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PAPER

A self-healing and multi-responsive hydrogel based on biodegradable ferrocene-modified chitosan

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Here, we present a novel and facile method for constructing a self-healing hydrogel capable of responding to multiple external stimuli via the self-assembly of biodegradable ferrocene-modified chitosan (FcCS) in an acid aqueous solution at a low concentration of 10 mg/mL. The hydrogel can re-adhere between cut surfaces and self-heal to its original shape and property after being cut, demonstrating excellent self-healing property, which is also quantitatively proved by rheological measurements. The hydrogel also presents stimuli-responses towards pH, redox, and different ions such as Cd^{2+}, Cr^{3+}, Pb^{2+}, and Cu^{2+}. In addition, the encapsulation and controlled release of doxorubicin hydrochloride (DOX•HCl) in buffer solutions with different pH values were successfully carried out, which suggests that the accumulative release of DOX•HCl increases as the pH value decreases. All these results indicate that this hydrogel is a promising functional and biomedical material.

Introduction

Self-healing hydrogels are capable of regaining original properties upon external or internal damage.[1] Self-healing hydrogels have been developed rapidly for their potential applications such as drug delivery systems,[2-4] remotely actuated biosensors[5-7] and shape memory materials[8-10] as self-healing can increase a hydrogel's lifetime, reduce replacement costs, and improve product safety.[11] Self-healing systems can be made from a variety of materials, among which polymers have been extensively explored because of their chemical and mechanical tunability, and the ability to create dynamic hydrogels.[9, 12-14] In particular, stimuli-responsive polymers that can identify and respond to small physical or chemical stimuli such as pH, light and temperature are favourable for the design of self-healing hydrogels, providing a feasible way to construct a system that possesses both stimuli-responsiveness and self-healing properties.[14-19]

Although much progress has been made on self-healing hydrogels, there are still some challenges. Hydrogels designed for biomedical applications require the component to be biodegradable, and non-toxic. At present, these medical hydrogels are usually made of amphiphilic polypeptides,[20] but the preparation of polypeptides is complicated and expensive, which hinders the wide application of these hydrogels. Therefore, constructing self-healing hydrogels based on cheap and biocompatible polymers is of practical interest and economically attractive. Chitosan, an abundant alkaline polysaccharide in nature, is one of the most important green and renewable materials. Hydrogels based on chitosan or chitosan derivatives have been used for many pharmaceutical and medical purposes for its non-toxicity, and biodegradability.[21-23] However, its self-healing ability has rarely been reported.[24] Meanwhile, most of reports on stimuli-responsive hydrogels formed by chitosan or chitosan derivatives are about pH or temperature response,[25, 26] whereas the redox response is rarely studied.[27]

Supramolecular hydrogels based on noncovalent intermolecular forces usually have good thixotropy, responding quickly to tiny stimulations, and easily achieving sol-gel reversible transformation and self-healing property.[28-31] Ferrocene (Fc) is of particular research interest in designing supramolecular hydrogels due to its unique sandwich structure, hydrophobic character and redox property. In 2011, Masaki Nakahata[28] first adopted cyclodextrin-modified poly (acrylic acid) as host polymer and Fc-modified poly (acrylic acid) as guest polymer to form a redox-responsive self-healing hydrogel through the redox-property of Fc and host-guest interaction between cyclodextrin and Fc. Since then, most studies on ferrocene-containing self-healing hydrogels have been mainly focused on obtaining supramolecular hydrogels via host-guest interaction,[32-34] and little attention has been paid to constructing them, using the hydrophobicity of ferrocene.[35] As a matter of fact, hydrophobicity can play an important role in forming supramolecular hydrogels, and the hydrophobic segment can aggregate again after external damage, which is of importance for developing self-healing hydrogels.[36, 37]

Ferrocene also has low toxicity and ferrocenyl derivatives have excellent effects as antitumor agents. Some of the derivatives are now in clinical trials.[38, 39] Therefore, Fc-based hydrogels equipped with self-healing and responsive characteristics would have unique advantage in the biomedical system. In this study, a polymer was obtained by connecting Fc to chitosan through amide linkage and its ability to form supramolecular hydrogels was carefully investigated in an acetic acid solution. The self-healing and multi-responsive properties were thoroughly studied, and meanwhile its controlled drug release behaviour under

different conditions was also investigated.

2. Experimental

2.1 Materials

Chitosan (Sinopharm Chemical Reagent Beijing Co., Ltd, degree of deacetylation: 80-95%) was utilized after further deacetylation to 100% according to the previous study.[40] Ferrocenecarboxylic acid (FcA, TCI Shanghai, 98%), 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide (EDC, J&K Chemical, 99%), N-hydroxysuccinimide (NHS, J&K Chemical, 98.5%), L-glutathione (GSH, J&K Chemical, 99%) were used as purchased. All solvents were used as received without further purification.

2.2 Preparation of FcCS

FcCS was synthesized by reaction between the amino group of chitosan and carboxyl group of FcA according to the reported literature.[41] Briefly, FcA (0.36 g) was dissolved in methanol and activated by adding equal amounts of EDC and NHS under stirring for 30min at room temperature. Chitosan (0.51 g) was dissolved in 2 wt% acetic acid solution (25 mL), diluted with methanol (25 mL) and stirred till optically transparent. Then activated FcA was added dropwise to the chitosan solution. The resulting mixture was stirred at room temperature for about 48h under a nitrogen atmosphere to conjugate FcA with chitosan molecules, and then adjusted to pH 10.0 with 0.1M NaOH solution to terminate the reaction. The resulting mixture was centrifuged and the precipitate was washed with water and methanol alternately. Finally, the precipitate was freeze dried..

2.3 Hydrogel preparation

FcCS was dissolved in a 2% (w/v) wt acetic acid solution to a concentration of 10 mg/mL. Then the solution was ultrasonically treated, stirred and left standing at room temperature.

The gels for all other analyses were prepared using the same procedures.

2.4 Self-healing experiment

1) A hydrogel disk was cut into two pieces, and then were put together to form a united disk.

2) Rheology analyses were carried out to qualitatively monitor the self-healing process. In brief, a gel was prepared utilizing the above described method. First, the storage modulus G' and loss modulus G'' of the original hydrogel were performed under 1% strain. The gel was subsequently cut into pieces on a plate, and the G', G'' of the broken gel values versus time were recorded. The G', G'' versus shear stress was also carried out under 1.6 Hz frequency, and the G' of the gel decreased quickly when the strain (γ) was 100%. Thus, the profile of G', G'' values to different amplitude was subsequently measured. Amplitude oscillatory forces were changed from γ= 500% to 1% under the same frequency (1.6 Hz) to test the self-healing mechanical property of the hydrogel. The G', G'' values versus frequency was also carried out to compare with the original hydrogel.

2.5 Multi-responsive experiments

2.5.1 pH responsiveness

Hydrogels of FcCS are prepared using the above described method. Then the pH value of the hydrogel was adjusted to above 6.5 and back to 4 again to test the pH response.

2.5.2 Redox responsiveness

Hydrogels of FcCS are prepared as above described. The pH value of the resultant hydrogels is 4.0. NaClO was then added, following by addition of GSH to test the redox response.

2.5.3 Ion responsiveness

Hydrogels of FcCS are prepared as above described. The pH value of the hydrogels is 4.0. Different ion, namely, $CdSO_4$ (14.0 mg), $CrCl_3$ (31.8 mg), $Pb(NO_3)_2$ (18.2 mg), and $Cu(NO_3)_2$ (28.5 mg) were added to the hydrogel, respectively. Chitosan in a 2 % acetic acid solution (10 mg/mL) was used as contrast.

2.6 Controlled release of DOX•HCl

First, drug-loaded hydrogels were prepared by dissolving FcCS and DOX•HCl in a 2 wt% acetic acid solution. Then the drug-loaded hydrogels were transferred to dialysis bags immersed in vials containing 25 mL buffer solutions at pH 4.0, 6.0, and 8.0, respectively and incubated at 37℃ in a thermostated shaker rotating at 100 rpm. At predetermined time points, 3 mL aliguots of this solution was withdrawn from the vials and 3 mL of fresh buffer solution was added to the vials. The released DOX•HCl was estimated by UV spectrophotometry at 481 nm.

2.7 Measurements

^{1}H NMR analysis was carried out on a JOEL JNM-ECA600 spectrometer in 2% CF_3COOD in D_2O at room temperature (solvents without TMS). FT-IR measurements were performed on an AVATAR 360 FT-IR spectrometer (Thermo Nicolet). The samples for FT-IR measurement were prepared by dispersing the powder in KBr and compressing the mixtures to form disks. X-ray diffraction (XRD) patterns were recorded on an X-ray diffractometer (MSAL-XD2) with Cu Ka (λ = 0.1541 nm) radiation (30 kV, 30 mA) and the XRD data were collected with 2θ in the range of 5 to 40º in 0.01 step. The ultraviolet–visible absorption spectra were recorded with a JASCO V-650 and a Hitachi U-4100 spectrometer in water with 1 cm quartz cell at room temperature. The electrochemical experiments were performed on a CHI 660A electrochemical work station (Shanghai CH Instruments Co., China) with a conventional three-electrode system consisting of a modified glass carbon electrode as working electrode, a platinum wire as auxiliary electrode, and a saturated calomel electrode (SCE) as reference electrode. The steady and dynamic rheological measurements were measured on a Physica MCR-300 rheometer with plate geometry, a diameter of 40 mm. Scanning electron microscope (SEM) was performed on a TECNAI T20 electron microscope. The specimens were freeze-dried under vacuum for SEM observation. The dried specimens were ground to fine powder and placed on the conducting glue and coated with gold vapor and analyzed on a TECNAI T20 electron microscope.

3. Results and discussion

3.1 FcCS synthesis and characterization

FcCS was synthesized by reaction between the amino group of chitosan and carboxyl group of FcA with NHS/EDC as catalyst (Fig. 1A）. The resulting FcCS was characterized by ^{1}H NMR, FT-IR and XRD and the data are shown in Fig. 1.

As shown in Fig. 1B, the peak at 3.09 ppm was attributed to the

C-2 protons of chitosan, and the peaks in the range of 3.62-3.82 attributed to the C-3, C-4, C-5, and C-6 protons. There was no amide proton signal at 2.0 ppm, suggesting that chitosan was completely deacetylated. The representative ^{1}H NMR spectrum of FcCS is shown in Fig. 1C, which contained the characteristic peaks of chitosan and the peaks in the range of 4.0-4.5 ppm that are attributed to the protons of the cyclopentadienyl rings, indicating that Fc-modified chitosan was successfully synthesized. However, these peaks overlapped with the solvent (HOD) peak, making it impossible to estimate the amount of ferrocenyl groups connected to chitosan.

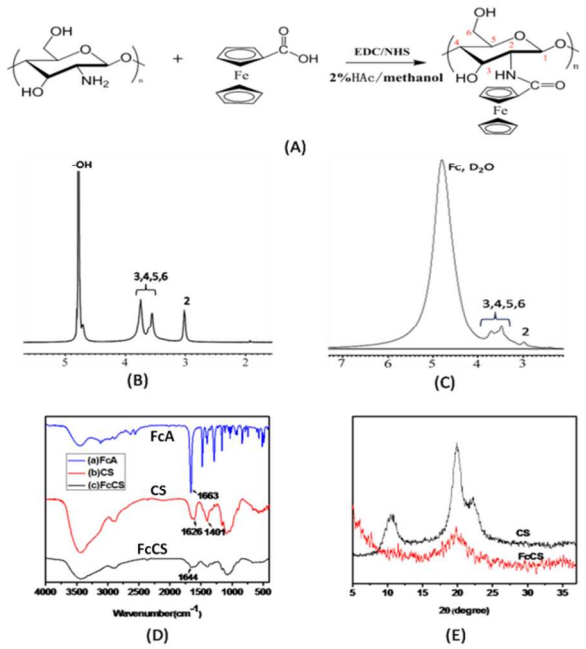

Fig. 1 Synthetic route and characterization of FcCS: (A) Synthetic route of FcCS; (B and C) ^{1}H NMR spectrum of CS and FcCS (2% CF_3COOD in D_2O）; (D) FT-IR spectra of FcA (a), CS (b), and FcCS (c). (E) XRD of FcCS and CS.

In the FT-IR spectra shown in Fig. 1D, chitosan showed characteristic peaks at around 1626 and 1401 cm^{-1}, which could be assigned to the amino groups of chitosan. These peaks were also observed in the spectrum of FcCS. However, the relative intensity of peaks at 1626 cm^{-1} versus 1401 cm^{-1} changed due to the consumption of the amino groups. Meanwhile, there was a new characteristic peak at 1644 cm^{-1} which could be assigned to carbonyl stretching of the amide bond appearing in the spectrum, indicating that Fc was successfully connected to chitosan chain through amide bond. Besides, the carboxyl vibration peak of FcA at 1663 cm^{-1} totally disappeared in the spectra of FcCS, showing that FcA was completely removed from the resulting product. The mass fraction of Fe is 2.59%, which was characterized by Atomic Emission Spectrometry (AES), thus the degree of substitution of ferrocene group is 8.2% by calculation.

XRD patterns of chitosan and FcCS are shown in Fig. 1E. Two characteristic diffraction peaks observed at 2θ=10º and 20º can be attributed to the hydroxyl and amino groups which tend to form intramolecular or intermolecular hydrogen bonds and thus crystallize. As Fc was introduced to the chitosan backbone, the regularity of the chitosan chain was damaged and the crystalline degree of chitosan decreased, resulting in the disappearance of the characteristic diffraction peak at 2θ=10º and a wider but weaker diffraction peak at 2θ=20º.

3.2 Gelation behavior and self-healing property

A supramolecular hydrogel obtained by dissolving FcCS in a 2 wt% acetic acid solution is shown in Fig. 2A. As contrast, only a transparent solution was formed by dissolving chitosan under the same condition (Fig. 2B). Chitosan is insoluble in water because of the strong hydrogen bonding force between amino and hydroxyl groups, but in acid solution the amino group is protonated, resulting in the decreased hydrogen bonding force, and dissolution of chitosan. With hydrophobic ferrocene groups connected to chitosan, the aggregation microdomain of ferrocene groups acts as cross-linking points. So both hydrophilic and hydrophobic interaction exists in the FcCS system, and the equilibrium of the hydrophilic and hydrophobic interaction leads to the formation of the hydrogel.

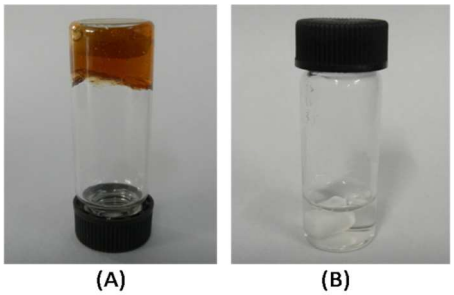

Fig. 2 Photographs of the supramolecular hydrogel and chitosan solution. (A) FcCS in a 2 wt% acetic acid solution at 10 mg/mL forming a hydrogel. (B) CS in a 2 wt% acetic acid solution at 10 mg/mL forming a transparent solution.

In 2011, Tuncaboylu[31] reported that hydrogels formed by stearyl methacrylate or dococyl acrylate copolymerized with acrylamide, exhibit tough and self-healing properties due to the strong hydrophobic interactions. The hydrophobic aggregation of Fc groups could act as reversible cross-linking points, thus the FcCS hydrogel is expected to be self-healable upon damage. The self-healing of FcCS is shown in Fig. 3. After being cut into two pieces and put together again for 4h, an annealed disk was formed and the disk could be stretched to almost twice as long as that of the original diameter.

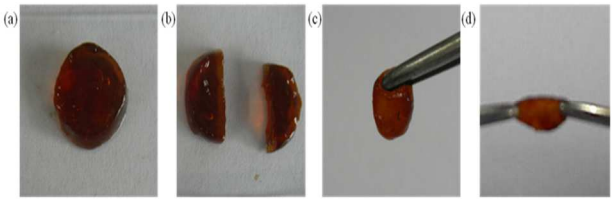

Fig. 3 Optical photos of the self-healing process: (a) the original FcCS hydrogel; (b) FcCS hydrogel was cut into two pieces; (c) the two pieces were put together; (d) the self-healing hydrogel was stretched.

The self-healing process was also traced by rheology analyses as shown in Fig. 4. The storage modulus (G') was much greater than the loss modulus (G'') over the entire range of frequency, suggesting that a hydrogel is formed. After the hydrogel was cut into pieces, the G' and G'' values of the self-healed hydrogel versus frequency were almost the same as those of the original hydrogel (Fig. 4A). Furthermore, the G' value was larger than G''

over the entire time range, indicating the self-healing property of FcCS hydrogel (Fig. 4B). The elastic response of the hydrogel was characterized through strain amplitude sweep, and the G' value decreased rapidly above the critical strain region (Fig. 4C, γ = 100%), indicating the collapse of the gel network. Thus, the hydrogel was operated with a large amplitude oscillatory force (Fig. 4D, γ = 500%, frequency = 1.6 Hz). It was observed that G' value decreased from 839 Pa to 51 Pa and the G' value was even smaller than G'' value, resulting in a loose network. However, the G' value returned immediately to initial value with decrease of the amplitude (γ = 1%, frequency = 1.6 Hz), and the hydrogel reverted to original state, indicating the quick recovery of the network. All the above results confirm that the gel has excellent self-healing property.

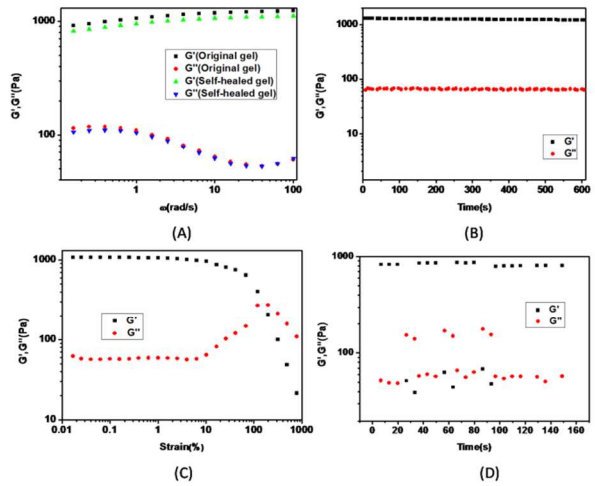

Fig. 4 Rheological measurements of the self-healing process. (A) Storage modulus G' and loss modulus G'' of original and self-healed hydrogels; (B) G' and G'' versus time during the self-healing process (frequency: 1.6 Hz; strain: 1.0%); (C) G' and G'' on strain sweep; (D) G' and G'' in continuous step strain measurements.

As above mentioned, chitosan is dissolved under acidic condition, so the chain of chitosan is of fluidity. Besides, Fc groups could self-assemble into hydrophobic microdomains, acting as reversible cross-linking points. When FcCS is damaged from cut, the moveable chitosan chain may allow ferrocene groups to reaggregate into hydrophobic microdomains, and the hydrophilic and hydrophobic interaction would reach equilibrium after damage, resulting in the reversion to the original state.

3.3 Multi-responsiveness of the hydrogel

3.3.1 pH responsiveness

FcCS presents significant gel-precipitate transition behavior under different pH values as shown in Fig. 5. At pH 4, FcCS dissolved in 2 wt% acetic acid solution resulted in hydrogel. However, the hydrogel turned into precipitate immediately when the pH value of FcCS hydrogel was adjusted to above 6.5 by adding sodium hydroxide solution. When the pH value was adjusted to 4 again, a hydrogel was obtained.

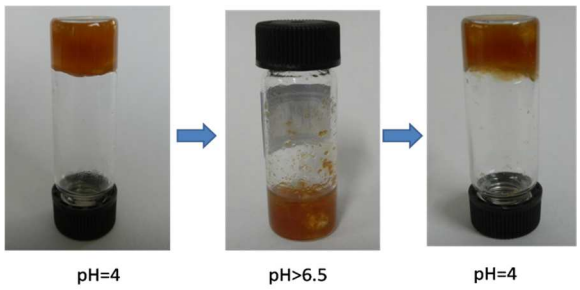

Fig. 5 pH responsiveness of FcCS hydrogel. (a) Original hydrogel; (b) hydrogel decomposition after pH was adjusted to above 6.5; (c) hydrogel regeneration after pH was adjusted to 4 again.

It is known that when pH value increases, the amino groups of chitosan backbone are deprotonated quickly and interact with hydroxyl groups to form intramolecular and intermolecular hydrogen bonds. The hydrogen bonding force is so strong that the chitosan chain becomes insoluble and the equilibrium of hydrophilic and hydrophobic interaction in the FcCS hydrogel system is broken, which leads to precipitate at higher pH. When pH was adjusted to 4, the amino groups of chitosan backbone were protonated, so the chitosan chain was dissolved and the system regained the equilibrium of hydrophilic and hydrophobic interaction, resulting in hydrogel formation again.

3.3.2 Redox responsiveness

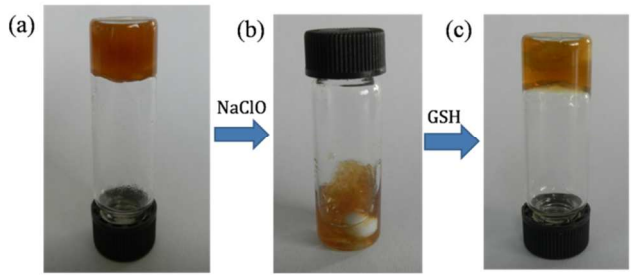

Fig. 6 Optical photos of redox responsiveness of FcCS hydrogel. (a) original hydrogel; (b) hydrogel decomposition after NaClO was added; (c) hydrogel regeneration after GSH was added.

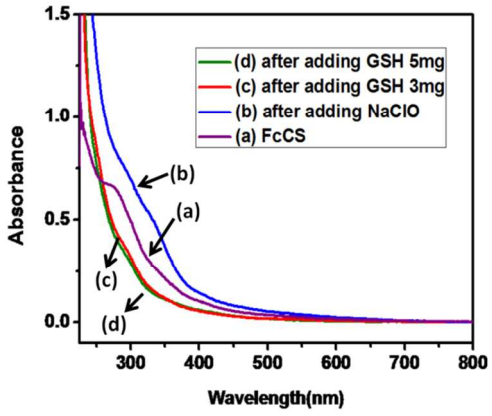

Fig. 7 Changes of UV-Vis spectra by redox: (a) The UV-Vis spectra of FcCS hydrogel; (b) after adding NaClO solution; (c) after adding GSH (3mg) to (b); (d) after adding GSH (5mg) to (b).

Fc possesses outstanding redox property, making FcCS hydrogel respond to redox stimuli sensitively. NaClO aq. was chosen as an

oxidant and glutathione (GSH) as a reductant. As shown in Fig. 6, after NaClO aq. was added, FcCS hydrogel turned into precipitate and then reverted to hydrogel again by adding GSH. The redox responsive process was tracked by ultraviolet–visible absorption spectra. As shown in Fig. 7, when NaClO was added the absorption at the wavelength between 250-400 nm increased due to the oxidation of FcCS and decreased to an even lower absorption than that of the original hydrogel upon addition of GSH which caused a reduction reaction.

After NaClO was added, Fc was oxidized to Fc cation and the π-π stacking of ferrocenyl moieties was damaged， disrupting the balance of hydrophilic and hydrophobic interaction and resulting in the destroy of the hydrogel. After GSH was added, Fc cation was reduced to Fc and the ferrocenyl moieties were re-aggregated. The equilibrium of hydrophilic and hydrophobic interaction was established again, leading to the formation of the hydrogel.

3.3.3 Ion responsiveness

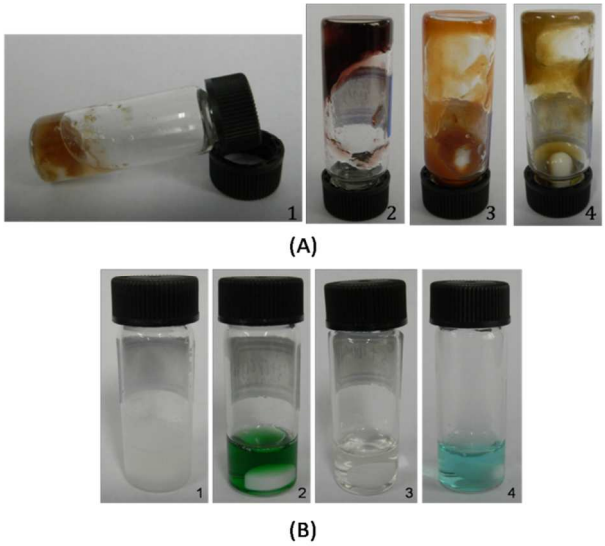

Fig. 8 Photographs of FcCS hydrogel and chitosan solution to different ion stimuli. (A) FcCS hydrogel after different ion stimuli were added: (A-1) after 14.0mg $CdSO_4$ was added; (A-2) after 31.8mg $CrCl_3$ was added; (A-3) after 18.2mg $Pb(NO_3)_2$ was added; (A-4) after 28.5mg $Cu(NO_3)_2$ was added. (B) Chitosan solution after different ion stimuli were added: (B-1) after 14.0mg $CdSO_4$ was added; (B-2) after 31.8mg $CrCl_3$ was added; (B-3) after 18.2mg $Pb(NO_3)_2$ was added; (B-4) after 28.5mg $Cu(NO_3)_2$ was added.

FcCS hydrogel demonstrates different phenomenon towards different ion stimuli. As shown in Fig. 8, FcCS hydrogel turned into precipitate, dark red , orange sol and yellow sol, respectively, after $CdSO_4$, $CrCl_3$, $Pb(NO_3)_2$ and $Cu(NO_3)_2$ were added, respectively. Chitosan solution was adopted to compare with FcCS hydrogel. However chitosan solution transformed from transparent solution to white turbid solution, green solution, and blue solution after $CdSO_4$, $CrCl_3$ and $Cu(NO_3)_2$ were added respectively under the same condition as that of FcCS hydrogel. Chitosan solution remained a transparent solution after added with $Pb(NO_3)_2$. All the above results show that FcCS hydrogel possesses responsiveness towards different ion stimuli.

It is widely accepted that Cd^{2+} is strong chelation with the amine group of chitosan. After Cd^{2+} was added to the chitosan solution, the chelation resulted in the precipitation of the chitosan chain (in Fig. 8B-1). After Cd^{2+} was added to FcCS hydrogel, Cd^{2+} was chelated by chitosan chain and the network of FcCS hydrogel was damaged and thus hydrogel turned into precipitation. As for Cr^{3+}, Pb^{2+}, and Cu^{2+}, their chelation with the amine group of chitosan was not so strong. As shown in Fig. 8B-2, B-3, and B-4, the chitosan solution did not precipitate after Cr^{3+}， Pb^{2+}, or Cu^{2+} was added, respectively. However, when Cr^{3+}， Pb^{2+}, or Cu^{2+} was added to FcCS hydrogel, the surrounding ion environment of ferrocenyl moieties was changed, and the π-π stacking of ferrocene group was damaged, resulting in the break of the cross-linking points of the hydrogel network, and thus the hydrogel turned into sol.

3.4 Controlled drug release

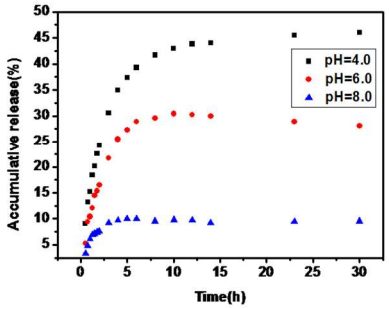

Fig. 9 Accumulative release of DOX·HCl versus time from FcCS hydrogel under different buffer solutions at pH 4.0, 6.0, and 8.0, respectively.

Different parts of the human body have different pH values. The pH response of the hydrogel suggests that it may be useful in controlled drug release. Therefore, we investigate the drug release behavior of the hydrogel under buffer solutions with different pH values (4.0, 6.0 and 8.0). As shown in Fig. 9, the FcCS hydrogel presents a good controlled release and pH responsive behavior for DOX•HCl. The hydrogels at pH 4.0, 6.0, and 8.0 released 37%, 27%, and 10% percent of loaded DOX•HCl within the first 5h, respectively. Then the hydrogels released the drug steadily after 10h, reaching an accumulative release of up to 42%, 30%, and 10%, respectively.

Conclusions

A biodegradable polymer Fc-modified chitosan FcCS was successfully synthesized in this research. FcCS easily formed a hydrogel in a 2 wt% acetic acid solution and the resulting hydrogel possessed excellent pH, redox, and ion responsiveness and outstanding self-healing property. The hydrogel also exhibited great drug controlled release behavior. All of the above properties suggest that the hydrogel has potential applications as functional and biomedical materials.

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Notes and references

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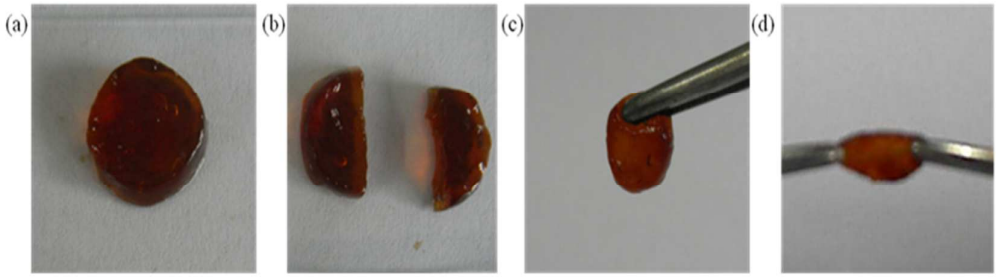
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1. V. Amendola and M. Meneghetti, *Nanoscale*, 2009, **1**, 74-88.
2. M. Guvendiren, H. D. Lu and J. A. Burdick, *Soft Matter*, 2012, **8**, 260-272.
3. M. N. Moghadam, V. Kolesov, A. Vogel, H. A. Klok and D. P. Pioletti, *Biomaterials*, 2014, **35**, 450-455.
4. H. Kuroki, I. Tokarev, D. Nykypanchuk, E. Zhulina and S. Minko, *Advanced Functional Materials*, 2013, **23**, 4390.
5. S. K. Ahn, R. M. Kasi, S. C. Kim, N. Sharma and Y. Zhou, *Soft Matter*, 2008, **4**, 1151-1157.
6. A. Sanyal, *Macromolecular Chemistry and Physics*, 2010, **211**, 1417-1425.
7. P. Schexnailder and G. Schmidt, *Colloid and Polymer Science*, 2009, **287**, 1-11.
8. C. Liu, H. Qin and P. Mather, *Journal of Materials Chemistry*, 2007, **17**, 1543-1558.
9. D. Y. Wu, S. Meure and D. Solomon, *Progress in Polymer Science*, 2008, **33**, 479-522.
10. A. Yasin, H. Li, Z. Lu, S. ur Rehman, M. Siddiq and H. Yang, *Soft Matter*, 2014, **10**, 972-977.
11. A. B. South and L. A. Lyon, *Angewandte Chemie*, 2010, **122**, 779-783.
12. J. A. Syrett, C. R. Becer and D. M. Haddleton, *Polymer Chemistry*, 2010, **1**, 978-987.
13. R. P. Wool, *Soft Matter*, 2008, **4**, 400-418.
14. M. W. Urban, *Progress in Polymer Science*, 2009, **34**, 679-687.
15. X. Yan, F. Wang, B. Zheng and F. Huang, *Chemical Society Reviews*, 2012, **41**, 6042-6065.
16. M. Burnworth, L. Tang, J. R. Kumpfer, A. J. Duncan, F. L. Beyer, G. L. Fiore, S. J. Rowan and C. Weder, *Nature*, 2011, **472**, 334-337.
17. K. Zhang, Y. Liang, D. Liu and H. Liu, *Sensors and Actuators B: Chemical*, 2012, 173, 367-376.
18. G. Mocanu, Z. Souguir, L. Picton and D. Le Cerf, *Carbohydr. Polym.*, 2012, **89**, 578-585.
19. C. W. Peak, J. J. Wilker and G. Schmidt, *Colloid and Polymer Science*, 2013, **291**, 2031-2047.
20. C. Yan and D. J. Pochan, *Chemical Society Reviews*, 2010, **39**, 3528-3540.
21. J. Yang, J. Chen, D. Pan, Y. Wan and Z. Wang, *Carbohydr. Polym.*, 2012, **92**, 719-725.
22. A. Sionkowska, *Progress in polymer science*, 2011, **36**, 1254-1276.
23. R. Jayakumar, M. Prabaharan, P. Sudheesh Kumar, S. Nair and H. Tamura, *Biotechnology advances*, 2011, **29**, 322-337.
24. K. M. Park, S. Y. Lee, Y. K. Joung, J. S. Na, M. C. Lee and K. D. Park, *Acta biomaterialia*, 2009, **5**, 1956-1965.
25. S. L. Jahren, M. F. Butler, S. Adams and R. E. Cameron, *Macromolecular Chemistry and Physics*, 2010, **211**, 644-650.
26. J. Yang, Z. Liu, Z. Yuan, Y. Chen and C. Wang, *Heart*, 2011, **97**, A12-A12.
27. C. Zheng, X. Zhang, L. Sun, Z. Zhang and C. Li, *Journal of Materials Science: Materials in Medicine*, 2013, 1-9.
28. M. Nakahata, Y. Takashima, H. Yamaguchi and A. Harada, *Nature communications*, 2011, **2**, 511.
29. Y. Chen, X. H. Pang and C. M. Dong, *Advanced Functional Materials*, 2010, **20**, 579-586.
30. D. C. Tuncaboylu, A. Argun, M. Sahin, M. Sari and O. Okay, *Polymer*, 2012, **45**, 1991-2000.
31. D. C. Tuncaboylu, M. Sari, W. Oppermann and O. Okay, *Macromolecules*, 2011, **44**, 4997-5005.
32. T. W. Chuo, T. C. Wei and Y. L. Liu, *Journal of Polymer Science Part A: Polymer Chemistry*, 2013, **4,** 2194-2205.
33. J. Elbert, M. Gallei, C. Rüttiger, A. Brunsen, H. Didzoleit, B. Stühn and M. Rehahn, *Organometallics*, 2013, **32**, 5873-5878.
34. B. V. Schmidt, M. Hetzer, H. Ritter and C. Barner-Kowollik, *Progress in Polymer Science*, 2014, **39**, 235-249.
35. X. Sui, X. Feng, M. A. Hempenius and G. J. Vancso, *Journal of Materials Chemistry B*, 2013, **1**, 1658-1672.
36. A. Phadke, C. Zhang, B. Arman, C.-C. Hsu, R. A. Mashelkar, A. K. Lele, M. J. Tauber, G. Arya and S. Varghese, *Proceedings of the National Academy of Sciences*, 2012, **109**, 4383-4388.
37. G. Jiang, C. Liu, X. Liu, Q. Chen, G. Zhang, M. Yang and F. Liu, *Polymer*, 2010, **51**, 1507-1515
38. S. Top, A. Vessieres, C. Cabestaing, I. Laios, G. Leclercq, C. Provot, G. Jaouen, *Journal of organometallic chemistry,* 2001, **637,** 500-506.
39. M. F. R. Fouda, M. M. Abd-Elzaher, R. A. Abdelsamaia, A. A. Labib, *Applied Organometallic Chemistry,* 2007, **21**, 613-625.
40. S. Mima, M. Miya, R. Iwamoto and S. Yoshikawa, *Journal of Applied Polymer Science*, 1983, **28**, 1909-1917.
41 . D. Sehgal and I. K. Vijay, *Analytical biochemistry*, 1994, **218**, 87-91.



Here, we present a novel and facile method for constructing a self-healing hydrogel with multi-responses to external stimuli via the self-assemble of biodegradable ferrocene-modified chitosan (FcCS) in an acid aqueous solution at a low concentration of 10 mg/mL. The hydrogel can re-adhere between cut surfaces and self-heal to its original shape and property after being cut, demonstrating excellent self-healing property, which is also quantitatively proved by rheological measurements. The hydrogel also presents stimuli-responses towards pH, redox, and different ion stimuli such as Cd^{2+}, Cr^{3+}, Pb^{2+}, and Cu^{2+}. In addition, the encapsulation and controlled release of doxorubicin hydrochloride (DOX•HCl) in buffer solutions with different pH values has been successfully carried out, which suggests that the accumulative release of DOX•HCl increases as the pH value decreases. All these results indicate that this hydrogel is promising for applications as functional and biomedical materials.