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Article

Polysaccharide-Based Supramolecular Hydrogel for Efficiently Treating Bacterial Infection and Enhancing Wound Healing

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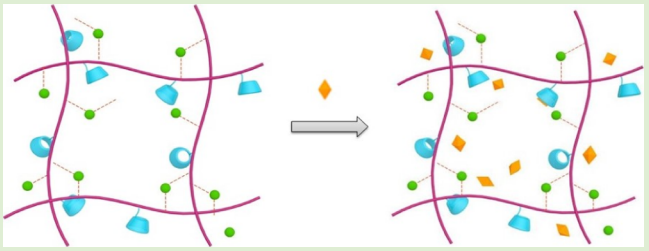
ABSTRACT: Nowadays, the rapid emergence of antibiotic-resistant pathogens has become a serious threat to human health. As an effective antimicrobial therapy, supramolecular materials show unprecedented advantages because of their flexible and adjustable interactions with biological molecules. Supramolecular hydrogels are now widely applied in biomedical fields because of their outstanding biocompatibility, high water content, easy preparation, and unique functions. Herein, we conveniently prepared a stable supramolecular hydrogel by simply mixing β-cyclodextrin-modified chitosan (CS−CD) with $AgNO_3$ in a basic environment. The obtained supramolecular hydrogel, which is positively charged and possesses numerous β-cyclodextrin cavities, could efficiently load anionic drug diclofenac sodium (DS) through the electrostatic interaction and host−guest inclusion. Significantly, the biological experiments demonstrated that this supramolecular hydrogel exhibited a high antibacterial effect and good ability of promoting wound healing owing to the cooperative contribution of CS, Ag^+, and DS.



INTRODUCTION

The rapid emergence of antibiotic-resistant pathogens has now become a serious threat to human health,[1] and supramolecular materials, especially supramolecular hydrogels, show unprecedented advantages as an effective antimicrobial therapy because of their flexible and adjustable interactions with biological molecules.[2] Similar to natural living tissue, hydrogels are capable of retaining high content of water or biological fluid.[3] Additionally, hydrogels also possess diverse structures and functions because of their tunable compositions.[4] In 1961, the hydrogel cross-linked with poly(hydroxyethyl methacrylate) was used for eye treatment, which is the first application of the hydrogel in the biomedical field.[5] From then on, continuous efforts were devoted to the development of hydrogels in fields of cell culture,[6] drug delivery,[7] wound healing,[8] and antimicrobial activity.[9] Among various hydrogels, the cyclodextrin (CD)-based supramolecular hydrogel that combines the advantages of the hydrogel and cyclodextrin becomes a booming research field, showing the significant applications in drug loading and transport[10] and detection[11] and removal of small molecules.[12] On the other hand, chitosan (CS) is one of the sugar-based biopolymers obtained from chitin *via* deacetylation reaction[13] and has many advantages including good biocompatibility, strong biodegradable ability, and low toxicity. Therefore, CS and its derivatives are widely applied in biomedical fields.[14] Because it is antibacterial, hemostatic, and mucoadhesive, CS is regarded as an ideal candidate of wound healing materials.[15] Lu *et al.* reported a series of multistimuli-responsive and moldable supramolecular hydrogels cross-linked by complexation of transition metal ions and biopolymers.[16] Herein, we constructed a stable supramolecular hydrogel *via* the complexation of a conjugated polysaccharide, that is, β-cyclodextrin-modified CS (CS−CD)[17] with Ag^+ followed by the noncovalent incorporation of a nonsteroidal anti-inflammatory analgesic, diclofenac sodium (DS). There are several inherent advantages of this Ag/CS−CD/DS supramolecular hydrogel as a potential material for treating bacterial infection and enhancing wound healing: (1) both CS and CD are water soluble, biocompatible, and biodegradable; (2) silver is an antimicrobial substance with low toxicity to mammalian tissues[18] and can be used in the prevention and treatment of burns, injuries, and infections;[19] and (3) DS has a strong anti-inflammatory effect and high safety[20] and becomes one of the most widely used nonsteroidal anti-inflammatory drugs for skin.[21] As a significant result, the Ag@CS−CD/DS supramolecular hydrogel can not only present the good antibacterial ability but also accelerate wound healing. Compared with previous reports,[22] the natural hydrogel matrix based on polysaccharides possesses several good qualities, including high oxygen permeability and improved biocompatibility, and thus becomes an ideal material for wound dressings. In addition, the main advantage of this

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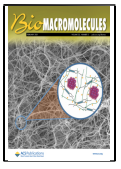

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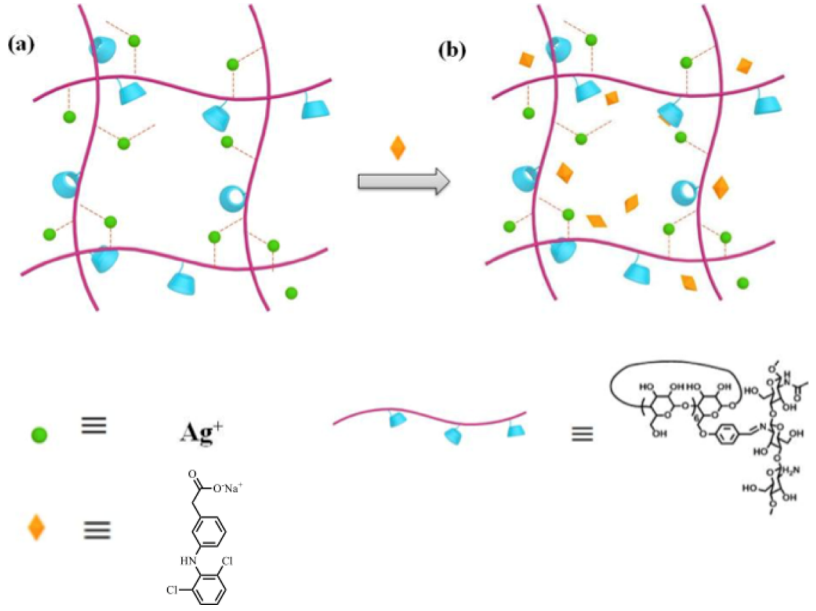
Scheme 1. (a) Illustration of the Preparaed Hydrogels through Supramolecular Complexation; (b) Illustration of the Supramolecular Hydrogel Loading Anionic Drugs-DS[a]



[a]The networks driven by the supramolecular complexation between Ag^+ and OH and NH_2 groups in the CS chains.

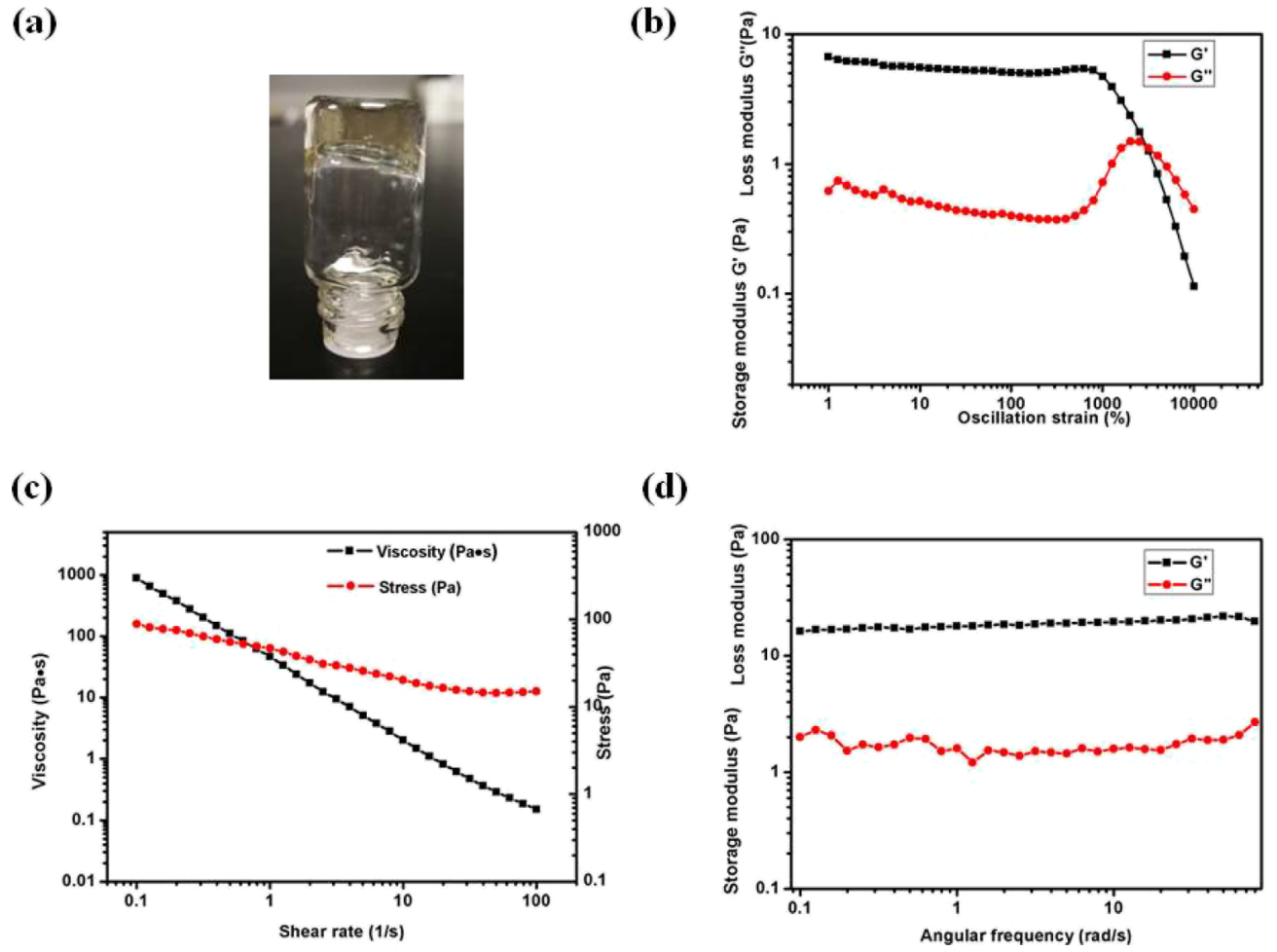


Figure 1. (a) Pictures of the supramolecular hydrogel. (b) Strain sweep tests of the supramolecular hydrogel at γ = 1−10,000% and ω = 1 rad s^{-1}. (c) Frequency sweep tests of the supramolecular hydrogel at ω = 0.1−100 rad/s and strain (γ) = 100% at 25 °C. (d) Continuous step strain tests of supramolecular hydrogels at γ = 0.1 and 100%.

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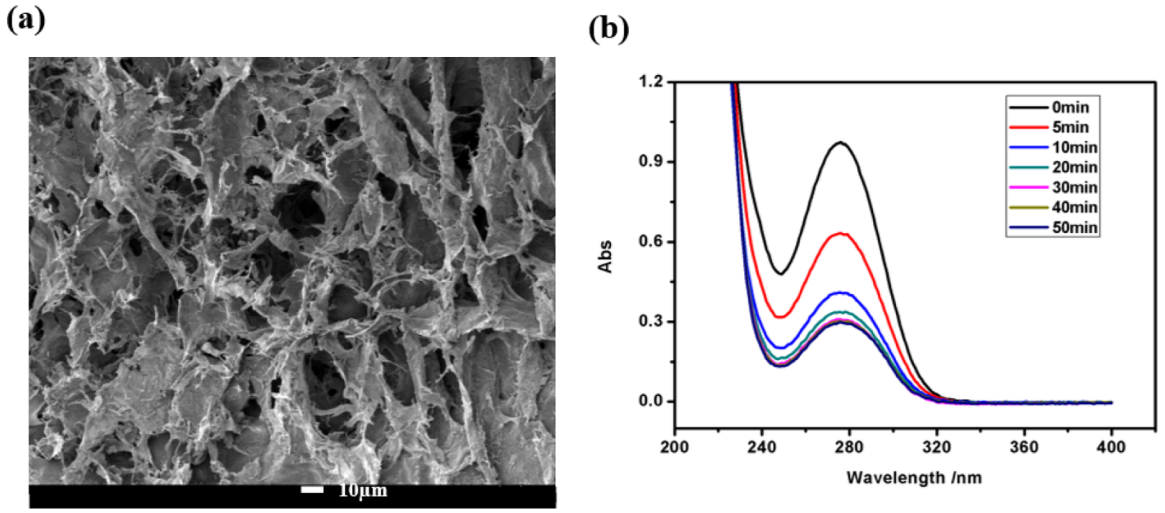

Figure 2. (a) SEM image of the supramolecular hydrogel (the scale bar in SEM image is 10 μm); (b) time-dependent UV−vis spectra of DS aqueous solution in the presence of the supramolecular hydrogel.

work is that the antibacterial activity of Ag@CS−CD + DS is assigned to cooperative contribution, which avoids the high silver content causing a potential cytotoxic hazard.[23]

EXPERIMENTAL SECTION

Materials. β-CD was purchased from Sigma-Aldrich. CS was purchased from Qingdao Brightmoon Seaweed Industry Co., Ltd. (Deacetylation: 75−80%, viscosity: 20−300 cps, and 15−22 kDa). DS was purchased from ApexBio.

NMR Spectroscopy. ^{1}H NMR was recorded at 298 K on a Bruker AVANCE III 500 MHz instrument. Chemical shifts are reported in ppm relative to the signals corresponding to the residual non-deuterated solvents (D_2O: δ_H = 4.79 ppm).

UV−Vis Spectroscopy. UV−vis spectra and the optical transmittance of the aqueous solution were determined in a quartz cell (light path 10 mm) on a Shimadzu UV-3600 spectrophotometer equipped with a PTC-348WI temperature controller.

SEM Experiments. Scanning electron microscopy (SEM) images were obtained on a Hitachi S-3500N scanning electron microscope.

Zeta Potential Measurement. Zeta potential was measured by a zeta PALS + BI-90 instrument (Brookhaven Co. USA).

Rheology Measurement. The rheological characterization of the hydrogel was carried out on an AR-G2 rheometer (TA instruments, Etten-Leur, The Netherlands) equipped with a 11 steel cone geometry of 20 mm diameter and a solvent trap. The gap was set at 1.0 mm.

β-CD-modified CHIT 1 was prepared according to the previous report,[17] and the substitution degree of CS−CD was 6.6%.

Preparation of the Ag@CS−CD Hydrogel. The Ag@CS−CD supramolecular hydrogel (1 mL) was prepared by mixing 100 μL of NaOH aqueous solution (0.2 M) with 800 μL of CS−CD solution (0.5 wt %, 1% acetic acid), followed by the addition of 100 μL of freshly prepared $AgNO_3$ aqueous solution (0.3 M) under vigorous stirring at room temperature.

Preparation of the Ag@CS Hydrogel. The Ag@CS supramolecular hydrogel (1 mL) was prepared by mixing 100 μL of NaOH aqueous solution (0.2 M) with 800 μL of CS solution (0.5 wt %, 1% acetic acid), followed by the addition of 100 μL of freshly prepared $AgNO_3$ aqueous solution (0.3 M) under vigorous stirring at room temperature.

Loading of DS to the Hydrogel. Ag@CS−CD (0.37 g) was put into a dialysis bag with a molecular weight cutoff of 5000, which was then put into 250 mL (0.03 g/L) of DS solution, and the mixture was stirred at a speed of 100 rpm for about 30 min. After freeze-drying, the loading efficiency of the supramolecular hydrogel toward DS was calculated by weighting. The DS loading conditions of the Ag@CS−CD hydrogel and Ag@CS hydrogel are the same, including the solution concentrations of DS and loading time.

The animal experiments were approved by the Nankai Ethical Committee in compliance with the Chinese law on experimental animals.

RESULTS AND DISCUSSION

The addition of Ag^+ to the solution of CS−CD in 1.0% acetic acid produced the free-standing Ag@CS−CD supramolecular hydrogel *in situ* (Scheme 1). After mixing the Ag^+ solution and the CS−CD solution at an appropriate pH value at room temperature, the complexation of Ag^+ and CS chains was rapid, leading to the formation of an interwoven network and then the formation of a hydrogel.[16] The mechanical properties of the hydrogel were characterized by the rheology measurement. As shown in Figure 1, the linear elastic-viscous area was obtained by the experiments of amplitude sweep at strain (g) = 0.01−10,000%. Under the strain from 1 to 400%, G' (storage modulus) and G'' (loss modulus) remained nearly unchanged. When the strain increased continuously, G' decreased dramatically, causing the intersection of G' and G'' curves at a strain of 50%. Meanwhile, a gel−sol state transition was observed, indicating the breakdown of the hydrogel network. With the angular frequency ranging from 0.1 to 60 rad/s, neither G' nor G'' exhibited obvious changes, and G' was always larger than G'', demonstrating a good stability of the hydrogel toward the oscillation condition (Figure 1c). In addition, the steady shear rheological experiments (Figure 1d) indicated that the hydrogels had shear-thinning properties, and the viscosity of the hydrogel decreased obviously as the shear force was applied.

SEM and zeta potential were also performed to characterize the structure features of the supramolecular hydrogel. As shown in Figure 2a, the SEM image of the supramolecular hydrogel showed a clear three-dimensional porous network structure. By the way, the water content of the supramolecular hydrogel was calculated as 93% based on the mass ratio of the dry gel to the freshly made gel, and the content of Ag was measured as 4.74% by the inductive coupled plasma−atomic emission spectroscopy. Figure S3 showed the time-dependent transmission curves of the supramolecular hydrogel, where the optical transmittance of Ag@CS−CD recorded at 1 min after

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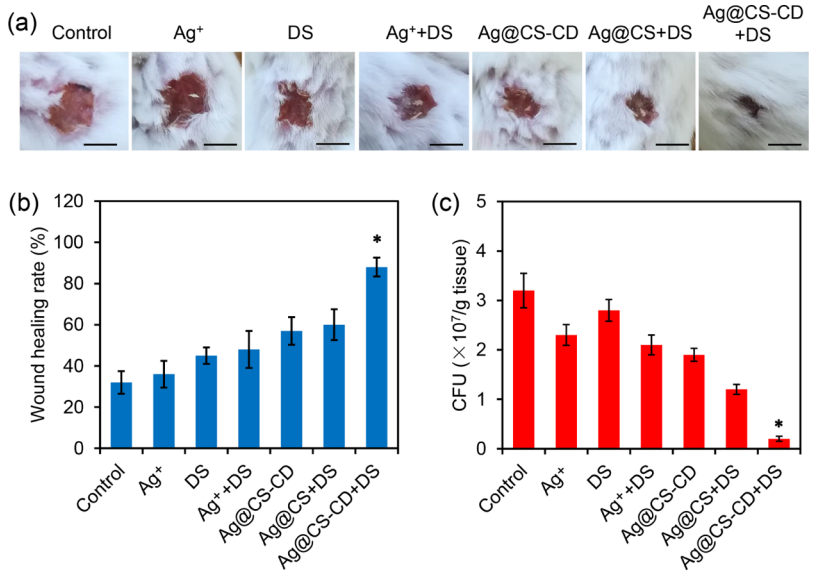

Figure 3. *In vivo* antibacterial and wound healing capacity of the hydrogels in the mouse wound-infection model. (a) Images of wounds on mouse back in different treatments after 6 days of treatment. Scale bar = 0.5 cm. The calculated areas of each wound were 0.56, 0.5, 0.33, 0.25, 0.17, and 0.08 cm^2 from light to right. (b) Wound healing rate of different groups. (c) Bacterial numbers of different groups in wound tissues evaluated by colony forming unit (cfu) assays.

mixing CS−CD solution with Ag^+ was similar to that recorded at 60 min, indicating that the complexation of CS−CD with Ag^+ was both fast and stable. In addition, the supramolecular hydrogels could keep intact for 6 months at room temperature, showing good biostability. Interestingly, the supramolecular hydrogel also presented good thermal stability and could endure heating to 95 °C without any phase transition. This thermal stability was better than most of the reported supramolecular hydrogels that usually presented a gel-to-sol transition after heating (Figure S4).[24] However, the supramolecular hydrogel would slowly turn black after being exposed to daylight and should be kept away from light.

Moreover, the zeta potential of the supramolecular hydrogel was measured as +47.77 mV (pH 5.76), indicating that the supramolecular hydrogel was highly cationic and might have the possibility of associating with anionic substrates *via* electrostatic interactions (Figure S2). In addition, the various CD cavities in the supramolecular hydrogel could also associate the substrates *via* the host−guest inclusion complexation. Herein, DS, a nonsteroidal anti-inflammatory analgesic, was selected to be loaded onto the supramolecular hydrogel because DS could incorporate into the supramolecular hydrogel through not only the inclusion of *β*-CD cavity toward DS but also the electrostatic attraction between the cationic supramolecular hydrogel and the anionic DS molecule. Job's plot of the *β*-CD/DS system showed an inflection point at a molar ratio of 0.5, indicating that the *β*-CD cavity could include DS *via* a 1:1 host−guest inclusion stoichiometry (Figure S6), and its association constant was reported to be 200−600 M^{-1}.[25] Owing to the joint contribution of the host−guest inclusion complexation and the electrostatic attraction, the as-made hydrogel exhibited the good ability of loading DS. By measuring the characteristic absorption of DS at 276 nm, the photometric standard curve of DS was obtained with the absorption intensity as the ordinate and the DS concentration in aqueous solution as the abscissa (Figure S5). Accordingly, the encapsulation efficiency and the loading efficiency of the supramolecular hydrogel toward DS were calculated as 69.3 and 16.7%, respectively, and the loading saturation was reached at 30 min (Figure 2b).

The antibacterial efficiency of the hydrogels was further evaluated by an *in vivo* wound healing model. The wounds on the mouse back with approximately 1 cm diameter were first infected by 5×10^7 cfu of the pathogenic *Pseudomonas aeruginosa* strain PAO1. The infected wounds were then treated by the hydrogel (100 mg/wound) per day. After 6 days of treatment, the wounds were imaged, and the wound tissues were sampled for detection of pathogenic numbers. As compared to the control, the groups of DS, Ag^+ + DS, Ag@CS−CD, Ag@CS + DS, and Ag@CS + DS exhibited reduced wound areas (Figure 3a). Among them, the Ag@CS−CD + DS group showed a much higher wound healing rate than other groups (Figure 3a,b), suggesting the highest wound healing efficiency of Ag@CS−CD + DS. cfu assays further showed that all the treated groups had a reduction of cfu as compared to the control group. More strikingly, the Ag@CS−CD + DS group showed the lowest cfus than other groups (0.2×10^7 *vs* $1.0-2.8 \times 10^7$ cfu) (Figure 3c), indicating the highest antibacterial efficiency of Ag@CS−CD + DS among the components. Therefore, the Ag@CS−CD + DS hydrogel could strongly accelerate wound healing and kill pathogenic bacteria.

CONCLUSIONS

In summary, we successfully constructed a supramolecular hydrogel through a simple but facile method from biocompatible building blocks CS, CD, and Ag^+. This supramolecular hydrogel is highly cationic and possesses numerous *β*-CD cavities. As a result, the supramolecular hydrogel could efficiently load the anionic drug through electrostatic interaction and host−guest inclusion. Owing to the cooperative contribution of CS, Ag^+, and DS, the resultant hydrogel exhibited high wound healing ability and excellent antibacterial effect.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.biomac.0c01401.

^{1}H NMR spectra, zeta potential, time-dependent transmission, thermal stabilities and long-term stabilities, UV−vis spectra, and Job's plot (PDF)

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Notes

The authors declare no competing financial interest.

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