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Review

Robust and Smart Hydrogels Based on Natural Polymers*

Jiang-jiang Duan and Li-na Zhang**
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China

Abstract This review summarizes recent progress of the robust and smart hydrogels prepared from natural polymers including polysaccharides, proteins, *etc.* These hydrogels exhibit outstanding mechanical properties due to their nanofibrous aggregated microstructures and special crosslinking networks. Furthermore, these hydrogels show some smart stimuli-responsive behaviors triggered by pH, temperature, light, electricity and magnetism. Hopefully, these hydrogels derived from natural polymers with inherent biodegradation and biocompatibility have great application potential in the fields of biomedicine, tissue engineering, soft robots and bio-machine.

Keywords Robust and smart hydrogels; Natural polysaccharides; Nanofiber; Biomedical applications

INTRODUCTION

Human body mainly consists of soft tissues, such as skin, tendons, ligaments, cartilage and muscle. These soft tissues containing 30%–80% water are excellent wet materials, which exhibit excellent mechanical performances including high toughness, shock absorbing, low sliding friction, and robust contraction[1]. Furthermore, these soft tissues combine some smart behaviors such as self-healing[2], self-activity[3] (controlled by the stretch and contract of muscle), self-sensing[4] and self-wrinkling[5]. The huge challenge for material scientists is to seek and synthesize soft materials with similar properties and functions as human soft tissues. Undoubtedly, hydrogels are the best candidates to fabricate artificial tissues.

Hydrogels, consisting of three-dimensional polymer networks and a large amount of water (> 50 wt% of the hydrogel mass), are also a kind of soft and wet materials. Because of this property, hydrogels are able to reversibly swell and shrink by absorbing or exuding water in response to a wide range of stimuli, such as light, temperature, pH, ionic strength, and others[6]. In recent years, smart hydrogels having similar structures and functions with human soft tissues based on their stimuli-swelling behaviors have been extensively studied, and some soft artificial tissues such as artificial-muscle[7], -lens[8] and -skin[9] have also been developed. It is worth noting that conventional hydrogels are soft, weak, and brittle. They usually fail at a tensile stress less than sub-MPa and strain less than 100%, and are notch-sensitive with low fracture energy within a range of 10^{-1}–10^{0} J·m^{-2}[1]. On the contrary, human soft tissues are much stronger. For example, cartilage, containing 75 wt% of water, exhibits a compressive fracture stress of 36 MPa, and a high fracture energy of about 10^{2}–10^{3} J·m^{-2}[10]. One reason for the lack in mechanical strength of a hydrogel is low density of polymer chains

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** Corresponding author: Li-na Zhang (张俐娜), E-mail: zhangln@whu.edu.cn
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and small friction between the polymer chains. Another reason is the heterogeneity of the network structure of the hydrogel formed during the gelation[11, 12]. In the last decades, many synthetic hydrogels with exceptional mechanical properties by introducing different energy dissipation mechanisms have been developed. Examples include poly(vinyl alcohol) hydrogels with crystalline domains[13], topological hydrogels with sliding crosslinkers[14], and tetra-arm polymer hydrogels from tetrahedron-like macromonomers[15], nanocomposite (NC) hydrogels from the mixture of polymer and nanoclay[16, 17], double-network hydrogels[18, 19], microgel-reinforced (MR) hydrogels[20], polyion complex (PIC) hydrogels from the oppositely charged polyelectrolytes[21]. Indeed, the mechanical behaviors of these robust hydrogels are comparable with and even beyond human soft tissues.

Nonetheless, these robust and smart hydrogels are almost developed from synthetic polymers, and their applications in biomedicine are extremely limited due to unsatisfactory biocompatibility and biodegradation[22]. Natural polymers including polysaccharides, proteins, *etc.* possessing good biocompatibility, and the nontoxic degradation products, have received increasing interest in biomedical fields in the past decades[23–26]. Although the poor mechanical performance of the natural polymer based hydrogels is still a major limitation for their medical applications, in recent years, bio-hydrogels from natural polymer with excellent mechanical properties and stimuli-responsive performances have been constructed by some new strategies, which extremely extended their application fields[27–29]. It is worth noting that a kind of novel solvents composed of alkali/urea aqueous solution for directly dissolving cellulose, chitin and chitosan at low temperature has been developed in our research group, and a series of robust and smart bio-hydrogels were constructed[30–34]. This short review aims to provide a brief overview about robust and smart hydrogels derived from natural polymers, and mainly consists of two parts: (1) robust bio-hydrogels made by different methods; (2) smart bio-hydrogels with aspect to sensitivity to different stimuli, as well as their applications.

ROBUST BIO-HYDROGELS

Bio-hydrogels mainly developed from polysaccharides and proteins usually are brittle with a tensile stress less than sub-MPa, strain less than 100%, and fracture energy within a range of 10^{-1}–10^{0} J·m^{-2}. The weak mechanical properties are dominated by their intrinsic semi-stiff molecule conformations, the heterogeneity of the network structure of the hydrogel formed during the gelation and lacking of energy dissipation mechanism due to highly crosslinked by hydrogen-bonds and hydrophobic interaction. To improve the mechanical properties, some strategies including designing homogeneous network structures woven with nanofibers (NF hydrogels) and introducing energy dissipation mechanisms such as double network hydrogels (DN hydrogels) and microgels-reinforced hydrogels (MR hydrogels) have been developed for fabricating robust bio-hydrogels.

NF Bio-hydrogels

Many biomacromolecules in nature can self-assemble into functional nanofibers through noncovalent interactions such as hydrogen-bonds (H-bonds), electrostatic interaction, hydrophobic interaction[29, 35, 36]. For example, cellulose/chitin nanofibers widely exist in the cell walls of plant tissues and skeleton of arthropods (including crabs, shrimps and insects, *etc*.), which as bearing structures protect plants and animals from damage of external environment[37–40]. Protein nanofibers existing in muscles and silks of animal contribute to the robust mechanical performances of muscle and silk. Inspired by nature, some robust bio-hydrogel consisting nanofibers networks (NF bio-hydrogels) have been reported in recent years.

In our previous work[33], high strength chitosan hydrogels with unique nanofibrous architecture have been developed from a new solvent (4.5 wt% LiOH/7 wt% KOH/8 wt% urea aqueous solution), for the first time. The novel chitosan hydrogels exhibit homogeneous architecture and high strength as a result of the strong networks woven with the compact nanofibers (Figs. 1a and 1b). The compression fracture stress of the chitosan hydrogels was nearly 100 times of that of the chitosan hydrogels prepared by the traditional acid dissolving method, revealing that the nanofibrous network microstructures contribute greatly to the reinforcement of the hydrogels (Fig. 1c). The results from ^{13}C-NMR, laser light scattering, atomic force microscopy, transmission electron microscopy, and scanning electron microscopy have confirmed that chitosan easily aggregates in the solution

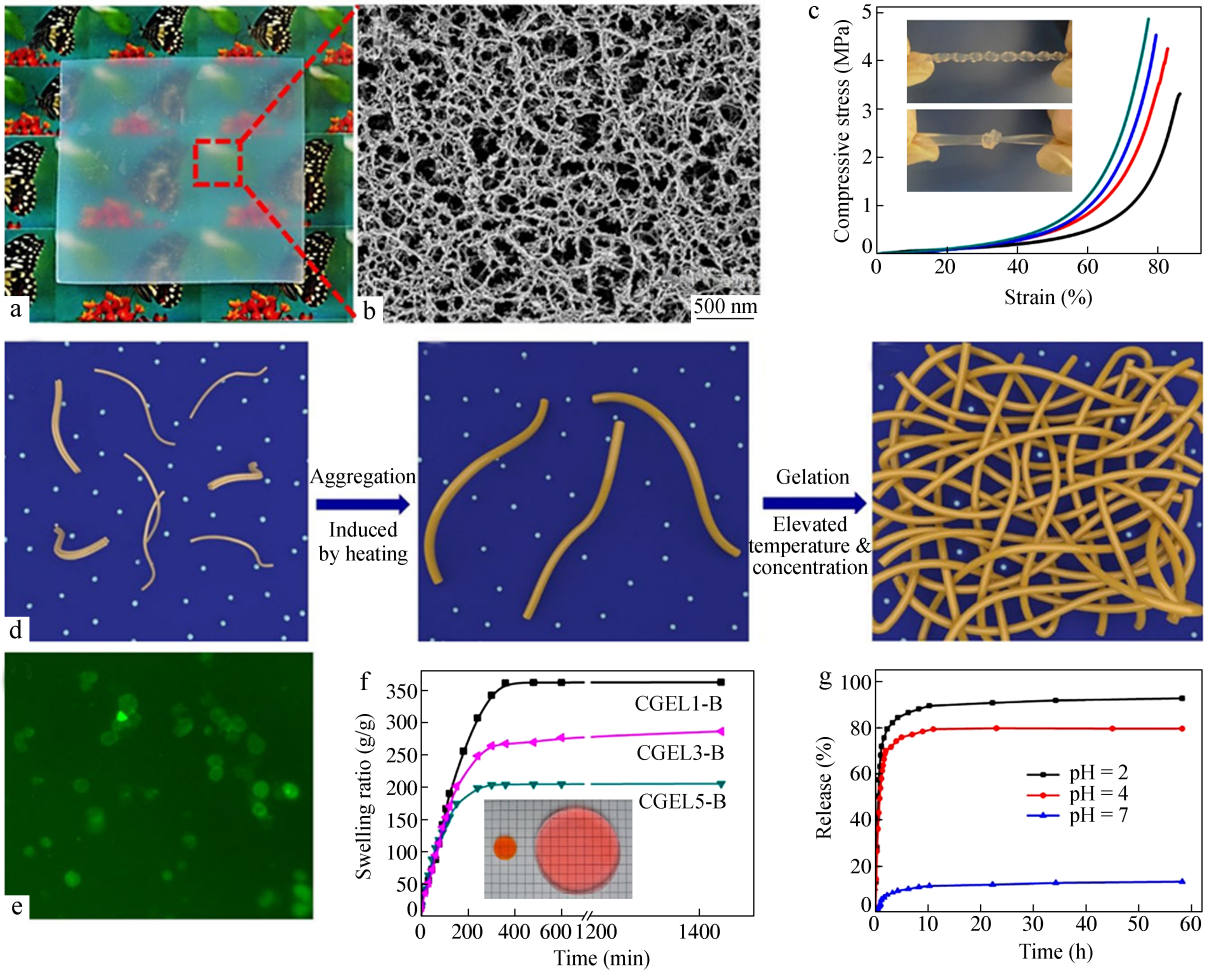


Fig. 1 The photo of PGEL-B and its cross-sectional SEM image (a, b); Typical compressive stress-strain curves and corresponding pictures of chitosan chemical and physical (c); Schematic illustration of the formation of chitosan hydrogel in alkaline aqueous solution by hot-water:chitosan dilute solution (d); The fluorescent images of one kind of mouse myoblast cells (C2C12 cells) stained with DiO cultured on the surface of PGEL-B (e); The swelling kinetics of the CGEL-B in 2% acetic acid aqueous solution at 37 °C and photographs of CGEL3-B before and after swelling in 2% acetic acid aqueous solution (f); The tetracycline release curves at different pH mediums (g) (Reprinted with permission from Ref. [33]; Copyright (2015) American Chemical Society) (The online version is colorful.)

and can self-assemble in parallel to form perfect regenerated nanofibers induced by heating. At elevated temperature and concentration, the regenerated chitosan nanofibers can entangle and crosslink with each other through hydrogen bonds to form hydrogels (Fig. 1d). Furthermore, the chitosan hydrogels exhibit excellent biocompatibility and safety (Fig. 1e) as well as a smart drug release behavior triggered by acid (Figs. 1f and 1g). This is a completely new avenue to construct high strength chitosan hydrogels for applications in biomedicine. Luo *et al.*[41] have reported a novel biocompatible hydrogel with excellent mechanical performance, comprised of regenerated silk fibroin (RSF) and hydroxypropyl methyl cellulose (HPMC) by simply mixing and heating (Figs. 2a–2c). The break energy of the optimal RSF/HPMC hydrogel is up to 3500 $J \cdot m^{-2}$, which is higher than that of some natural elastomers, such as cartilage, cork, and skin. The investigation of gelation mechanism reveals that more uniform and smaller RSF nanofibers with β-sheet conformation dispersed in hydrogel matrix, which as crosslinking sites greatly contribute to the enhancement of the mechanical performance of hydrogel (Figs. 2d and 2e). The superior mechanical performance combined with desirable biocompatibility and

biodegradability endows this novel robust silk based hydrogel with great potential in tissue engineering and other biomedical fields. Guo *et al.*[29] have also reported a robust NF bio-hydrogel fabricated by pH-induced assembly of C12-GAGAGAGY, a peptide amphiphile (PA) based on silk fibroin. Due to the different acid dissociation constants of the carboxyl and phenolic hydroxyl groups on tyrosine residue (Y), the PAs show unique pH sensitive assembly and aggregation behavior, resulting in a hierarchically structured robust and plastic hydrogel, and their rheological moduli reach around 10^5 Pa. Li *et al.*[42] have reported a facile way to prepare robust silk protein hydrogels simply by adding surfactant (SDS) into silk fibroin aqueous solution and incubating at 60 °C. The silk protein hydrogels demonstrate fairly good mechanical properties, which are close to some tissues in the body, such as cartilages, tendons, and ligaments. They proposed that the surfactant speeds up the formation of more and smaller β-sheet nanofibers, which act as the cross-linking points, endowing good mechanical properties of the protein hydrogels.

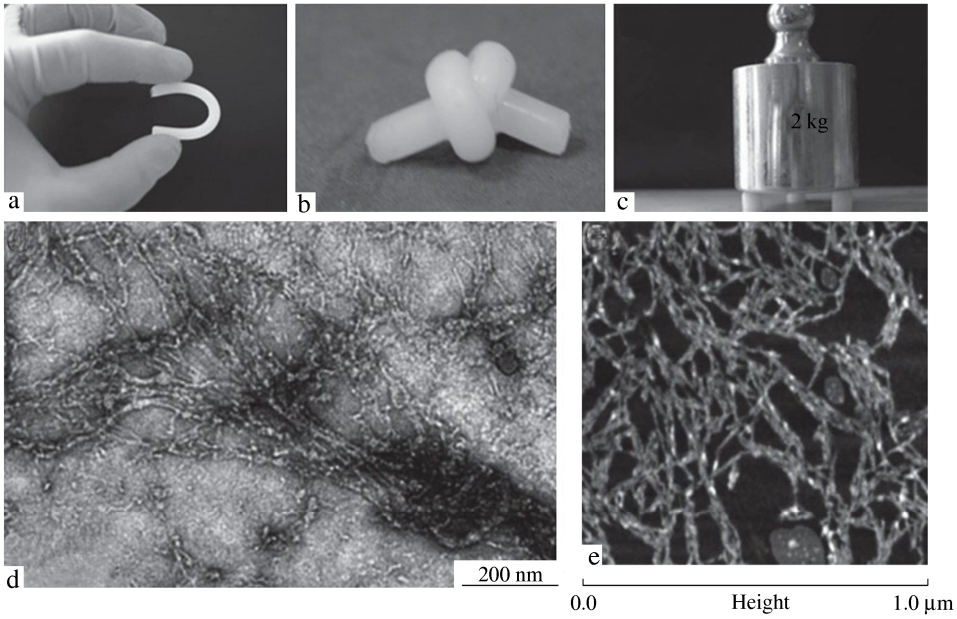


Fig. 2 Digital photos of RSF/HPMC9 hydrogels subjected to different external forces: bending (a), knotting (b), compressing (c); TEM image (d) and AFM height image (e) of fibrillar network of RSF/HPMC9 mixture incubated in water bath at 70 °C (Reprinted with permission from Ref. [41]; Copyright (2016) John Wiley and Sons)

DN Bio-hydrogels

Double-network hydrogels (DN hydrogels) created by Jian-ping Gong are tough and strong, with mechanical properties comparable to those of rubbers and cartilages[43]. These gels consist of two interpenetrating polymer networks with contrasting mechanical properties. The first network is densely cross-linked with short chains, making it stiff and brittle. The second network is flexible and sparsely cross-linked with long chains, making it soft and stretchable. When the gel is stretched, the short-chain network ruptures and dissipates energy, while the elasticity of the second net-work allows it to return to its original configuration after deformation. Thus, by sacrificing the rupture of the covalent bonds of the brittle first network, the material gains toughness[44]. However, the rupture of the short-chain network causes permanent damage. After the first loading, the gel does not recover from this damage; thus, on subsequent loadings, the fracture energy is much reduced[45]. To enable recoverable energy-dissipating mechanisms, several recent works have replaced the sacrificial covalent bonds with recoverable non-covalent bonds such as ionic crosslinks[46], hydrogen-bonds[47] and hydrophobic interaction[47–49].

Sun *et al.*[50] have reported an extremely stretchable and tough hydrogel by mixing two types of crosslinked

polymers: ionically crosslinked alginate, and covalently crosslinked polyacrylamide (Figs. 3a–3c). An alginate chain comprises mannuronic acid (M unit) and guluronic acid (G unit), arranged in blocks rich in G units, blocks rich in M units, and blocks of alternating G and M units. In an aqueous solution, the G blocks in different alginate chains form ionic crosslinks through divalent cations (for example, Ca^{2+}); the robust hydrogels can be stretched by over 20 times their initial length, and have fracture energies of 9000 $J \cdot m^{-2}$. Even for samples containing notches, a stretch of 1700% is demonstrated (Fig. 3d). They attribute the gels' toughness to the synergy of two mechanisms: crack bridging by the network of covalent crosslinks, and hysteresis by unzipping the network of ionic crosslinks. Furthermore, the network of covalent crosslinks preserved the memory of the initial state, so that much of the large deformation can be removed on unloading. The unzipped ionic crosslinks cause internal damage, which heals by re-zipping. These gels can serve as model systems to explore mechanisms of deformation and energy dissipation, and expand the scope of hydrogel applications. Chen *et al.*[28] have reported a robust and recoverable agarose/polyacrylamide DN hydrogel by using one-pot synthesis. These DN hydrogels exhibit excellent mechanical and recoverable properties. The recovery ability of the DN hydrogels is attributed to the unique thermoreversible sol-gel property of agarose. Noted that these as-reported recoverable DN hydrogels all unexceptionally consisted of bio-polymer as first network and flexible synthetic polymer as second network, and their applications in biomedicine still are restricted due to their inability for fully bio-degradation.

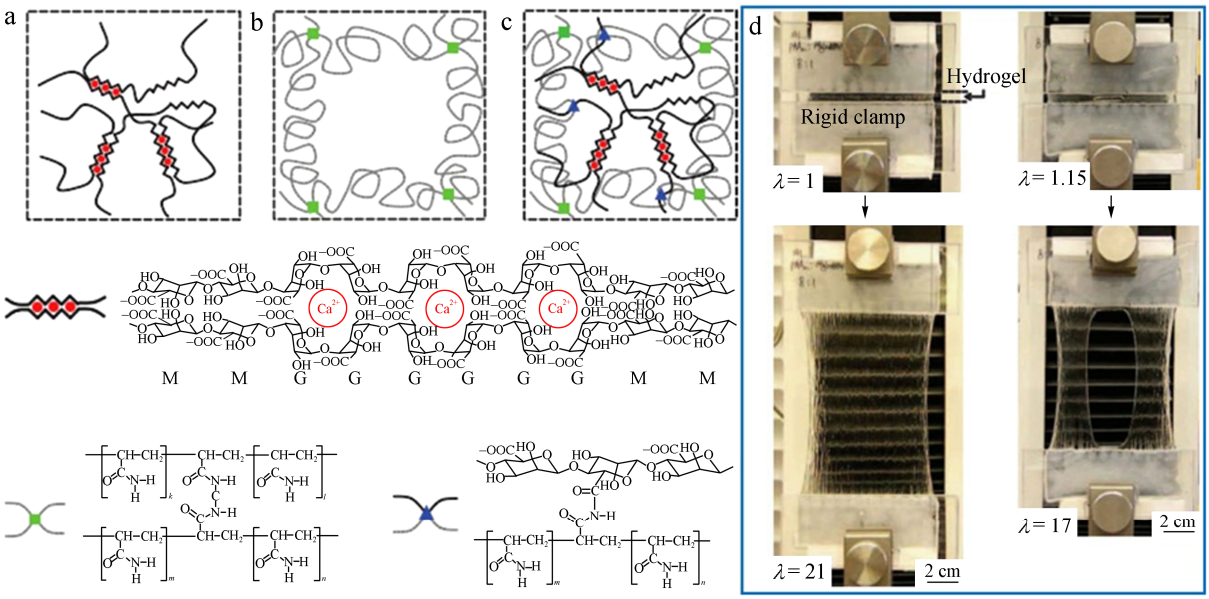


Fig. 3 Schematics of three types of hydrogels: an alginate gel (a), polyacrylamide gel (b) and alginate-polyacrylamide hybrid gel (c); The photos of free and stretched hybrid gel without and with a notch (d) (Reprinted with permission from Ref. [50]; Copyright (2012) Nature Publishing Group) (The online version is colorful.)

Recently, a novel robust double-cross-linked (DC) chitin hydrogel[51] by sequential chemical cross-linking with epichlorohydrin (ECH) and physical cross-linking involving hydrogen bonding and hydrophobic interactions has been reported by our laboratory (Fig. 4a). The DC chitin hydrogels exhibit excellent mechanical properties (Figs. 4b–4e), which are superior to both single chemically cross-linked and physically cross-linked chitin hydrogels. The results of confocal Raman microscopy and atomic force microscopy have demonstrated that the DC chitin hydrogels consist of microscopically separated chemically and physically cross-linked domains, leading to good mechanical properties. Furthermore, robust double-cross-linked (DC) cellulose hydrogels[52] also have been prepared in our laboratory by using the same method. In this case, the molar ratio of

epichlorohydrin to anhydroglucose units of cellulose and the concentration of the aqueous ethanol solution are two critical parameters for obtaining mechanically strong and tough DC cellulose hydrogels.

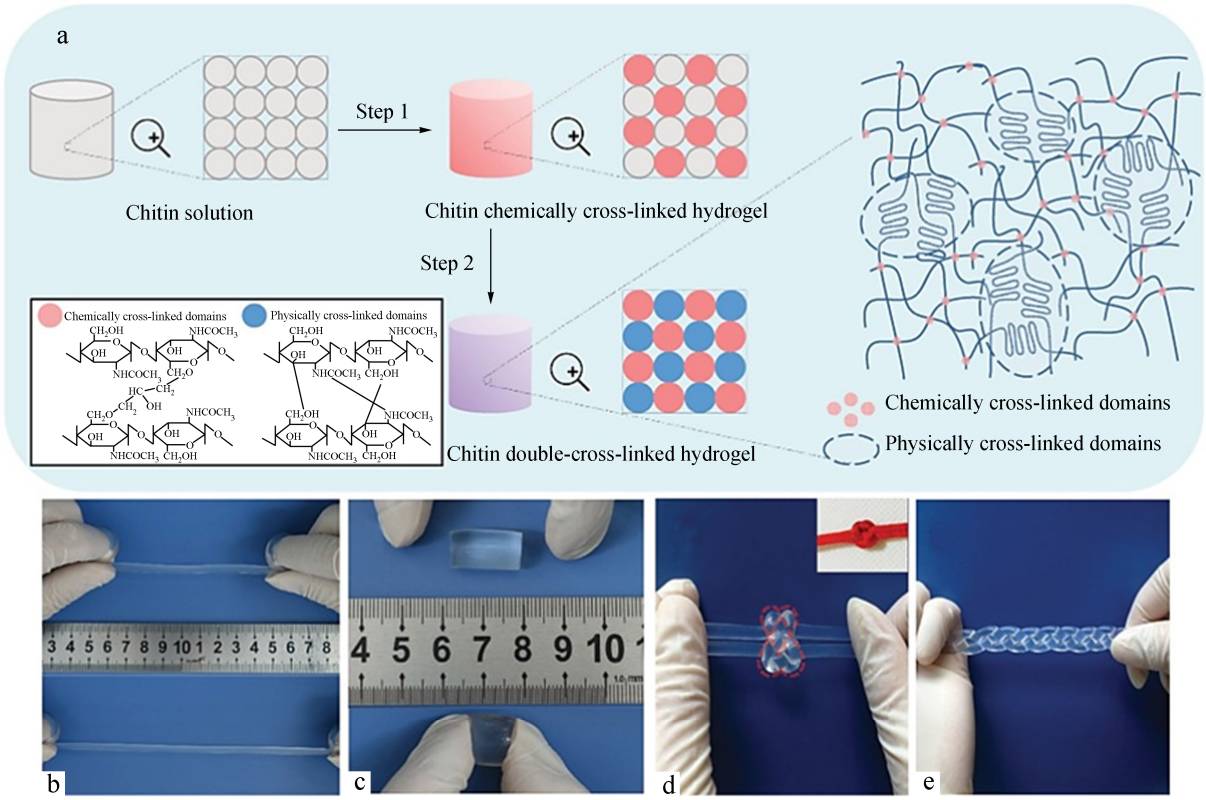


Fig. 4 The schematic preparation process of DC chitin hydrogels (a); Photographs of the DC chitin hydrogels under stretching (b), compression (c), knotting (d), and wrapping (e) (The inset shows a traditional Chinese knot.) (Reprinted with permission from Ref. [51]; Copyright (2016) John Wiley and Sons) (The online version is colorful.)

MR Bio-hydrogels

Microgels-reinforced hydrogels (MR hydrogels) can be regarded as a two-phase composite, where the disperse phase is the rigid double-network (DN) microgels, and the continuous phase is the soft single-network matrix[53, 54]. Under large deformation, the discontinuous microgel phase serves as sacrificial bonds and dissipates energy, whereas the elasticity of continuous phase allows it to return to its original configuration after deformation[20]. Thus, MR hydrogels also exhibit robust mechanical performances. A novel type of biocompatible MR bio-hydrogels with self-wrinkled surface structures by *in situ* polymerization of acrylamide and aniline in the swollen chitosan microspheres colloid has been fabricated for the first time, in our laboratory[55] (Fig. 5a). The MR bio-hydrogels exhibit excellent mechanical properties (Figs. 5b and 5c), conductivity and force sensitivity with high strength and ultra-stretchability (strain 600%) and a wide detection range (10^2–10^6 Pa). The hydrogels as electronic skin devices can precisely monitor grasping motions of human hands (Figs. 5d and 5e), showing wide applications including implantable biomedical devices, wearable electronics, smart clothes, and sensory skin for robotic systems. Ma *et al.*[56] have reported a highly stretchable and notch-insensitive MR bio-hydrogel by integrating casein micelles into polyacrylamide (PAAm) networks. In the casein/PAAm hybrid gels, casein micelles and polyacrylamide chains synergistically enhanced the mechanical properties. The casein-PAAm hybrid gels are highly stretchable, stretching to more than 35 times their initial length under uniaxial tension. These hybrid gels are notch-insensitive and tough with a fracture energy of approximately 3000 J·m^{-2}.

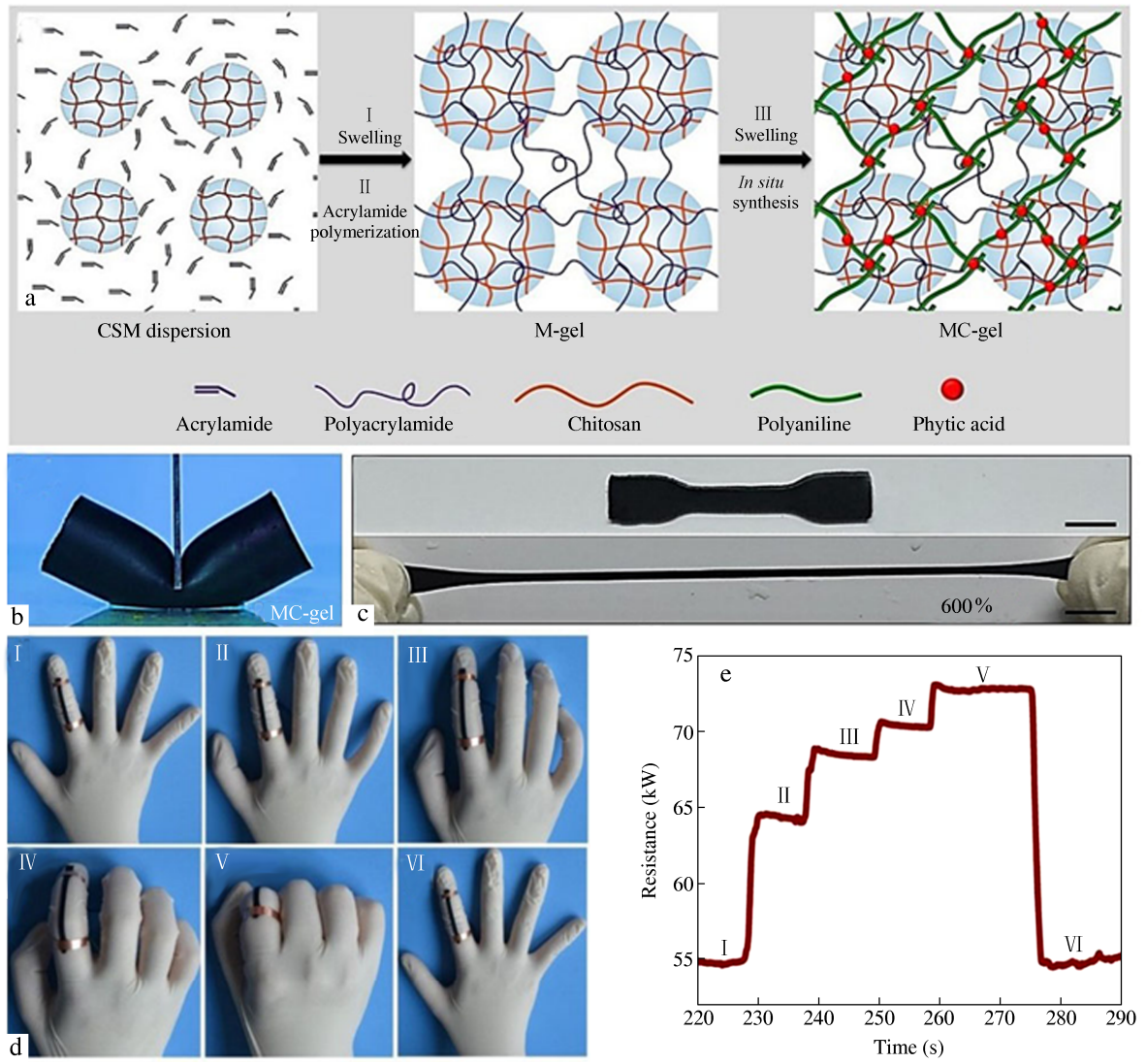


Fig. 5 The schematic preparation process of the MR-gel (a); Photographs of MR-gel pressed by a sharp object (b) and severely stretched by hands (c); The MR-gel as an electronic skin fixed on forefinger of a human hand to monitor its grasping motions (d) and its corresponding resistance variations (e) (Reprinted with permission from Ref. [55]; Copyright (2016) John Wiley and Sons) (The online version is colorful.)

SMART BIO-HYDROGELS

As we all know, hydrogels are three-dimensional polymer networks strongly imbibed with water, and the amount of water can approach up to 99 wt% of the hydrogel mass. Because of this property, hydrogels are able to considerably swell and shrink (> 10 times in volume) when the amount of water in the polymer network changes, which may occur in response to different stimuli such as pH, ionic strength, temperature (*T*), solvent, and others[57–59]. As a result, hydrogels display some smart behaviors during swelling/deswelling process, such as tunable mechanical properties inspired by the sea cucumber[60, 61], tunable volume inspired by valve[62] and human lens[63], soft actuator[6, 64, 65], *etc.* Furthermore, by introduction of the functional components including conductive polymers, magnetic nanoparticles and redox ion into hydrogels matrix, smart hydrogels with electrical- and magnetic-sensitivity are also developed. Smart bio-hydrogels with good biocompatibility and biodegradability exhibit potential applications in wide fields including drug delivery, soft robot, microfluidic

chip, biomimetic machines, *etc*. In this section, a brief overview about smart bio-hydrogels is mainly divided into three parts including: (1) smart bio-hydrogels with tunable mechanical properties; (2) smart bio-hydrogels with tunable volume; (3) smart bio-hydrogel actuators.

Smart Bio-hydrogels with Tunable Mechanical Properties

Sea cucumbers, like other echinoderms, have the ability to rapidly and reversibly alter the stiffness of their inner dermis[66]. The modulus of the tissue can be controlled by regulating the interactions among collagen fibrils, which reinforce a low-modulus matrix[67, 68]. Inspired by the capability of sea cucumbers, Capadona *et al*.[61] have developed a novel nanocomposite based on a rubbery host polymer and rigid cellulose nanofibers, which mimic the architecture and display similar chemo-responsive mechanic adaptability of sea cucumbers (Figs. 6a and 6b). The nanocomposite exhibited a reversible reduction by a factor of 40 of the tensile modulus, for example, from 800 MPa to 20 MPa, upon exposure to a solvent that mediates nanofiber interactions (Fig. 6c). Kong *et al*.[69] have reported a novel protein-hydrogel that translated molecular level protein folding-unfolding conformational changes into macroscopic reversibly tunable mechanical properties based on a redox controlled protein folding-unfolding switch. Molecular level conformational changes (folding/unfolding) in this redox-responsive protein hydrogels can result in significant macroscopic changes in hydrogel's mechanical properties due to the change of the effective chain length between two crosslinking points in the protein hydrogel network. This novel protein hydrogel with dynamic mechanical and physical properties can find numerous applications in material sciences and tissue engineering. Lee *et al*.[70] have fabricated a novel DNA hydrogel metamaterial with unusual mechanical properties. They use a polymerase enzyme to elongate DNA chains and weave them noncovalently into a hydrogel with bird nest-like microstructures (Figs. 7a and 7b). The resulting material has liquid-like properties when taken out of water and solid-like properties when in water. Moreover, upon the addition of water, and after complete deformation, the hydrogel can be made to return to its original shape due to ultralow elastic modulus of the DNA hydrogel (Figs. 7c and 7d).

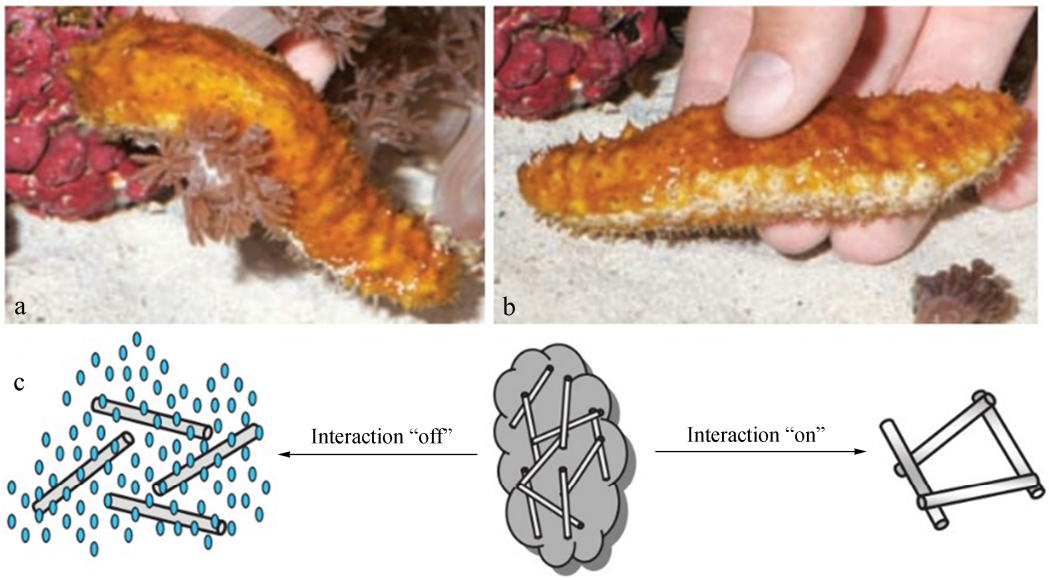


Fig. 6 Pictures of a sea cucumber in relaxed (a) and stiffened (b) positions; Schematic representation of the architecture and switching mechanism in the artificial nano-composites with dynamic mechanical properties (c)
In the "on" state, strong hydrogen bonds between rigid, percolating nanofibers maximize stress transfer and therewith the overall modulus of the nanocomposite. The interactions are switched "off" by the introduction of a chemical regulator that allows for competitive hydrogen bonding. (Reprinted with permission from Ref. [61]; Copyright (2008) The American Association for the Advancement of Science) (The online version is colorful.)

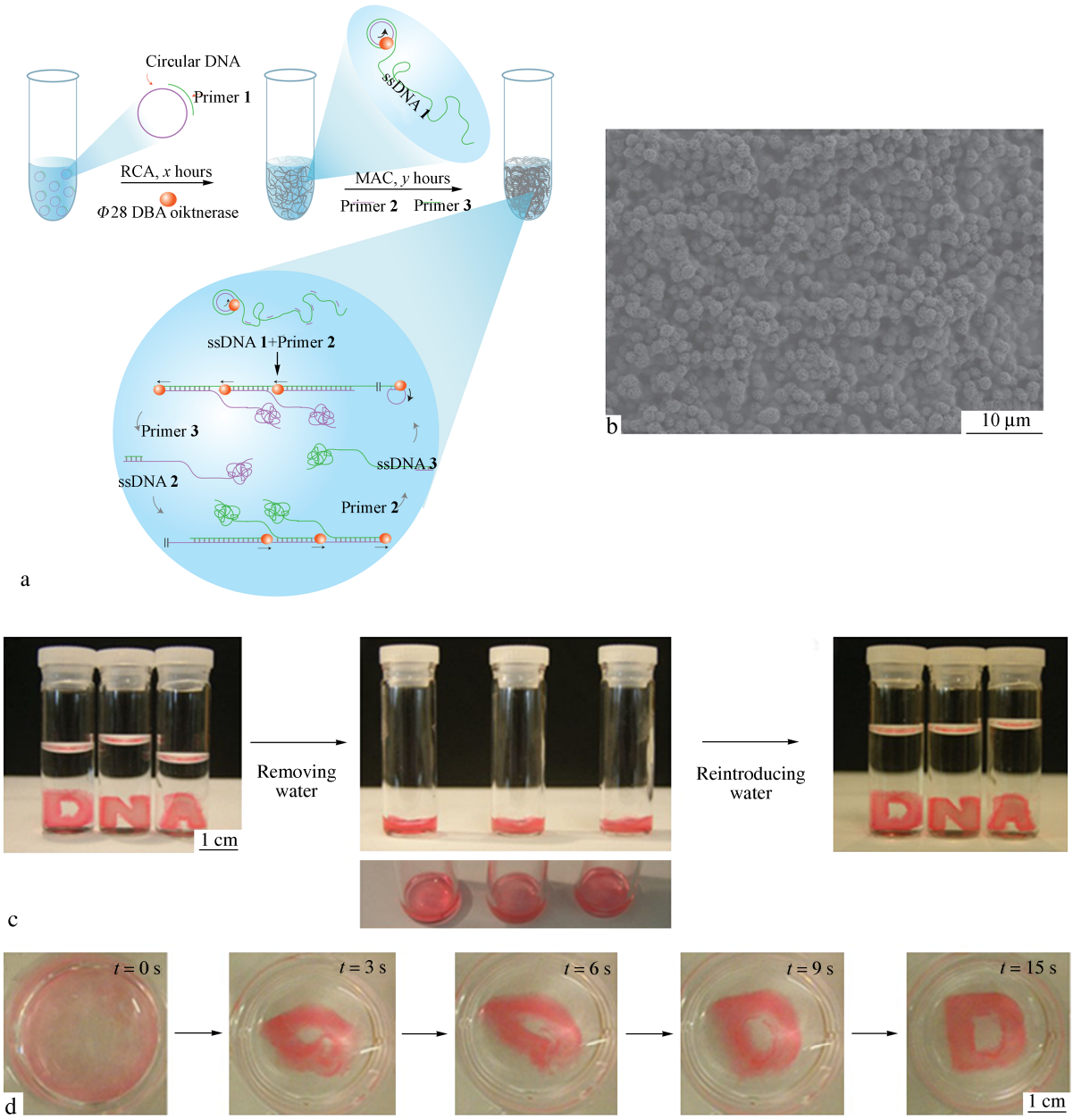


Fig. 7 Schematic diagram of the stepwise approach for DNA hydrogel synthesis (a); Morphology of the DNA hydrogel (b); Liquid- and solid-like properties of the DNA hydrogel by removing and replacing water (c); Series of photographs showing the process of DNA hydrogel returning to its original shape after reintroducing water at 25 °C (d) (Reprinted with permission from Ref. [70]; Copyright (2012) Nature Publishing Group) (The online version is colorful.)

Smart Bio-hydrogels with Tunable Volume

Bio-hydrogels from natural polyelectrolyte, such as alginate, chitosan and gelatin, are able to significantly swell and shrink with the change of pH or ionic strength of surrounding aqueous medium, leading to remarkable volume change of hydrogels. The smart bio-hydrogels will have wide applications in the fields of drug delivery, tissue engineering and biomedicine[71–73]. In our laboratory, a novel ampholytic hydrogel with pH and salt responsive properties has been synthesized by cross-linking quaternized cellulose (QC) and carboxymethyl cellulose (CMC) with epichlorohydrin (ECH) in NaOH aqueous solution[74]. The equilibrium swelling ratio of

the hydrogel in ultrapure water strongly depends on the composition, and increases dramatically from 8.6 g/g to 498 g/g with the change of the weight ratio of QC to CMC from 3:1 to 1:3 (*W*:*W*) (Figs. 8a and 8b). The hydrogel (Gel32) composed of QC and CMC in the ratio of 3:2 (*W*:*W*) exhibits the minimum swelling ratio, and it is electrically neutral (Fig. 8c). Furthermore, all hydrogels exhibit excellent pH sensitivity in the range of pH from 1 to 13 and salt sensitivity in NaCl, $CaCl_2$, and $FeCl_3$ aqueous solutions. Sun *et al.*[63] have provided a promising approach for the production of biomimetic protein microlenses by facile and rapid maskless femtosecond laser direct writing (FsLDW). In this study, commercial bovine serum albumin and a photosensitizer are used to fabricate micro/nanoarchitectures. Once the microlens is immersed into a solution with an either high or low pH value, the microlens starts to swell. When the pH value decreases from 7.0 to 1.0, the clear image becomes out of focus. The clear image is restored when the pH value increases to 10.0. The image is then completely obscured when the pH value increases to 13.0. However, the clear image is again restored when the pH value reduces to 7.0 (Fig. 9). Because of their dynamically adjustable properties and full biocompatibility, the protein microlenses show great promise for optical, electronic, and biomedical applications. Xu *et al.*[75] have developed a novel pH-sensitive hydrogel based pachyman, which as protein carriers can protect the loaded protein drugs from degradation by the harsh environment of the stomach. Importantly, the hydrogel offers superior polyfunctionality, biocompatibility, biodegradability and low cost. The experimental results presented the great potential of the pachyman-based hydrogel as a safe, pH-responsive and controllable protein drug delivery vehicle.

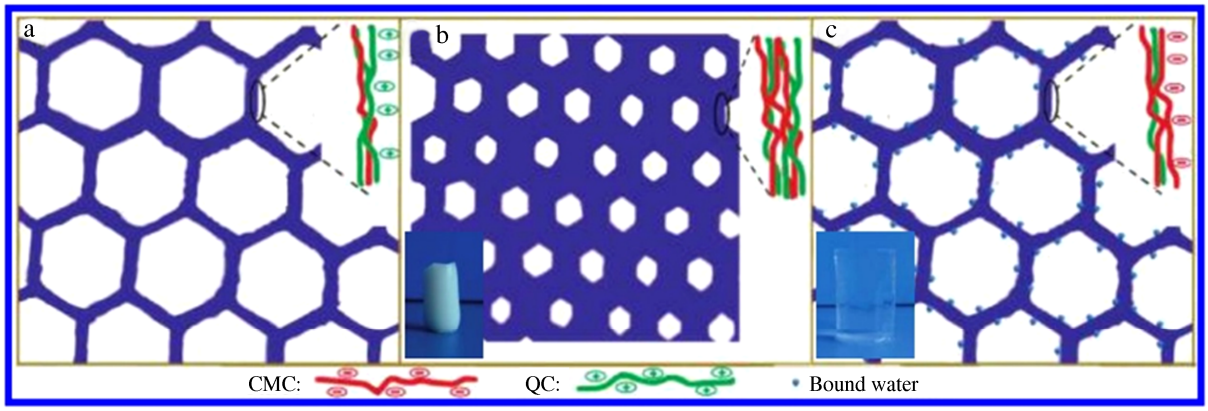


Fig. 8 Schematic illustrations of the structures and photos of QC/CMC hydrogels: Gel31 (a), Gel32 (b) and Gel13 (c) (Reprinted with permission from Ref. [74]; Copyright (2011) American Chemical Society) (The online version is colorful.)

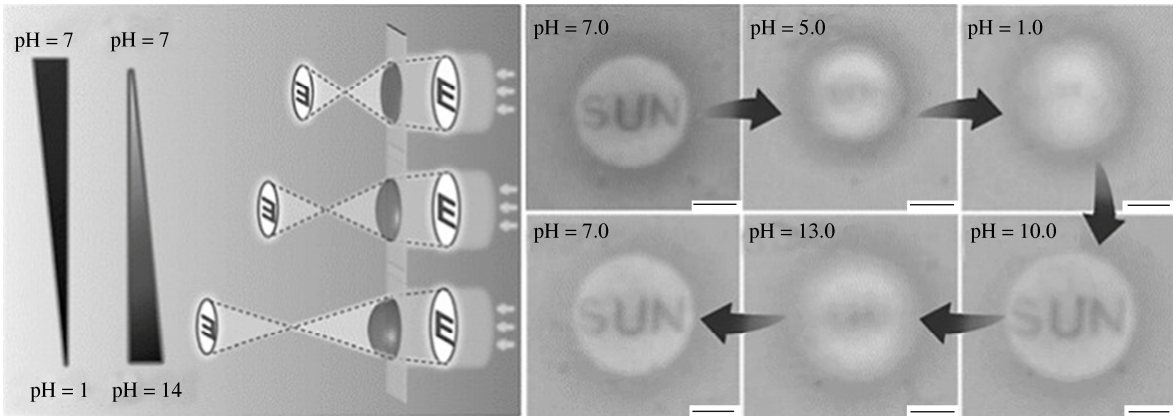


Fig. 9 The effect of changing the pH value on the focusing and imaging of a protein microlens (Scale bar: 10 mm.) (Reprinted with permission from Ref. [63]; Copyright (2012) John Wiley and Sons)

Hydrogels based on chitin, cellulose or alginate have attracted enormous attention in the field of biomaterials, due to their biodegradability, biocompatibility and structural similarity to extracellular matrix. In our laboratory[76], biocompatible polyelectrolytes composite hydrogels composed of alginate and chitin whiskers have been fabricated, and the resultant hydrogels have been successfully applied as bone scaffolds for MC3T3-E1 osteoblast cells (Fig. 10). Their mechanical properties are significantly improved, compared to alginate hydrogels, and the swelling trends are inhibited as a result of the electrostatic interactions between the chitin whiskers and alginate. Moreover, the addition of chitin whiskers into the nanocomposite hydrogels markedly promote the cell adhesion and proliferation of the osteoblast cells. This biocompatible nanocomposite hydrogels have potential applications in bone tissue engineering. Furthermore, Shou *et al.*[77] have utilized chitin nanofibers based hydrogels as a 3D environment to encapsulate bone marrow mesenchymal stem cells (BMSCs) for cellular therapy on rat skin wound. The stem cell laden hydrogel is formed *via in situ* physical gelation of chitin nanofiber suspension under physiological conditions. As suggested by *in vitro* and *in vivo* experiments, the CNFs hydrogels not only act as a three-dimensional "protection" to improve the viability of exogenous BMSCs, but also play an important role in inducing BMSCs differentiation into the angiogenic cells and fibroblasts, which are beneficial for accelerated wound repair. This may help to overcome the current stem cell therapy limitations faced by the field of wound regeneration.

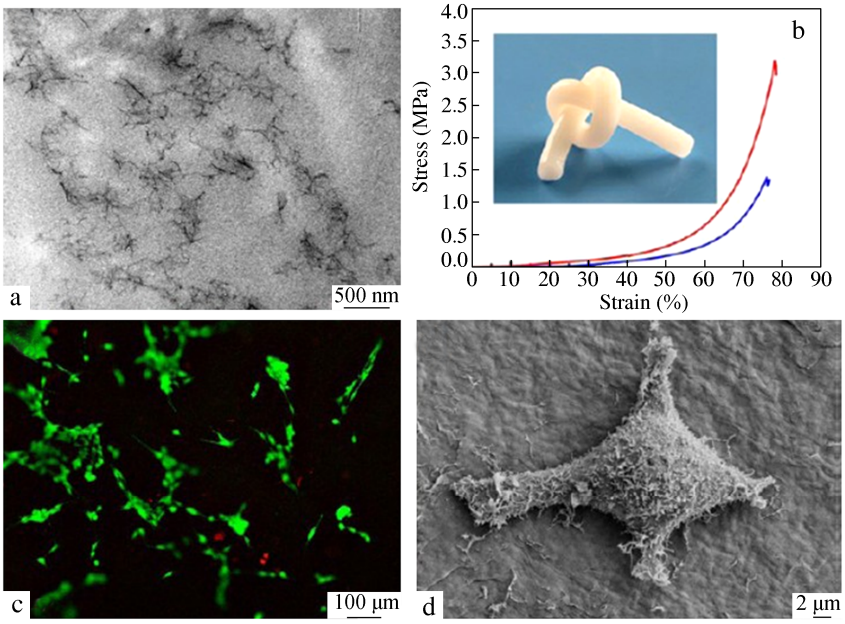


Fig. 10 TEM image (a), mechanical properties (b), photographs (b insert) of chitin whisker/alginate hydrogels; Fluorescent photograph (c), and SEM image (d) of osteoblast cultured on the composite hydrogel (Reprinted with permission from Ref. [76]; Copyright (2015) American Chemical Society) (The online version is colorful.)

Smart Bio-hydrogel Actuators

Smart bio-hydrogel actuators with excellent biocompatibility and biodegradation are able to undergo desired, programmable three-dimensional (3D) shape transformations and perform mechanical work under external triggers including pH, temperature, light, electricity and magnetism, showing potential applications such as in soft micro-robotics, cell scaffolds, soft actuators, and in drug delivery[75, 78–83]. In our laboratory[84], the bio-hydrogel actuators inspired by the bilayer structures of plant organs from chitosan and cellulose/carboxymethylcellulose (CMC) solution in an alkali/urea aqueous system containing epichlorohydrin (ECH) as a crosslinker have been fabricated (Fig. 11a). The bilayer hydrogels with excellent mechanical properties and tight interface adhesion can carry out rapid, reversible, and repeated self-rolling deformation actuated by pH-triggered swelling/deswelling, and can transform into various 3D hydrogels (Figs. 11b and 11c).

The bio-hydrogel actuators can carry out tasks as soft actuators such as grippers, smart capsules, and bioinspired lenses, showing potential applications in a wide range of fields including biomedicine, biomimetic machines, *etc.* Zheng *et al.*[27] have constructed a bilayer hydrogel robotic based on Al-alginate/poly(*N*-isopropylacrylamide) (PNIPAM), which can perform mechanical work triggered by temperature.

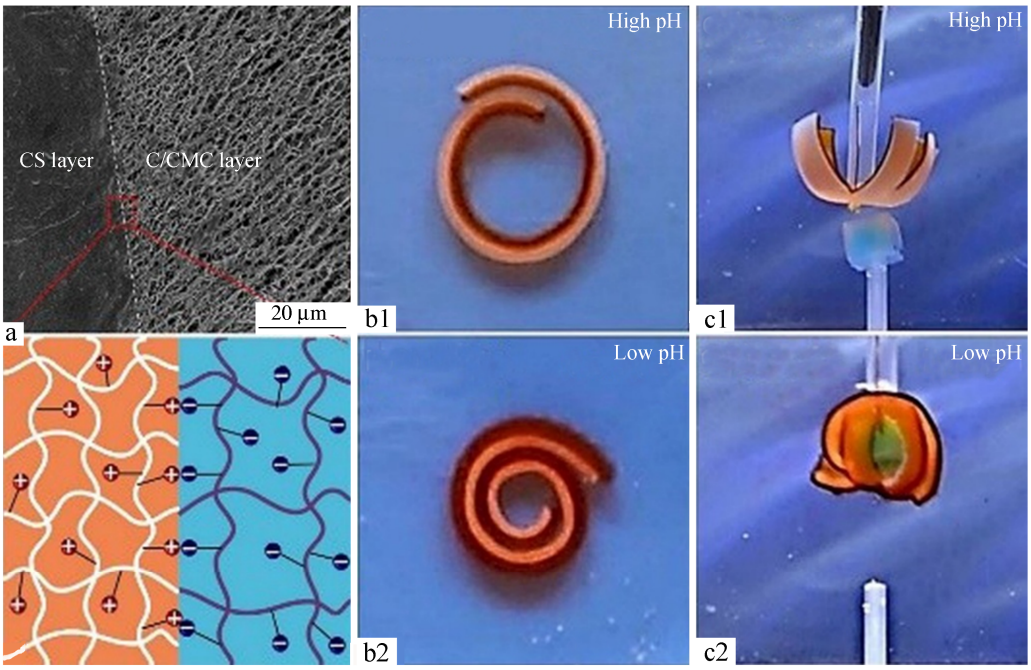


Fig. 11 The cross-sectional SEM image of a bilayer hydrogel at pH = 7, and schematic electrostatic interaction in the interface of bilayer hydrogels (a); Photographs of a bilayer roll (b1, b2) and gripper (c1, c2) in different pH mediums (Reprinted with permission from Ref. [84] from the Royal Society of Chemistry) (The online version is colorful.)

Furthermore, smart bio-hydrogel actuators triggered by electricity and magnetism are also developed by the introduction of functional components including conductive polymers, magnetic nanoparticles and redox ion into hydrogels matrix. Olsson *et al.*[85] have reported a novel lightweight porous magnetic aerogel by *in situ* synthesizing magnetic nanoparticles in the templates of freeze-dried bacterial cellulose nanofibril aerogels. The 20–70-nm-thick cellulose nanofibrils act as templates for the non-agglomerated growth of ferromagnetic cobalt ferrite nanoparticles (Fig. 12, top). The magnetic aerogel is dry, lightweight, porous (98%), flexible, and can be actuated by a small household magnet. Moreover, it can absorb water and release it upon compression (Fig. 12, bottom). Owing to their flexibility, high porosity and surface area, these aerogels are expected to be useful in microfluidics devices and as electronic actuators. Helminger *et al.*[86] have provided a gelatin/Fe_3O_4 nanocomposite hydrogel by the facile *in situ* synthesis method. The gelatin hydrogels crosslinked by Fe_3O_4 nanoparticles with electrostatic interaction can be driven by external magnetic fields, which has promising applications as biocompatible actuators. Haider *et al.*[87] have reported a facile and versatile strategy to prepare a tough and magnetic hydrogel by uniformly dispersing alginate-coated Fe_3O_4 nanoparticles into the interpenetrated polymer networks of alginate and PAAm. The magnetic hydrogels can quickly navigate guided by a non-contact magnet, which demonstrated the potential applications of the magnetic hydrogels for soft robotics and clinical operations.

In recent years, polyaniline (PANI) doped with acidic phosphate ester has been successfully dissolved in a cellulose aqueous solution with a 7 wt% NaOH-12 wt% urea system at low temperature to obtain a blue PANI-cellulose solution in our laboratory[88]. Subsequently, an electromechanical PANI-cellulose hydrogel (Fig. 13a), for the first time, has been prepared from a PANI-cellulose transparent solution dissolved in a NaOH-urea

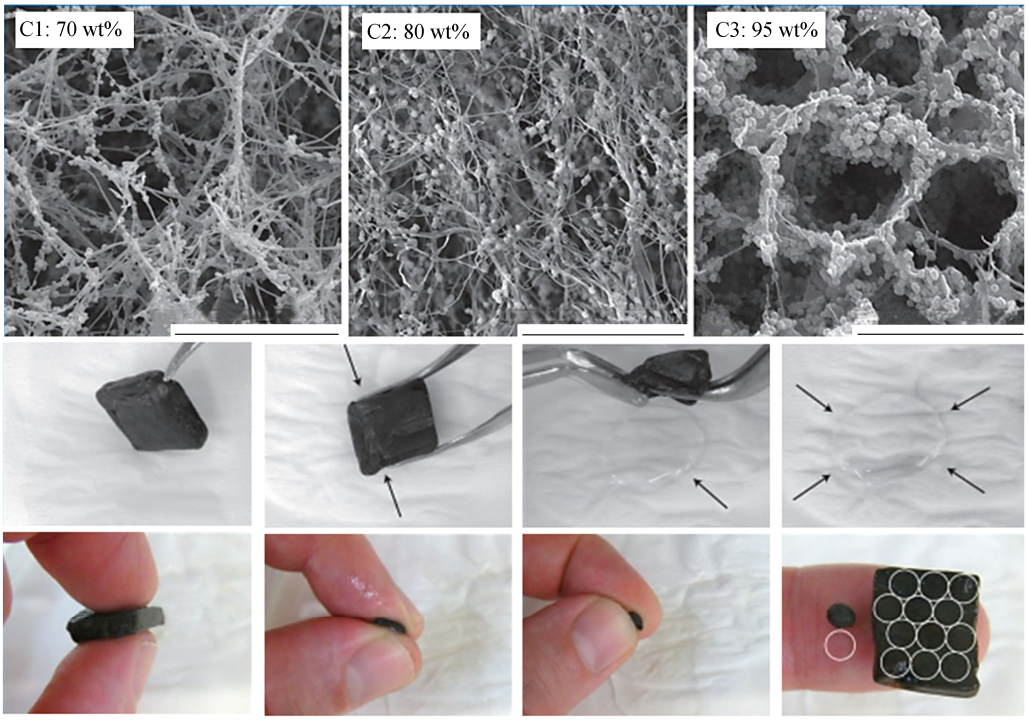


Fig. 12 SEM images (from left to right) of sample C1 (70 wt% of particles), sample C2 (80 wt% of particles) and sample C3 (95 wt% of particles) with scale bars equal to 4 mm (top); Water release and deformability (bottom) (Reprinted with permission from Ref. [85]; Copyright (2010) Nature Publishing Group) (The online version is colorful.)

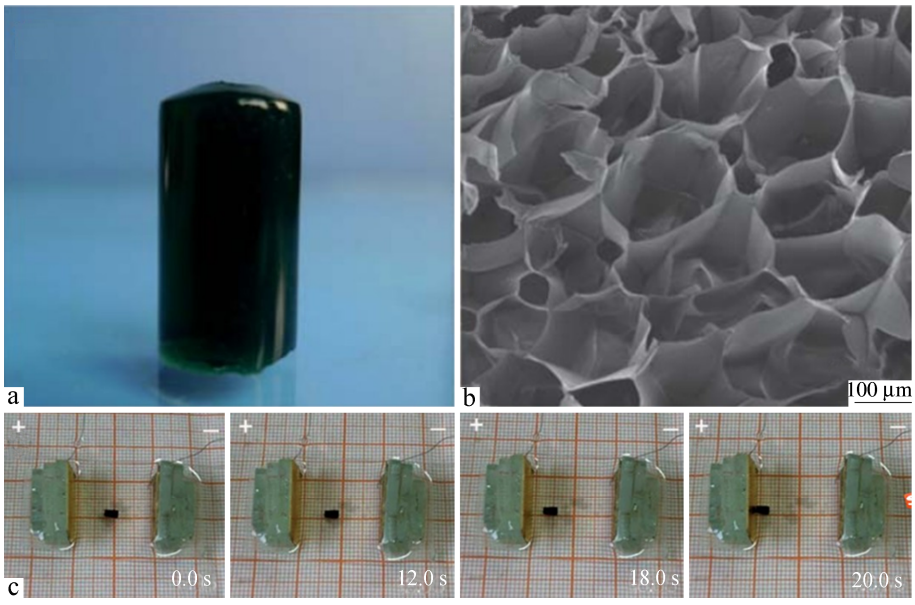


Fig. 13 Photograph of PANI-cellulose hydrogel (H25) (a) and SEM image of a cross-section of the H25 hydrogel in a freeze-dried state (b); Time profiles of H25 hydrogels in motion under a low applied electric field (c) (Reprinted with from permission from Ref. [89] from The Royal Society of Chemistry) (The online version is colorful.)

aqueous system at low temperature by cross-linking with epichlorohydrin[89]. The composite hydrogels display a homogeneous macroporous structure (Fig. 13b), good miscibility, and excellent mechanical strength, as a result of the association of the PANI chains with the cellulose crosslinked networks held together by noncovalent

interactions. Moreover, the hydrogels exhibit a continuous and linear crawling motion under a low applied electric field (Fig. 13c), showing the great potential of a smart hydrogel for applications in the field of biomimetic materials. The proposed response mechanism for this actuator could be explained as follows. The positive charges fixed on the backbones of acid doped PANI-cellulose hydrogels are immobile in electric field, while the counterions drift to the direction of positive electrode, leading to the hydrogels experiencing an electrostatic force along the applied electric fields. Therefore, when the electric field exceeded a certain critical driving threshold, the doped PANI-cellulose hydrogels could crawl from the negative to positive electrode with a slowly increasing velocity. Xue *et al*.[90] have reported the engineering of an electrically controllable supramolecular hydrogel as an actuator from a self-assembling short peptide, in which a catechol moiety is introduced as the stimuli-responsive motif. This kind of electrochemically responsive hydrogel can perform the unidirectional expansion and rotational motion under electrical stimulations. The applications of the actuators for controllable drug release and actuation of microfluidic devices are also illustrated, indicating that the hydrogels have applications as novel biosensors, artificial robots, and smart soft materials.

CONCLUSIONS AND OUTLOOK

Scientists around the world have predicted that a new era, that is, artificial intelligence (AI) is coming in the future. The AI technology will be applied in every field, especially in biomedicine and wearable products. Robust and smart bio-hydrogels with inherent biocompatibility, biodegradability and stimuli-responsibility have promising applications in AI biomedicine and wearable products. In spite of such huge advantages, the use of bio-hydrogel is limited to aqueous solutions. The design of hydrogel-based actuators acting in air conditioners is possible by adsorbing water molecules from air (humidity). Another limitation of hydrogels is slow response speed which is related to slow diffusion of water molecules. This problem can, however, be solved by using porous hydrogels[6].

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