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Chiral, pH-sensitive polyacrylamide hydrogels: Preparation and enantio-differentiating release ability

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ABSTRACT

Both pH-sensitive hydrogels and chiral hydrogels have evoked large interest in recent years. In the study, we designed and prepared a novel type of hydrogels simultaneously showing pH-sensitivity and chirality. Such hydrogels were prepared by free radical co-polymerization using *N*-acryloyl-L-alanine as chiral hydrophilic monomer and octadecyl acrylate as hydrophobic monomer, with $K_2S_2O_8$ as initiator and *N*,*N*′-methylenebisacrylamide as chemical cross-linking agent. The obtained hydrogels exhibited remarkable pH-sensitive swelling ability in water. The optical activity of the hydrogels was characterized using circular dichroism spectroscopy. More interestingly, the hydrogels showed enantio-differentiating release ability towards proline enantiomers, in which D-proline was preferentially released. The hydrogels also demonstrated remarkable enantio-differentiating release ability toward chiral drug ibuprofen.

1. Introduction

As one unique type of smart hydrogels, chiral hydrogels have aroused increasing attention [1]. New chiral hydrogels have been continuously established, for instance, chiral nanocomposite hydrogels [2], molecular imprinting hydrogels [3], and crystal structure hydrogels [4]. Among the reported chiral hydrogels, a majority of them were originated in amino acids [5–7], cholesterol [8], peptide [9], saccharides [10], and other chiral derivatives [11]. The potential applications of chiral hydrogels include chiral adsorption [12], chiral release [13,14], chiral catalysis [15], etc.

Among stimulus-sensitive hydrogels, pH-responsible hydrogels, derived from both natural and synthetic polymers, have been investigated intensively [16,17]. This unique class of hydrogels may find significant applications. For example, Liu et al. [18] reported that pH sensitive hydrogels could be used to release drugs towards different pH environment due to the hydrogels' varied swelling ability, namely controllable release of the drugs to target position. Additionally, pH sensitive hydrogels can also be used in gene releasing [19]. Even though a large number of pH sensitive hydrogels have been investigated, hydrogels simultaneously showing optical activity and pH sensitivity are still limited.

We prepared chiral polymer microspheres [20,21] and chiral polymer amphiphilic networks [22] in our previous studies, and all these materials with optical activity showed chiral recognition and enantioselective release ability. Based on these studies, we in the present study designed and prepared a new kind of chiral hydrogels by copolymerization of chiral hydrophilic monomer *N*-acryloyl-L-alanine (NAA) and hydrophobic monomer octadecyl acrylate (C18), with *N*,*N*′-methylenebisacrylamide (BIS) as crosslinking agent. The strategy is schematically presented in Scheme 1. Herein, PNAA (the polymer from monomer NAA) chains containing chiral structures and carboxyl groups, could enable the hydrogels to show both optical activity and pH sensitivity. Meanwhile, the hydrophobic monomer (C18) could form hydrophobic regions with the aid of emulsifier sodium dodecyl sulfate (SDS). After polymerization, the hydrophobic polymer chains of C18 tend to aggregate to form physical crosslinking regions [23,24] inside the hydrogels. The chemical crosslinks formed by BIS and the physical crosslinking regions of poly(C18) are beneficial to adjust the water swelling ratio of the hydrogels. Our preceding study [25] clearly showed that it is critical to control the swelling degree of the hydrogels to achieve enantioselective release behavior. Accordingly, C18 was utilized to construct the hydrogels in the present study.

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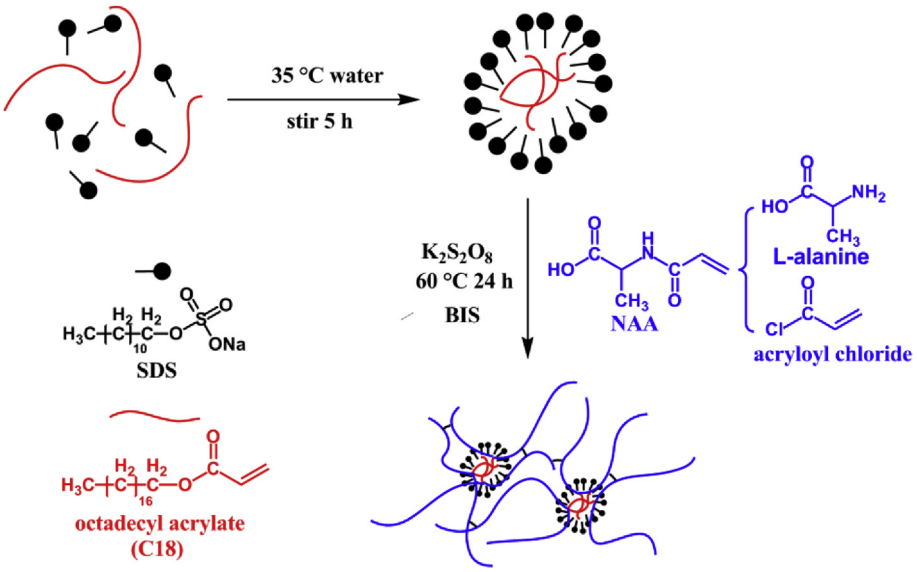

Scheme 1. Schematic strategy for preparing the hydrogels.

2. Experimental section

2.1. Materials

L-Alanine and acryloyl chloride were obtained from Aladdin. Octadecyl acrylate (C18) was bought from Sigma–Aldrich. *N*,*N*′-Methylenebisacrylamide (BIS), potassium persulfate ($K_2S_2O_8$), sodium dodecyl sulfate (SDS), L- and D-proline, and racemic ibuprofen (IBU) were purchased from Alfa Aesar and used without further purification. All the solvents were purified by standard methods.

2.2. Measurements

FT-IR spectra of monomer NAA and the obtained hydrogels were recorded using a TENSOR 27 spectrometer (KBr tablet). Circular dichroism (CD) and UV–vis absorption spectra were recorded on a Jasco 810 spectropolarimeter, referring to our earlier study [25]. A small amount of dry hydrogel (approx. 0.05 g) was swollen in deionized water, and then the swollen hydrogel was clamped between two quartz plates at room temperature, and it was applied to measure UV–vis absorption and CD spectra. Optical rotation was measured on a JASCO P-1020 digital polarimeter at room temperature.

2.3. Synthesis of monomer NAA

The method for preparing monomer NAA was reported in detail in our earlier study [22]. A typical preparative process is briefly stated below. Sodium hydroxide (5 g, 125 mmol) was dissolved in water (25 mL) in a flask under stirring. L-Alanine (5.568 g, 62.5 mmol) was added in the flask. After complete dissolution of L-alanine, acryloyl chloride (5 mL, 62.5 mmol) was dropwise added in the solution at 0 °C. The solution was continuously stirred for two more hours. Then the reaction solution was heated up to room temperature and further stirred for another 1 h. After the reaction completed, the pH of the mixture was adjusted to 2 with 2 mol/L HCl aqueous solution with stirring for 20 min at room temperature. The precipitate was extracted for five times with ethyl acetate to obtain the coarse product. The product was further purified by recrystallization from ethanol and then drying under vacuum.

2.4. Preparation of hydrogels

A schematic for preparing the hydrogels is shown in Scheme 1. The hydrogels were prepared by free radical co-polymerization of NAA, C18 and BIS. The formulae are summarized in Table 1. The major procedure is described briefly as follows. SDS and C18 were added in 0.5 mol/L NaCl aqueous solution, and the solution was stirred for 5 h at 35 °C to form the emulsion [26]. Then NAA, NaOH, and BIS were dissolved in the emulsion under stirring, and it was degassed for 20 min by nitrogen bubbling. $K_2S_2O_8$ was dissolved in aqueous solution (1 mL) and added in the above solution under nitrogen atmosphere. Polymerization lasted for 24 h at 60 °C. After the reaction, the product was taken out from the reactor and soaked in water for 3 days to remove the unreacted monomers and initiator, if any. The water was changed every day. Then, the hydrogel was immersed in aqueous solution (pH = 2) for one day to shrink the swollen hydrogel, during which the –COONa groups in the hydrogel were transferred to –COOH groups. The hydrogel after acidification treatment was soaked in ethanol for one day and then dried at 50 °C under vacuum.

2.5. Swelling ratio of hydrogels

Referring to the method introduced in previous study [27], the swelling ratio of the hydrogels was measured at room temperature. Approximately 0.1 g dry hydrogel was immersed in deionized water for a certain time. The hydrogel was carefully taken out, and the excess water on the surface of the hydrogel was wiped with filter paper. Then, the hydrogel was weighed and subsequently immersed in deionized water again. This procedure was repeated for several times until the weight of the hydrogel did not change. The swelling ratio was determined by calculating the ratio of the weight of swollen hydrogel to the weight of dry hydrogel. The equation of swelling ratio was: $Q = W_s/W_d$, where Q is the swelling ratio, W_s is the weight of swollen hydrogel, and W_d is the weight of the dry hydrogel. The measurement was repeated for 5 times for

Table 1
Parameters for preparing hydrogels.

Hydrogels	NAA (mmol)	C18 (mmol)	BIS (mmol)	$K_2S_2O_8$ (mmol)	NAA/C18/BIS (in mmol)
HG-0[a]	4	0.6	0	0.04	10/1.5/0
HG-1	4	0.2	0.2	0.04	10/0.5/0.5
HG-2	4	0.4	0.2	0.04	10/1/0.5
HG-3	4	0.6	0.2	0.04	10/1.5/0.5

[a] No hydrogel was formed.

each sample and the average swelling ratio was accordingly obtained.

2.6. pH responsivity of hydrogels

The swelling behaviors of the hydrogels at different pH were studied as follows. A piece of a dry hydrogel was immersed in deionized water with pH 12 for 2 h. The weight of the swollen hydrogel was recorded and the sample was immersed in deionized water with pH 7 for another 2 h. The weight of the swollen hydrogel was recorded again. Then, the sample was immersed alternately in deionized water with pH 2 and pH 12 and weighed. In this process, the pH of the solution was adjusted with NaOH and HCl aqueous solutions. The measurement was repeated for 3 times for each sample and the average value was accordingly obtained.

2.7. Enantio-differentiating release of proline

Referring to our early studies [28,29], enantio-differentiating release of proline in deionized water was conducted in two different modes: simultaneous release and separate release. In the first mode, a certain amount of racemic proline enantiomers was added in the polymerization system before adding initiator to prepare the hydrogel containing racemic proline enantiomers. The thus-obtained hydrogel was immersed in water (20 ml) and the optical rotation of the outer solution was measured by a polarimeter. The concentration of the outer solution at different intervals was determined based on optical rotations. The difference between proline enantiomers released out of hydrogel was determined by calculating the ratio of the weight of the difference released to the weight of the enantiomers initially added. In the second one, release of L- or D-proline was performed in the same way, and the only difference is that L- or D-proline instead of racemic proline enantiomers was added in the reaction system to obtain the hydrogel containing L-proline or D-proline. All the release tests were repeated for three times, and the corresponding average value was determined.

2.8. Enantio-differentiating release of racemic ibuprofen

Ibuprofen (IBU), as a drug model, was also chosen to investigate enantio-differentiating release of the chiral hydrogels in phosphate buffered saline (PBS, pH = 7.4). The PBS solution was prepared by mixing 250 ml of 0.1 M KH_2PO_4 and 195.5 ml of 0.1 M NaOH aqueous solutions. The hydrogel with racemic IBU was prepared by adding 0.05 g racemic IBU dissolved in NaOH aqueous solution into the polymerization system. The enantio-differentiating release of racemic IBU in PBS was measured by polarimeter, and the total release amount of racemic IBU was determined using UV–vis spectroscopy. UV–vis spectra were measured as follows [30]. Firstly, UV–vis absorption of the IBU solution in PBS (0.01/20 g/ml) was measured as the reference. The IBU-loaded hydrogel (0.7066 g) was placed in 20 ml PBS, and the UV–vis absorption of the outer solution was measured at 1 h interval from 1 h to 8 h. Herein, the UV–vis absorption at λ = 265 nm (the maximum absorption of ibuprofen) was adopted to calculate the released IBU amount [31,32]. The release tests were repeated for three times to obtain average values.

3. Results and discussion

3.1. Preparation of the hydrogels

The synthesis of chiral, pH-responsive hydrogels with adjustable cross-linking density was the primary purpose in the present study, and it was also expected that the prepared hydrogels could show enantio-differentiating release capability for chiral drugs. The major preparation procedure is illustratively shown in Scheme 1. The hydrogel networks were formed by free radical copolymerization of hydrophilic monomer NAA and hydrophobic monomer C18 emulsified by SDS, by using $K_2S_2O_8$ as initiator and BIS as chemical cross-linking agent. In our earlier study, we noticed that the swelling ratio of the hydrogels constructed by PNAA and hydroxypropyl-®-cyclodextrin (HP-β-CD) was too large, which led to fragile hydrogels after swelling [25]. In the hydrogels prepared in the present study, the hydrophobic regions formed by C18 provided physical cross-linking effects, and correspondingly led to the decreased swelling ratio of the hydrogel. PNAA chains provided chirality and pH-responsivity, since NAA derived from L-alanine and acryloyl chloride.

The strategy illustrated in Scheme 1 proved to be highly effective, providing hydrogels simultaneously showing pH responsibility and optical activity. The hydrogels also demonstrated the expected enantio-differentiating release ability. All these investigations will be stated below.

Four hydrogels were designed mainly by changing the amount of the hydrophobic monomer C18, by which to adjust the physical crosslink regions in the obtained hydrogels. Table 1 shows the specific formulae for preparing the hydrogels. Among the four samples, HG-0 was prepared in the absence of BIS, and only formed a sticky liquid rather than bulk hydrogel. It demonstrates that physical crosslinking itself was too weak to provide hydrogels. Namely, chemical cross-linking is still required to form hydrogels. HG-1, HG-2 and HG-3 all formed hydrogels in quantitative due to a reasonable combination of physical crosslinking regions derived from C18 and chemical crosslinking formed by BIS.

The FT-IR spectrum of HG-1 is taken as the representative and illustrated in Fig. 1. The spectra of NAA and C18 are also presented for a clear comparison. Compared to the spectra of the two control samples, the characteristic bands of C18 at 2934, 2885 cm^{-1} (C–H), 1731 cm^{-1} (–C=O) and the characteristic bands of NAA at 1652, 1559 (amide, –C(O)N–) and 1731 cm^{-1} (acid, –C=O) can be found clearly in the spectrum of HG-1, demonstrating the successful formation of the hydrogel. In addition, the peak around 1600 cm^{-1} (C=C in both NAA and C18) vanished in HG-1, indicating that no monomer remained in the hydrogel.

3.2. Swelling ratios of hydrogels

The swelling behavior of hydrogels is closely correlated with their cross-linking density. Fig. 2 shows the swelling ratios of the three hydrogels (HG-1, HG-2, and HG-3) as a function of swelling

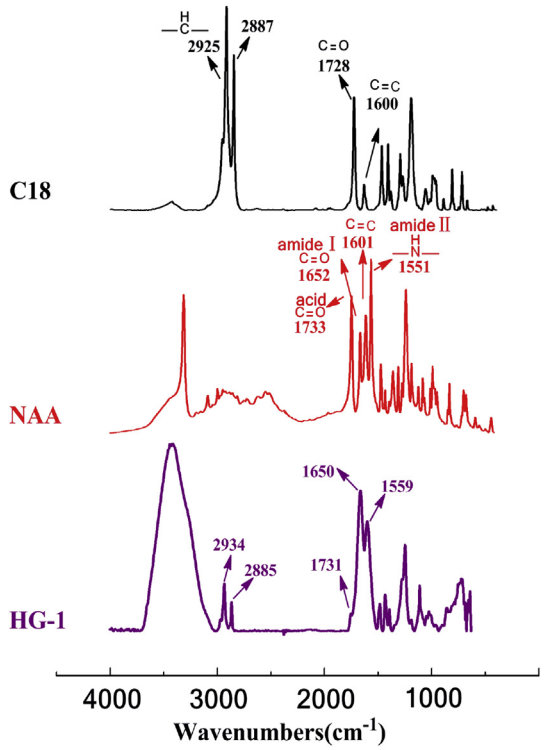

Fig. 1. FT-IR spectra of HG-1, NAA and C18 (KBr tablet).

time in deionized water. All the hydrogels exhibited the same trend, namely, the swelling ratio reached equilibrium within 2 h in water and then changed little. A comparison among the three hydrogels shows that their equilibrium swelling ratios decreased with increasing the content of C18, which gave rise to increased physical cross-linking regions inside the hydrogels.

3.3. pH responsivity of hydrogels

The pH-responsive behavior of the hydrogels was highly expected due to the existence of carboxylic acid groups in PNAA. In the present study, the swelling ratios of the three hydrogels in water with different pH are presented in Fig. 3. A cyclic swelling behavior of HG-1 at different pH was also investigated and the corresponding photographs are shown in Fig. 4.

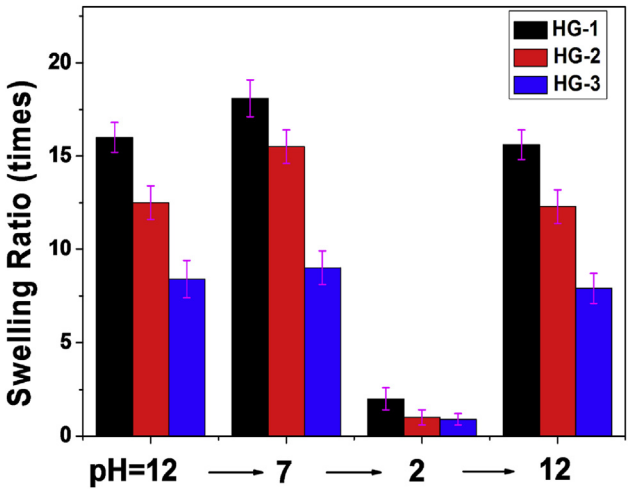

Fig. 3. Swelling ratio of hydrogels in water as a function of pH.

Figs. 3 and 4 show that pH has a large effect on the swelling ratio of the hydrogels. When pH was 7 and 12, the swelling ratios of the hydrogels were much larger (>15 times). However, the swelling ratios were only approximately 2–3 times when pH was adjusted to 2. The difference of the swelling ratios between acidic and basic environment is remarkable. This phenomenon is attributed to PNAA, which is soluble in alkaline water (pH > 10), but insoluble in acidic water. In alkaline environment, the carboxylic acid groups in PNAA transformed to salt by acid–base reaction, so the swelling ratio of the hydrogels increased. In the cycle experiment, when pH was adjusted from 12 to 7, the swelling ratio of the hydrogels continued to increase. It can be explained as follows. At pH 12, a large amount of Na^+ entered the hydrogel; when the hydrogel was placed in aqueous water with pH 7, the ions concentration difference between inside and outside the hydrogel resulted in more water diffusing inside the hydrogels. Fig. 4 presents a direct observation on the swelling of the hydrogel (HG-1) as a function of pH. The remarkable pH sensitivity enables the hydrogels to be potential candidates for developing novel chiral carriers for drugs, chiral smart biomaterials, among other significant applications.

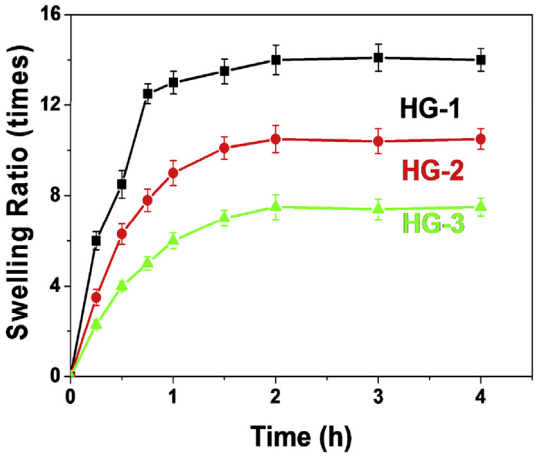

Fig. 2. Swelling ratios of the hydrogels with different content of C18 as a function of swelling time in deionized water.

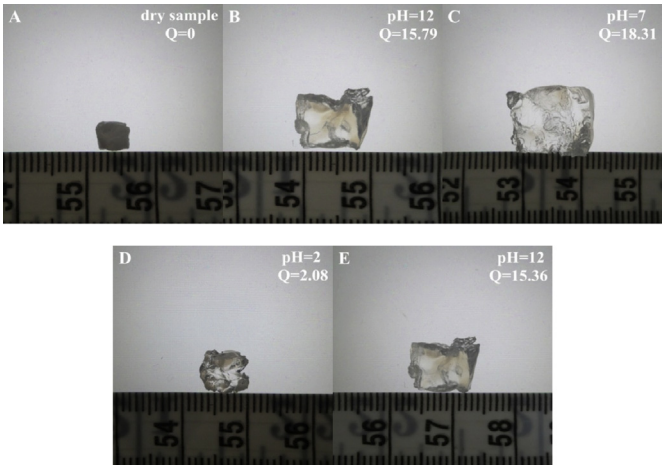

Fig. 4. Photographs of HG-1with cyclic changing pH from 12 to 2 and back to 12.

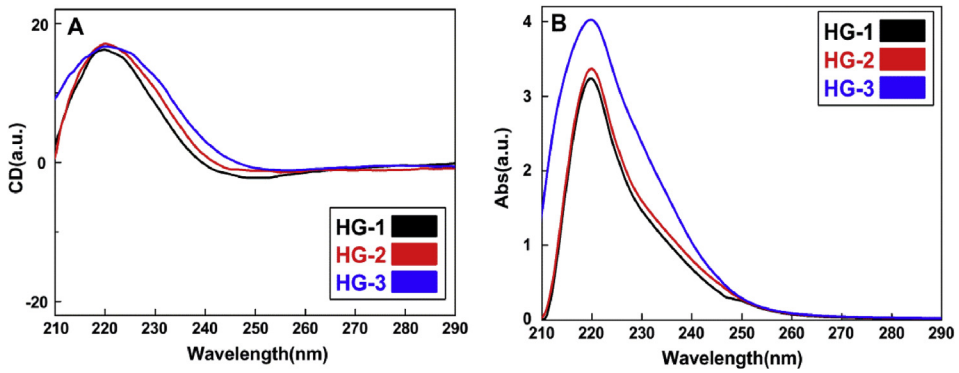

Fig. 5. CD (A) and UV–vis (B) spectra of the hydrogels with varied contents of C18, measured by placing the swollen hydrogels between two pieces of quartz glass at room temperature.

3.4. Optical activity of hydrogels

We expect that the hydrogels to exhibit optical activity, due to the use of chiral monomer NAA. CD and UV–vis spectroscopy were utilized to examine whether the hydrogels have optical activity, according to our earlier investigations concerning optically active polymer materials [28,33]. The CD and UV–vis spectra of the hydrogels are shown in Fig. 5. Strong CD signals around 220 nm can be observed in all the spectra in Fig. 5A. This clearly indicates the intense optical activity of the hydrogels. In Fig. 5B, UV–vis absorptions also appeared around 220 nm. We thus envision that the chiral hydrogels may be used for chiral release, as reported later on.

3.5. Chirally controlled release of proline

According to our early study [25], release of proline enantiomers from the hydrogels based on PNAA was evidently dependent on pH, and the enantio-differentiating release ability at pH = 7 was remarkable. Accordingly, deionized water was chosen as the release medium in the present study. Both separate and simultaneous release behaviors of HG-1 were carried out and the results are shown in Fig. 6.

The time–release profiles of L- and D-proline separately released by HG-1 in deionized water (Fig. 6A) show that within the first 2 h, the release profiles were almost the same and the release rate was fast; then, the release rate gradually became slow with increasing time. Within the first 1 h, the separate release of L- and D-proline kept the same. In the subsequent release process, the release of D-proline became obviously faster than L-proline, indicating that HG-1 preferably released D-proline, which is consistent with our previous study [25]. For a clear observation, the corresponding differences between L- and D-proline released are displayed in Fig. 6B. After 12 h, the maximum difference between D- and L-proline reached up to 19%.

The simultaneous release of L- and D-proline was also investigated, and Fig. 6C shows the difference of cumulative release profile

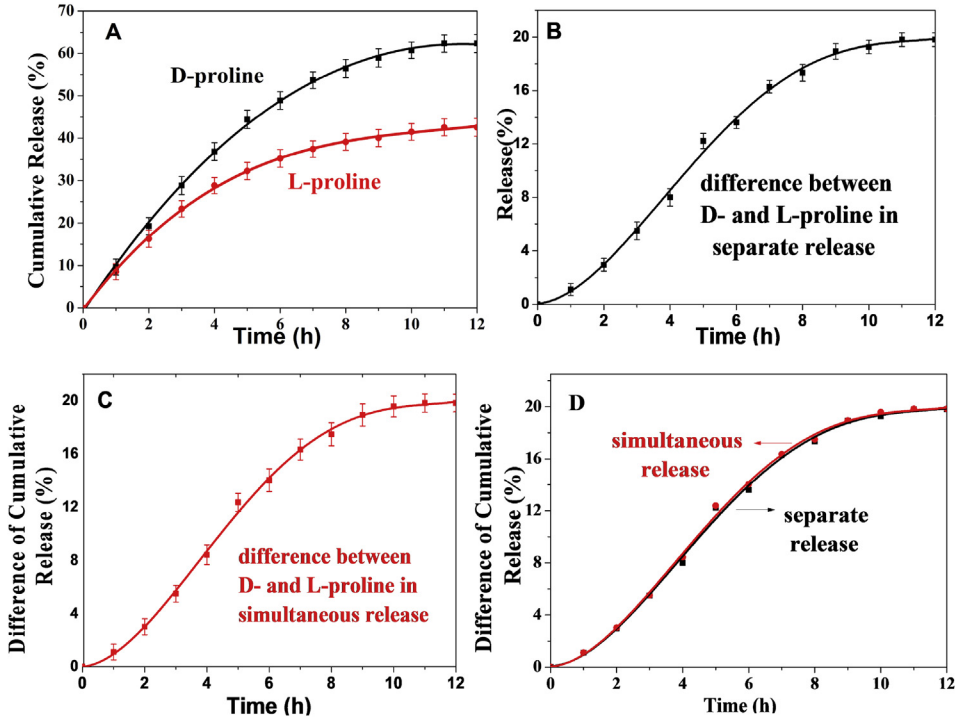

Fig. 6. Time-release profiles of L- and D-proline released by HG-1 in deionized water: L- and D-proline separately released (A) and the corresponding difference between L- and D-proline released (B); the difference between L- and D-proline when simultaneously released (C); a comparison of the difference between L- and D-proline released in the two cases (D), simultaneous release vs. separate release.

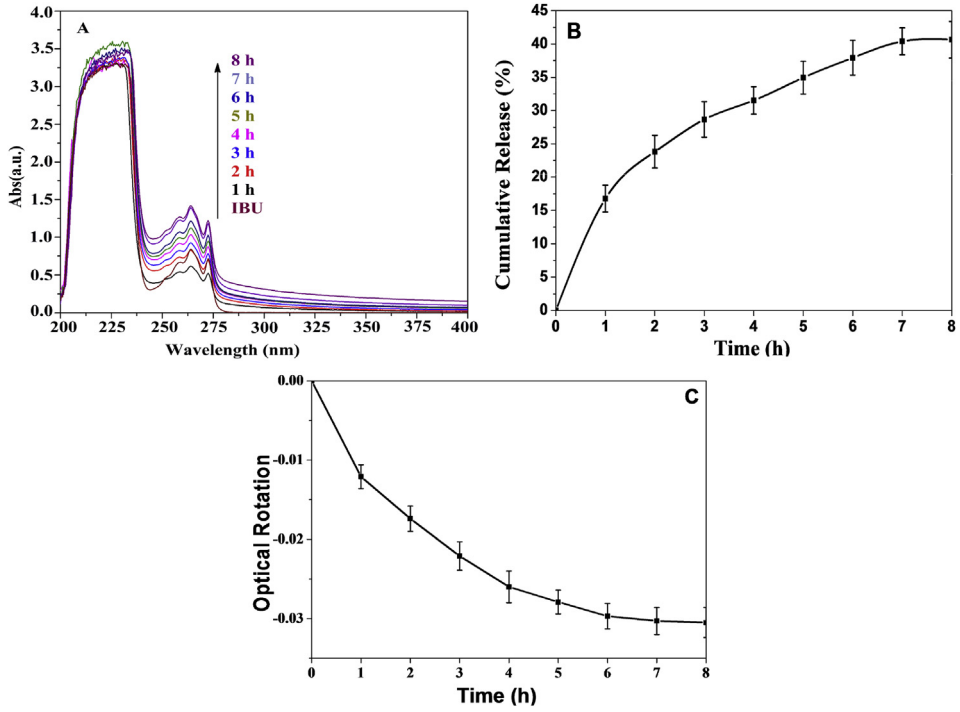

Fig. 7. (A) The UV–vis spectra of outer solution of ibuprofen released as a function of time; the curve of IBU represents the solution of 0.01 g IBU in 20 ml PBS. (B) Time-release profiles of ibuprofen of racemic IBU-loaded HG-1 in 20 ml PBS (pH, 7.4) determined according to UV–vis absorption. (C) Time-optical rotation of racemic IBU by HG-1 in 20 ml PBS (pH, 7.4).

of proline with the time. In this case, the release difference of D- and L-proline increased initially and then tended to level off gradually. This is in well agreement with the separate release mode as discussed above (Fig. 6B). For a vivid comparison between the two release modes, the release differences in both separate and simultaneous release are illustrated in Fig. 6D. The two curves are almost overlapped, demonstrating that the two release modes had little effect on the release profiles; in other words, there was no interference between the two enantiomers during the release process. This is different from the results in our previous study dealing with PNAA hydrogels containing hydroxypropyl-β-cyclodextrin (HP-β-CD) [25]. In the earlier one, the HP-β-CD units may took part in the releasing practice. Also notably, from Fig. 6D, the maximum release difference between D- and L-proline was 19%, much higher than that (12%) in the previous system (simultaneous release mode) [25]. Therefore, the present hydrogels show some advantages over the earlier ones in terms of enantio-selective release.

3.6. Release of ibuprofen by hydrogels

Now we know that the hydrogels (e.g. HG-1) exhibited enantio-differentiating ability towards proline enantiomers, and the enantio-differentiating feature between the two enantiomers was the same for both separate and simultaneous release modes. Next we took ibuprofen (IBU) as a chiral drug model to further explore the release behavior, since IBU is widely used in the treatment of hypertension, angina pectoris and cardiovascular disorders. Racemic IBU was selected as the drug example for performing simultaneous release experiments under similar conditions for prolines, as reported above. For this purpose, a certain amount of racemic IBU was added in the polymerization systems before forming hydrogels, and then the thus-obtained hydrogel was put in the PBS (pH = 7.4, according to literature[34]) medium to measure the release of IBU. The outer solution was subjected to UV–vis absorption and optical rotation measurements.

The UV–vis spectra are shown in Fig. 7A. Initially, the absorption at 265 nm increased with the time, showing that the IBU in the hydrogel was gradually released into the medium [34]. According to the time–release profile (Fig. 7B), which was determined from the UV–vis absorption based on Fig. 7A, IBU cumulative release reached about 40% within 8 h. Based on the optical rotation of the outer solution shown in Fig. 7C, R-ibuprofen was released faster than S-ibuprofen, due to the increasing optical rotation in minus sign. The interesting enantio-differentiating release of drug ibuprofen demonstrated the possibility to utilize the chiral hydrogels as drug carrier, in particular as controlled releasing material for chiral drugs.

4. Conclusion

Chiral and pH responsive hydrogels were successfully prepared by the copolymerization of hydrophilic monomer NAA and hydrophobic monomer C18 emulsified by SDS, with $K_2S_2O_8$ as initiator and BIS as cross-linking agent. The hydrogels demonstrated remarkable pH-sensitive behavior: Shrinking in acid environment but swelling in alkaline environment. CD spectra verified the optical activity of the hydrogels. The chiral hydrogels exhibited enantio-differentiating release ability toward proline as a model chiral compound and ibuprofen as a chiral drug example. The release differences toward proline in both separate and simultaneous release modes are the same. The facile preparative method and intriguing performances facilitated the hydrogels to be potentially used as chiral drug carriers in novel drug delivery systems.

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