pH 5.0, was mixed with multilamellar lipsomes made from phosphatidylcholine (PC) and cholestrol (Chol) to form a hydrogel. Calcein as a hydrophilic model drug was encapsulated

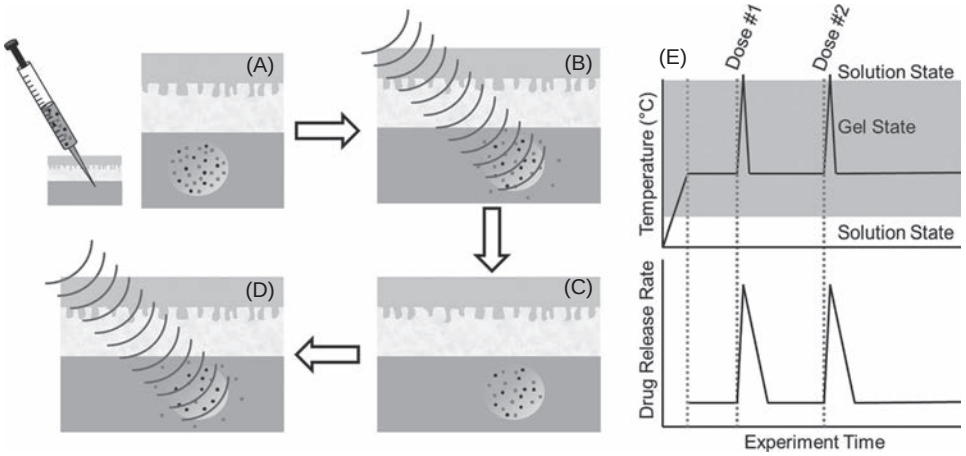

Figure 8. **Proposed mechanism and application of remote controlled drug delivery using nanocomposite sol–gel systems. Reprinted with permission from [54], Y. Y. Liang, et al., Embedding magnetic nanoparticles into polysaccharide-based hydrogels for magnetically assisted bioseparation. *ChemPhysChem.* 8, 2367 (2007). © 2007, Wiley.**

in the lipsome before mixing with the terpolymer. This mixture of terpolymer and PC/Chol lipsome solution was injectable at pH lower than 3.0 but turned to hydrogel at pH 7.4. Controllable release of calcein could be achieved by adjusting the terpolymer concentration. For example, drug release time could be prolonged from 14 days to 32 days when the the concentration of terpolymer was increased from 1.0 wt% to 1.5 wt%.

In another study, Papaphilippou et al. prepared novel multi-responsive (magnetoresponsive, thermoresponsive, and pH-responsive) nanocomposite conetworks consisting of oleic acid-coated magnetite nanoparticles, hydrophilic/thermoresponsive hexa(ethylene glycol) methyl ether methacrylate, hydrophobic/metal binding 2-(acetoacetoxy) ethyl methacrylate, and pH-responsive/thermoresponsive *N*-diethylaminoethyl methacrylate and 2-(dimethylamino) ethyl methacrylate moieties. These systems were evaluated toward their ability to absorb and release benzoic acid as a model drug in a controlled manner upon varying the pH.[63]

Hezaveh et al. synthesized NC gels from modified kappa-carrageenan and MgO nanoparticle, methylene blue was used as the model drug to investigate. It was found that the amount of methylene blue released from NC gel can be 67.5% higher in intestine medium and 56% lower in the stomach compared to kappa-carrageenan hydrogel. They also investigated silver and magnetite nanofillers in the same modified kappa-carrageenan matrix gel. *In vitro* release studies revealed that the drug release in intestine was improved while that in the stomach was minimized.[64–66]

Tissue Engineering

Scaffolds provide three–dimensional (3D) environment which supports cell attachment, proliferation, and differentiation, as well as enable transportation of nutrient and cell metabolite in tissue engineering. Hydrogels have been intensively studied as scaffolding material especially for soft tissue regeneration. However, hydrogels usually have inferior mechanical properties as well as lack adequate functionality, which hinder their wide applications in regenerative medicine. By incorporating various functional nanoparticles (i.e., clay, CNTs, and HAp), NC gels with improved mechanical properties and functionalities could fulfill the requirements of tissue engineering.

Kawaguchi et al. fabricated a NC gel from sodium alginate and CNTs, and evaluated its mechanical properties and biocompatibility. The NC gel exhibited a mild inflammatory response and non-cytotoxicity. These results suggested that NC gel was a promising scaffolding material in tissue engineering.[66] CNTs were also incorporated in gelatin gel, and the NC gels proved to be photopatternable and allowed for easy fabrication of microscale structures without harsh processes (Fig. 9). This NC gel retained good cytocompatibility and tunable stiffness, and can guide osteogenic, neurogenic, and myogenic differentiation of human mesenchymal stem cell (hMSC), which make it suitable for various complex 3D biomimetic tissue engineering applications.[67]

Adhesion of different cell types, including fibroblasts (L929), human lung adenocarcinoma epithelial cells (A549), and human cervical cancer cells (HeLa), on PNIPAm/hectorite clay NC gel was investigated to evaluate its cytocompatibility. The phase transition of PNIPAm gels could induce cell sheet detachment in the absence of trypsin;[68] this cell sheet may be subjected to further proliferation or potential tissue engineering applications. Since the cell adhesion on and detachment from the NC gel can be affected by the LCST and surface roughness of the gel, the NC gel could have better thermoresponsivity and faster cell sheet detachment by copolymerization with hydrophilic PEG.[69]

A number of studies have indicated that incorporation of HAp in hydrogel matrix could produce complex structures meeting the requirements of tissue engineering. Sinha et al. fabricated a biomimetic PVA/HAp NC gel using freeze-thawing technique, this NC gel may have potential application in cartilage repair and replacement.[70] Shen et al. fabricated a HAp/collagen NC gel by multilevel freeze-drying technique.[71] The NC gel was found to have hierarchical structures consisting of two parts: primary macroporosity and submicroporosity. This NC gel provided an efficient approach toward biomimetic tissue engineering scaffold for the biomedical applications with enhanced intensity/bioactivity and controlled resorption rates. In another report, calcium alginate/HAp NC gel was prepared with dynamic stiffness in compression as high as 400% by adding a mere 0.32 wt% of HAp.[72] The results implied that the NC gels have the potential use in load-bearing bone replacement. Kumar et al. incorporated HAp into chitin hydrogels including both α-chitin and β-chitin, and controlled swelling ratio in the range of 15~20 and well interconnected pores with pore size in the range of 150~400 μm were achieved. Controlled degradation and adequate protein absorption was also observed. The viability, attachment, and proliferation of different cell lines confirmed the cytocompatibility of the NC gels, implying this NC gel can be a potential scaffold for bone tissue engineering.[73] In some other reports, bio-ceramic nanoparticles such as BCP (biphasic calcium phosphate), ACP (amorphous calcium phosphate), and apatite also were mixed with hydrogels matrix to prepare NC gel scaffolds.[74, 75]

Plastically compressed dense collagen (DC) gels can mimic the microstructural, mechanical, and biological properties of native osteoid. Marelli et al. fabricated a NC gel from DC hydrogel matrix and the osteoinductive bioactive glass nanoparticles (nBG) to produce implantable, mineralizable, and cell seeded hydrogel scaffolds for bone tissue engineering. MC3T3-E1 pre-osteoblasts were viable up to day 28 in the NC gel scaffold in culture. In the absence of osteogenic supplements, MC3T3-E1 metabolic activity and alkaline phosphatase production were affected

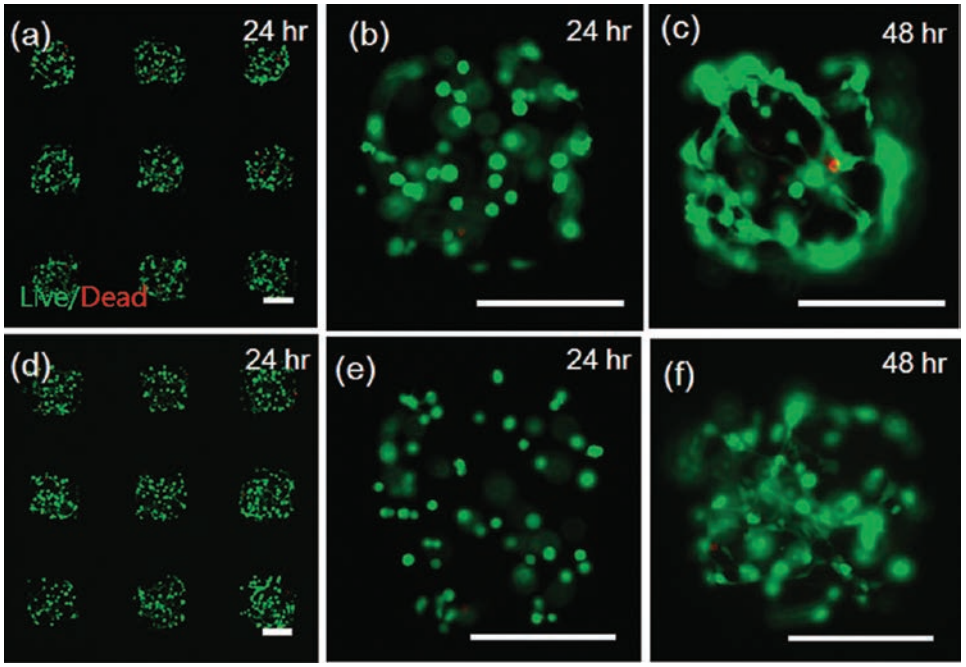

Figure 9. **Representative images of 3T3 fibroblasts embedded in gelatin gels (a)–(c) and gelatin-CNTs NC gels micropatterns (d)–(f) which were stained with calcein-AM (green)/ethidium homodimer (red) Live/Dead assay 24 and 48 h after encapsulation. (scale bar = 250 μm). Reprinted with permission from [59], A. K. Bajpai and R. Gupta, Magnetically mediated release of ciprofloxacin from polyvinyl alcohol based superparamagnetic nanocomposites. *J Mater. Sci.-Mater. M.* 2, 357 (2011). © 2011, Springer.**

by the presence of nBG, indicating accelerated osteogenic differentiation.[76]

PEG hydrogels are widely studied as tissue engineering scaffold. Chang et al. synthesized a biocompatible PEG diacrylate (PEGDA)/laponite NC gel that can support both two-dimensional (2D) and three-dimensional (3D) cell culture of hMSC.[76] Unlike PEG hydrogels, PEG NC gels supported cell adhesion and their subsequent spreading in a 2D culture. In addition to supporting the 2D cell growth, the PEG NC gels supported 3D cell encapsulation similar to that of widely used PEG hydrogel systems. Additionally, the ability of PEG NC hydrogels to support 3D culture of encapsulated cells makes them an ideal injectable system with minimally invasive strategies for *in vivo* applications. Yang and co-workers recently reported a NC gel from PEGDA and hydroxyl mesoporous silica nanoparticles (MSNs-OH). Increased protein adsorption, the integration of hierarchical macro-mesoporous structure, as well as the introduction of silica, provided a favorable environment for the adhesion and spreading of rat marrow stem cell (rMSC). This NC gel shows promise as scaffolds for tissue engineering.[77]

Incorporating functional nanoparticles into hydrogel matrix could obtain NC gels with good wound dressing properties. Wound dressing material is usually used in direct contact with the wound and could stop bleeding, absorb exudates, relieving pain, remove slough, and protect the wound from infection and mechanical damage. In addition to those traditionally used wound dressing materials such as films, foams, and pastes etc., hydrogels can be an excellent wound dressing material owing to its unique properties such as good swelling, tensile strength, mechanical properties, and biocompatibility.[78] PVA hydrogel is regularly used as the matrix for its nontoxic, hydrophilic, and good film-forming properties. By adding nanoclay into PVA hydrogel matrix, NC gel could be prepared via the cyclic freeze-thaw method.[79,80] The results demonstrated that the quantity of the nanoclay was the key factor in obtaining suitable properties required for wound dressing with relative good swelling, appropriate water vapor transmission rate, excellent barrierity against microbes penetration, and mechanical properties; improved healing process was achieved for wounds covered by the NC gels compared with others. Chitosan has good biocompatibility, biodegradability, and hemostatic properties, the blend of chitosan and PVA by γ-irradiation can also be used in wound dressing.[81] Silver nanoparticle has antimicrobial capability, which is a highly desirable property in wound dressing materials. NC gels consisting of Ag nanoparticles were found to be excellent materials for antibacterial applications.[82] The hydrogel matrix could be PAA, PEG[26] and a series of PVA/PVP based hydrogels.[83] Some researchers have demonstrated that Ag NC gel with beta-chitin or nanoparticle-curcumin could greatly enhance their antibacterial efficacy.[84]

CONCLUSIONS

Compared with traditional hydrogels, NC gels showed undoubtedly improved performances, including

mechanical properties, higher swelling/deswelling rates, good biocompatibility, and biodegradability. One could expect it to attract much more attention of biomaterial scientists and biomedical engineers in the next few years. To better advance the application of such NC gels in biomedical fields, biological properties such as protein adsorption, cell adhesion, and cell differentiation should be considered in the design of such NC gels in addition to chemical and physical parameters.

Despite of the vast potential research and applications of NC gels in biomedical fields, ranging from microswitches to drug delivery, controlled release, artificial muscles, tissue engineering, and wound dressing materials etc., there are still lots of challenges under this topic; for example, the mechanism of the interactions in NC gel remains unknown. New techniques are to be developed to elucidate the internal structure of different NC gels. Long-term evaluation of the biocompatibility and biodegradability of NC gels is also an emerging field before they can be applied in clinical use.

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