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pH-Dependent and Self-Healing Properties of Mussel Modified Poly(vinyl alcohol) Hydrogels in Metal-Free Environment

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3,4-Dihydroxyphenylalanine (DOPA)-based polymers are well-known to form the functional hydrogels with self-healing property by chelating metal ions. However, the DOPA-based self-healing properties are difficult to be obtained in the absence of the metal ions, as the previous reported. Thus, this study is aim to prepare the self-healable DOPA-based hydrogel in the absence of metal ions. Firstly, poly(vinyl alcohol)-DOPA (PVA-DOPA) was synthesized by modifying PVA with DOPA through esterification reaction. The composition of PVA-DOPA polymer was measured by proton nuclear magnetic resonance (^{1}H NMR). Then, the PVA-DOPA hydrogel in metal-free environment could be easily prepared by dissolving the polymer into buffer solution. Rheology analyses showed that the PVA-DOPA polymers had different dynamic modulus depending on the pH buffer solutions. The results from FTIR and UV-Vis spectra indicated that there were hydrogen bond interactions among the PVA-DOPA polymers in the low pH conditions, while both hydrogen bond and covalent interactions in the high pH condition. The PVA-DOPA hydrogel could be rapidly self-healed within 270 s, which was much quicker than the hydrogel in the presence of Fe^{3+} (about 600 s). The metal-free PVA-DOPA hydrogel had the potential application in coating and bio-medical fields.

Introduction

Self-healing gels possess the capability of partially or completely repairing the cracks at macro- or micro-scale in polymer gels and further restore their original properties, thus, becoming one of the emerging field in advanced smart materials research[1-2]. The self-healing property of the gels could be developed and regulated by both non-covalent interactions[3-5] including hydrophobic interaction, host-guest interaction, hydrogen bond, π-π stacking, polymer-nanocomposite interaction, electrostatic interaction, and covalent interactions[6-7] such as phenylboronate ester, disulfide, acylhydrazone, and Diels-Alder cycloaddition. Various self-healing gels with soft structures have been developed for the proposed applications to cell culture, tissue engineering, drug delivery, coating, and soft actuator[8-11]. For the biomedical applications, the self-healing gels are requested to have good biocompatibility and nontoxicity. Poly(vinyl alcohol) (PVA) possesses advantages of low cost, easy manufacture and good biocompatibility[12-13]. Yue Zhao group[14] discovered self-healing PVA hydrogel using the freezing/thawing method, whose self-healing ability relied on formation of hydrogen bonds between hydroxyl groups of PVA

chains by exposed at room temperature without any stimulus or healing agent. Michael W. Keller et al.[15] developed to sequester an epoxy healing agent within electrospun PVA fibers that could be successfully embedded within a composite material for use in self-healing materials. Jingbin Han group[16] fabricated hybrid films via layer-by-layer assembly of layered double hydroxide (LDH) nanoplatelets and poly(sodium styrene-4sulfonate) (PSS) followed by subsequent permeation of poly(vinyl alcohol) (PVA), which showed excellent oxygen barrier performance with humidity-triggered self-healing capability. However, in these examples, the preparation of PVA self-healing gel was complicated or PVA did not play an important role in the self-healing.

3,4-Dihydroxyphenylalanine (DOPA), a catechol derivative, is a synthetic mimic of natural amino acid[17-18]. It plays a key role in mussel foot protein adhesion in an aqueous environment. By virtue of the excellent adhesion, DOPA has been demonstrated to show strong binding affinity to diverse kinds of metal ions or metal oxides (such as Fe^{3+}, TiO_2, SiO_2) through the formation of hydrogen bonding and metal coordination[19-22]. By adjusting the pH value from acid to base, metal ions could coordinate with DOPA to form mono-, bis-, and tris-catechol/metal complexes with black color[23-24]. Interestingly, the DOPA modified hydrogel showed self-healing property in the presence of metal ions or metal oxides. However, the DOPA-based hydrogel without metals could not show the self-healing property[23]. Moreover, the obtained DOPA hydrogels were generally black color, which limited their application for a wild area. If the DOPA hydrogel in metal-free condition has the self-healing property as well as the colorless or light color, it will be more interesting and useful as advanced functional materials[25].

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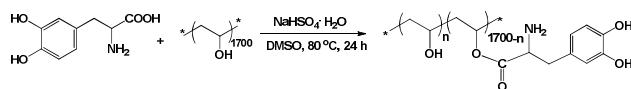
Scheme 1. Synthesis of the PVA-DOPA polymer.

Herein, we describe a strategy of the DOPA-based hydrogel with pH-dependent and self-healing properties in the absence of metal ions. PVA-DOPA polymer was firstly prepared by modifying PVA with DOPA by esterification reaction (Scheme 1). Then, hydrogel was facilely prepared by dissolving the PVA-DOPA polymer into buffer solution at room temperature. The pH dependent properties and self-healing properties of the hydrogels were investigated. For comparison, PVA-DOPA/Fe^{3+} complex hydrogel was also prepared by adding PVA-DOPA into Fe^{3+} solution in buffer solution to detect the self-healing properties. The DOPA-based hydrogels without metal ions showed the better performance.

Experimental Section

Materials

3,4-Dihydroxyphenylalanine (DOPA, 99%) was obtained from Aladdin Reagent Co., Ltd. (Shanghai, China) and used without purification. Poly(vinyl alcohol) (PVA, 1799) was purchased from Sichun Weilun Co., Ltd. Dimethyl sulfoxide (DMSO), sodium bisulfate monohydrate ($NaHSO_4 \cdot H_2O$), ethanol, acetone, sodium hydroxide (NaOH) and ferric chloride ($FeCl_3$) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China) and used as received.

Synthesis of DOPA modified PVA (PVA-DOPA) polymer

PVA (1.76 g, 40 mmol) was dissolved in DMSO (30 mL) at 100 ^{o}C. After decreasing the temperature to 80 ^{o}C, DOPA (1.97 g, 10 mmol) was added into the PVA solution with $NaHSO_4 \cdot H_2O$ (1.5 g) as catalyst. The reaction was kept at 80 ^{o}C for 24 h under N_2. The PVA-DOPA polymer was obtained by precipitation in acetone, filtration and washing with acetone for three times to remove the PDOPA homopolymer. The final white product was dried at 50 ^{o}C under vacuum for 24 h. Various PVA-DOPA polymers with different DOPA compositions were also synthesized at the same condition.

Preparation of PVA-DOPA hydrogels

The PVA-DOPA polymers were dissolved in various buffer solutions at pH 3, 7.4, 9, and 12, respectively, with the concentration of the PVA-DOPA polymer at about 30%. The PVA-DOPA hydrogels immediately formed within about 1 min after the PVA-DOPA polymer dissolved.

Preparation of PVA-DOPA/Fe^{3+} hydrogel

The PVA-DOPA polymer (200 mg) was added into 150 mM $FeCl_3 \cdot 6H_2O$ aqueous solution (0.57 mL), and the stoichiometry of DOPA to Fe^{3+} was 3:1. Then, the PVA-DOPA/Fe^{3+} complex hydrogel could be prepared after by adjusting the pH value to 9 with NaOH.

Characterization

UV-vis spectrum was recorded on a TU-1901 spectrophotometer (Beijing Purkinje General Instrument Co. Ltd). Fourier transform infrared spectroscopy (FTIR) spectrum (Nicolet iN10, Thermo Fisher

Scientific Co., Ltd.) was recorded on an attenuated total reflection (ATR) method with a FT-IR spectrometer. Proton nuclear magnetic

Table 1. Molar ratios of PVA to DOPA.

Sample	PVA(-OH) mmol	DOPA mmol	PVA:DOPA (mol%)[a]	PVA:DOPA (mol%)[b]	PVA:DOPA (mol%)[c]
PVA-DOPA3	12	3	100: 25	100: 8	100: 11
PVA-DOPA6	12	6	100: 50	100: 30	100: 28
PVA-DOPA8	12	8	100: 67	100: 57	100: 51
PVA-DOPA10	12	10	100: 83	100: 77	100: 70
PVA-DOPA12	12	12	100:100	100: 82	100: 80

[a] Feed molar ratio. [b] Molar ratio calculated from ^{1}H NMR spectrum. [c] Molar ratio calculated from UV-vis spectrum.

resonance (^{1}H NMR) spectrum was recorded at 400 MHz on a Bruker AVANCE Ⅲ 400 NMR spectrometer with a sample spinning rate of 5 kHz at 25 ^{o}C in D_2O. Rheological properties of various hydrogels were monitored using a rotating rheometer (TA Instruments, DHR-2) at 25 ^{o}C. Storage moduli (G') and loss moduli (G'') were collected using a parallel plate (25 mm) with frequency sweep at 25 ^{o}C.

Results and Discussion

Synthesis of PVA-DOPA polymer

The PVA-DOPA polymer was prepared by esterification reaction between hydroxyl groups in PVA and carboxyl groups in DOPA using $NaHSO_4 \cdot H_2O$ as the catalyst. A serial of PVA-DOPA polymers were obtained by changing the molar ratio of DOPA to PVA (Table 1). ^{1}H NMR spectra of the PVA and DOPA mixture and the PVA-DOPA polymer (PVA-DOPA12 was as an example) are shown in Fig. 1. Chemical shifts at 1.5 and 3.2 ppm assigned to the methene and methine groups in the PVA chains (Fig. 1a), respectively. Peaks at 4.1, 2.9 and 6.56~6.90 ppm belonged to the methine, methene and benzene groups in DOPA. After modifying PVA by DOPA, the chemical shift of the methine groups in PVA shifted to 3.8 ppm (Fig. 1b), suggesting the successful synthesis of the PVA-DOPA polymer. By calculation of the peak areas of the methine groups before and after reacted with DOPA (marked as b and b' in Fig. 1b), the compositions of DOPA were obtained, as listed in Table 1. Moreover, FTIR and UV-vis results also confirmed the chemical structure of PVA-DOPA (Fig. S1 and S2). Comparing to the specific absorbance of DOPA at 280 nm in UV-vis spectra, compositions of DOPA could be also calculated, and are also listed in Table 1, which were well consistent with the results from ^{1}H NMR spectra.

Rheological behavior of PVA-DOPA hydrogels

PVA-DOPA polymer contained many functional groups such as hydroxyl, amine and ester groups. By dissolving the PVA-DOPA polymer in buffer solutions at pH 9 at room temperature (the concentration of PVA-DOPA3 was 30 %), the PVA-DOPA hydrogel could be formed with a white color (Inset figure in Fig. 2a), due to the hydrogen bond interactions among the hydroxyl, catechol and amine groups. However, the PVA homopolymer without DOPA could not form the hydrogel by this method. Since rheological measurement of the hydrogel is useful for characterization of mechanical property[26], the rheological behavior of the PVA-DOPA hydrogel was evaluated detail in this study. Linear viscoelastic behavior, constant strain/stress relationship and dynamic modulus including storage moduli (G') and loss moduli (G'') of the PVA-DOPA
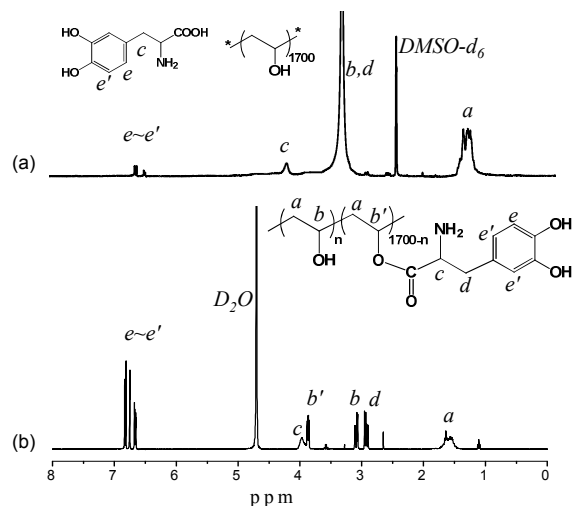
Fig. 1 ^{1}H NMR spectra of the mixture of PVA and DOPA in DMSO-d_6 (a) and PVA-DOPA12 in D_2O (b).

hydrogel (PVA-DOPA3 as an example) were observed in a strain range with 6.28 rad/s of the constant frequency at 25 °C, as shown in Fig. 2a. When the strain was ranged from 0.3% to 16%, PVA-DOPA3 showed the linear viscoelastic behavior. Then, the frequency sweep experiment of PVA-DOPA3 was performed from low to high frequency (0.1~100 rad/s) by fixing the strain at 1%, and the results of G' and G'' are shown in Fig. 2b. The obtained G' was around 10000 Pa and G'' was 2800 Pa, which was higher than that of the reported DOPA-based gels[23-24]. G' is a measure of elastic energy stored in the network, and thus, a higher G' value means a stronger elastic network. Accordingly, PVA-DOPA3 hydrogel formed relatively high elastic network. Moreover, both G' and G'' displayed a relatively weak frequency dependency, indicating that a broad range of relaxation times was involved in stress relaxation of the associated network.

For the PVA-DOPA polymers with various compositions of DOPA, the hydrogels were also formed by dissolving the polymers into buffer solution at pH 9, except of the PVA-DOPA12 polymer. The linear viscoelastic ranges were 0.4~3% for PVA-DOPA6, 0.3~3% for PVA-DOPA8, and 0.5~2.5% for PVA-DOPA10. G' of the formed PVA-DOPA hydrogel was measured by the frequency sweep experiments at 1% strain, as shown in Fig. 3. From the results, with increasing composition of DOPA, G' decreased strongly. The storage moduli is proposed to be directly related to the crosslinking density of the network. Thus, the results indicated that the PVA-DOPA hydrogel with high DOPA composition resulted in low network. For the PVA-DOPA6, the DOPA composition was about 30 mol% (in Table 1). In pH 9 buffer solution, DOPA molecules easily self-react each other[27-28]. The higher DOPA composition in PVA chains might induce the intra-molecular interactions between DOPA molecules, leading the less inter-molecular interactions in chains and low storage modulus. Further increasing the DOPA composition to 50 mol% and 70 mol% (for PVA-DOPA8 and PVA-DOPA10), G' decreased almost to 100 Pa. For PVA-DOPA12 with 80% of the DOPA composition, the intra-

molecular interactions between DOPA molecules were too strong and the gel could not form anymore.

For comparison, the hydrogel of the PVA-DOPA polymer and Fe ion was also prepared at pH 9. After adding Fe^{3+} into the PVA-DOPA polymer, a dark hydrogel was formed (Fig. S3a), due to DOPA could strongly bind to Fe ions to form crosslinking-like structure. Resonance Raman spectroscopy illustrated that the chelated interaction between PVA-DOPA polymer and Fe ions was occurred to form the complex hydrogel (Fig. S3b). The G' of the PVA-DOPA3/Fe^{3+} complex hydrogel was detected to be around 21000 Pa at 6.28 rad/s (Fig. S3c), which was higher than the PVA-DOPA3 (~10000 Pa). There were existing hydrogen bonds and coordination (between catechol and Fe) interactions in complex hydrogels, resulting in the more crosslinking bonds. Therefore, the dynamic modulus of the complex hydrogel was higher than that of the PVA-DOPA hydrogel.
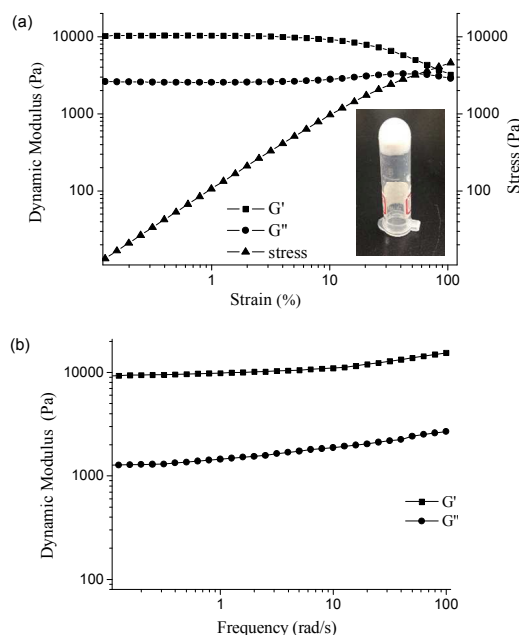

Fig. 2 (a) Storage moduli (G'), loss moduli (G'') and stress of the PVA-DOPA3 hydrogel prepared in pH 9 buffer solution, from strain amplitude sweep (25 °C, frequency: 6.28 rad/s). The inset image for the formed PVA-DOPA hydrogel in pH 9. (b) Frequency sweep of the PVA-DOPA3 hydrogel in pH 9 (25 °C, strain = 1%).
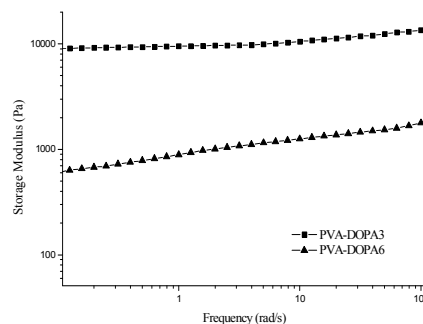

Fig. 3 G' of the PVA-DOPA hydrogels with various DOPA compositions (25 °C, strain = 1%).
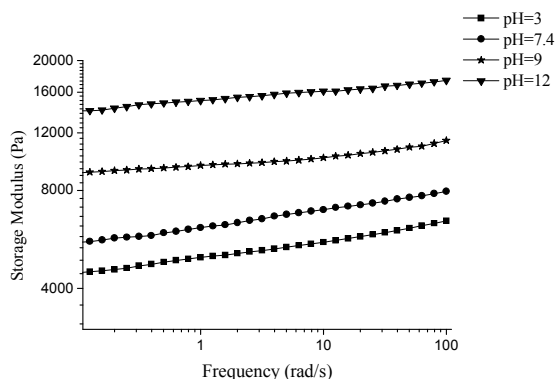
Fig. 4 Effect of pH on rheological behavior of the PVA-DOPA3 hydrogel.

pH dependent property of PVA-DOPA hydrogels

By dissolving PVA-DOPA polymers in different buffer solutions, the formed hydrogels exhibited different rheological properties. The PVA-DOPA3 hydrogel was used as an example to measure the frequency sweep at 6.28 rad/s, showing in Fig. 4. In acidic condition (pH 3), G' was lowest, around 5500 Pa. G' increased to 6800 Pa for the hydrogel formed in neutral condition at pH 7.4. Adjusting pH to 9 and 12, G' further increased to 10000 Pa and 16000 Pa, respectively. Part catechol groups in DOPA were reported to oxidize easily and form o-quinonyl groups in basic solutions, and then DOPA could self-polymerize between quinonyl and amine groups by Michael addition to form crosslinked structures[27-28]. Thus, both the hydroxyl and quninonyl groups existed in the DOPA molecules, i.e. both hydrogen interaction and Michael addition occurred in the PVA-DOPA hydrogel. On the other hand, the catechol groups could keep stable in acid solution and could form hydrogen bonds with other functional groups. Accordingly, there is only hydrogen bond interaction in the PVA-DOPA hydrogel in the acid condition. The covalent crosslinking bond is stronger than the non-covalent crosslinking bond such as hydrogen bond, resulting in the dynamic modulus of the PVA-DOPA hydrogel in pH 12 significantly higher than that in pH 3 and 7.4.

Since FTIR spectrum on the change of stretching of amine groups (ν_{N-H}) can determine the intermolecular hydrogen bond interactions between amine and hydroxyl groups[29], FTIR spectrum was measured to discuss the mechanism of the pH dependent property of the PVA-DOPA hydrogel. As shown in Fig. 5a, peak of the free amine (II) groups for the PVA-DOPA polymer was at 3230 and 3102 cm^{-1}. The peak was clearly red shifted to around 3210 and 3087 cm^{-1} for the PVA-DOPA gel formed in pH 3 and 9 (Fig. 5b-5c). These prominent red-shifts clearly indicated that the hydrogen bond interactions between hydroxyl groups and amine groups via various combinations H and N or O atoms. For the PVA-DOPA gel formed in pH 12, the amine peak shifted to 3146 and 3023 cm^{-1} (Fig. 5d). Moreover, there was one shoulder peak at 3105 cm^{-1}, which assigned to the amine (I) groups by the formation of the cycloaddition of DOPA in basic condition. These results indicated the formation of the hydrogen bond and the hydrogen and covalent bond interactions in the PVA-DOPA chains depending on the pH values.

To further confirm the structure of DOPA after self-polymerization, UV-vis spectrometer was also employed to detect the specific adsorption of the PVA-DOPA polymer in pH 7.4 and 12. From UV-vis spectra (Fig. 5e), a peak at 280 nm that assigned to the catechol groups appeared in both neutral and basic solutions. By dissolving PVA-DOPA polymer in pH 12, a shoulder peak at about 315 nm appeared, suggesting the formation of dehydro-dopamine[30]. A new peak at 410 nm belonged to o-quinonyl groups was also observed. These adsorption changes suggested that DOPA was oxidized and self-polymerized to form the quinonyl and crosslinked structure.

According to the above results, we proposed the possible interactions and structures in the formed PVA-DOPA hydrogels, as shown in Fig. 5f. The PVA-DOPA hydrogel was crosslinked via hydrogen bond interactions in the low pH condition. In weak basic solution, most of hydrogen bond interactions and less Michael addition existed the PVA-DOPA hydrogel, whereas less hydrogen bond interactions and most of Michael addition existed the PVA-DOPA gel in strong basic condition (Fig. 5f).
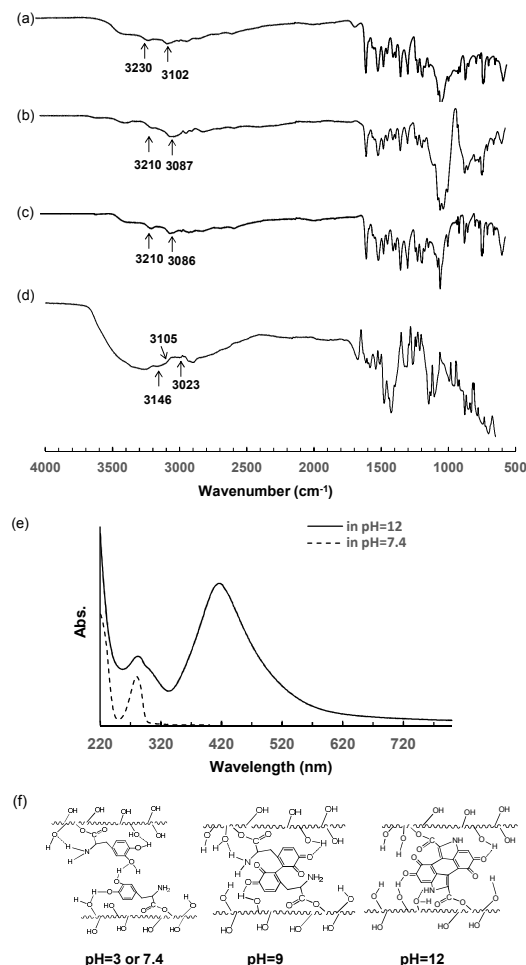

Fig. 5 FTIR spectra of the PVA-DOPA3 polymer (a) and PVA-DOPA3 hydrogel in pH 3 (b), pH 9 (c) and pH 12 (d). (e) UV-vis spectra of the PVA-DOPA polymer in pH 7.4 and pH 12. (f) Scheme of the interactions among the PVA-DOPA polymer chains in different pH buffer solutions.

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The PVA-DOPA3/Fe^{3+} complex hydrogels also had the pH responsive property, as reported in several researches[22,23].

Self-healing property of PVA-DOPA hydrogels

The PVA-DOPA hydrogel was cut into two pieces and then brought back together at the fracture surfaces. The two pieces of fractured hydrogel healed autonomously and rapidly by contacting the fractured surfaces together (Fig. 6a). Moreover, there was no obvious border to be observed between the connected gels after healing. The self-healing property was also confirmed by the rheological measurement. Fig. 6b shows the time-dependent dynamic modulus of the PVA-DOPA3 hydrogel. The time sweep of the PVA-DOPA3 hydrogel was performed after cutting the gel into 9 pieces with 6.28 rad/s of the constant frequency at 25 ^{o}C. G' of the fractured hydrogel firstly decreased from 10000 Pa to 6500 Pa, whereas G'' increased to 2900 Pa, due to the crosslinked bond was broken. With the healing time, G' slowly increased and returned to the original value at around 10000 Pa within 270 s. While G'' correspondingly decreased and reached balance. These results indicated that the fractured hydrogel was self-healed and returned to the original crosslinking structure, i.e. the PVA-DOPA hydrogel had self-healing property.
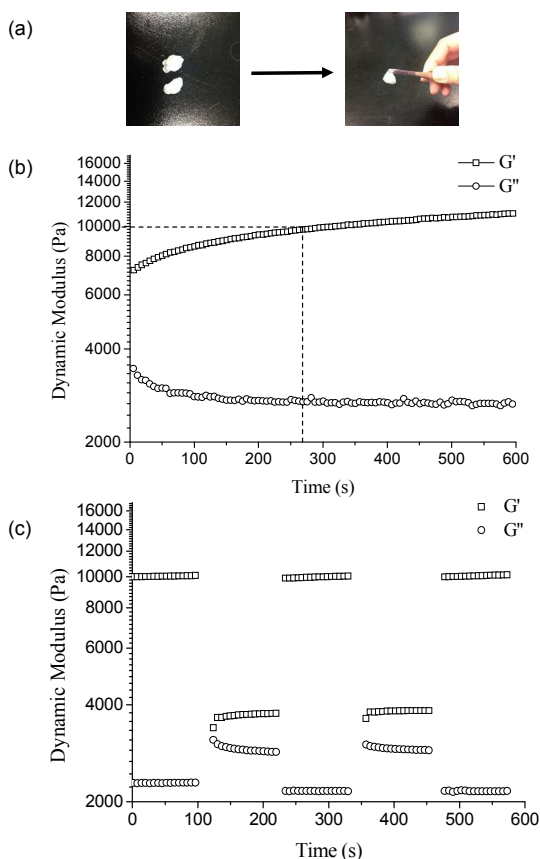
The changes of the dynamic modulus G' and G'' with the strains were also investigated with 6.28 rad/s of the constant frequency at 25 ^{o}C, as shown in Fig. 6c. When the hydrogel suffered high strain at 100%, G' significantly decreased from 10000 Pa to 3700 Pa and G'' increased slightly from 2200 Pa to 3000 Pa, suggesting the broken of the PVA-DOPA structure. Subsequently, changing the strain to 1 %, G' and G'' rapidly returned to the original value and kept stable. Accordingly, the structure of the hydrogel was recovered and the hydrogel had the rapidly self-healing property. Moreover, by re-increasing the strain to 100%, G' decreased and G'' increased again. This self-healing property could be cycled several times. The mechanism of self-healing properties is mainly attributable to the dynamically reversible hydrogen bonds between hydroxyl and amine groups in PVA and catechol groups. Upon return of fractured interfaces together, hydroxyl groups, catechol and amine functional groups could interact with each other at the interface to reform the network.

The PVA-DOPA hydrogels in different pH solutions also showed the self-healing properties. However, the self-healing efficiency of the PVA-DOPA hydrogel in pH 12 was 92% (Fig. S4b), which was lower than other PVA-DOPA hydrogels in pH 3 and 9 (around 100%, Fig. 4a and Fig. S4a) after healed for the second time. This lower self
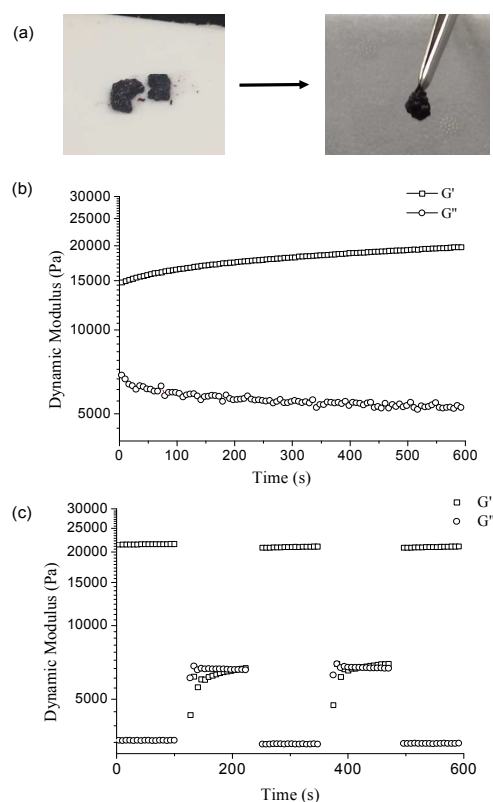

Fig. 6 (a) Images of the self-healing property of the PVA-DOPA hydrogel. (b) G' and G'' of the PVA-DOPA3 hydrogel in pH 9 versus time during the self-healing process (frequency: 6.28 rad/s, strain = 1%). (c) Storage moduli G' and loss moduli G'' of the PVA-DOPA3 hydrogel in pH 9 from continuous strain sweep with alternate small oscillation force at 1% of strain and at 100% of strain.

Fig. 7. (a) Images of the self-healing property of the PVA-DOPA/Fe^{3+} complex hydrogel. (b) G' and G'' of the PVA-DOPA3/Fe^{3+} hydrogel in pH 9 versus time during the self-healing process (frequency: 6.28 rad/s, strain = 1%). (c) Storage moduli G' and loss moduli G'' of the PVA-DOPA3/Fe^{3+} hydrogel in pH 9 from continuous strain sweep with alternate small oscillation force at 1% of strain and at 100% of strain.

healing property was possibly due to the existing less dynamically hydrogen bond interactions in the PVA-DOPA hydrogel in pH 12, and the covalent bond interactions could not be healed.

For the PVA-DOPA/Fe^{3+} complex hydrogels, they also showed the self-healing properties (Fig. 7a). The self-healing property of the PVA-DOPA3/Fe^{3+} complex hydrogel was also confirmed by the rheological measurement with 6.28 rad/s of the constant frequency at 25 ^{o}C. After cutting the gel, G' of the PVA-DOPA3/Fe^{3+} hydrogel decreased to 15000 Pa, and the G'' increased to 7000 Pa (Fig. 7b), due to the crosslinked bond was broken. During healing, G' increased and finally returned to 21000 Pa, whereas G'' correspondingly decreased, indicating the hydrogel self-healed to the original structure. The self-healing time of the PVA-DOPA/Fe^{3+} complex hydrogel was around 600 s, much longer than the PVA-DOPA hydrogels. The coordination interactions in the PVA-DOPA/Fe^{3+} hydrogel might increase the distance of the polymer chains, and then reduce the hydrogen interaction between PVA and DOPA. Thus, it needs longer time to recover. By changing the strain from 1% to 100% during the rheological measurement with 6.28 rad/s of the constant frequency at 25 ^{o}C, the dynamic modulus G' and G'' correspondingly to vary (Fig. 7c), which was as same as the PVA-DOPA hydrogel. By the fracture gels combined together, the catechol groups and Fe ions should be capable of complexing, as well as the healing of the hydrogen bond interactions. The reversible hydrogen bonds and coordination (between catechol and Fe) interactions played the role of the self-healing property.

According to the results, the PVA-DOPA hydrogel showed more rapid self-healing time and might have wider applications, as compared to the PVA-DOPA/Fe^{3+} complex hydrogel.

Conclusions

We have designed the DOPA-based hydrogel with self-healing property in the absence of metal ions. By changing the pH conditions from acid to base, the hydrogels showed low to high dynamic modulus, which were induced by the oxidation and self-polymerization of DOPA in basic solution. The hydrogels without Fe ions had the pH dependent and self-healing properties, and showed more rapidly self-healing property than the hydrogel with Fe ions. The metal-free PVA-DOPA hydrogel had the potential applications in coating and bio-medical fields.

Acknowledgements

Notes and references

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Graphic Abstract

pH-Dependent and Self-Healing Properties of Mussel Modified Poly(vinyl alcohol) Hydrogels in Metal-Free Environment

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We describe a strategy of the DOPA-based PVA hydrogel with pH-dependent and rapidly self-healing properties in the absence of metal ions by a simple way. The PVA-DOPA hydrogel could be rapidly self-healed within 270 s, which was much quicker than the hydrogel in the presence of metal.

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