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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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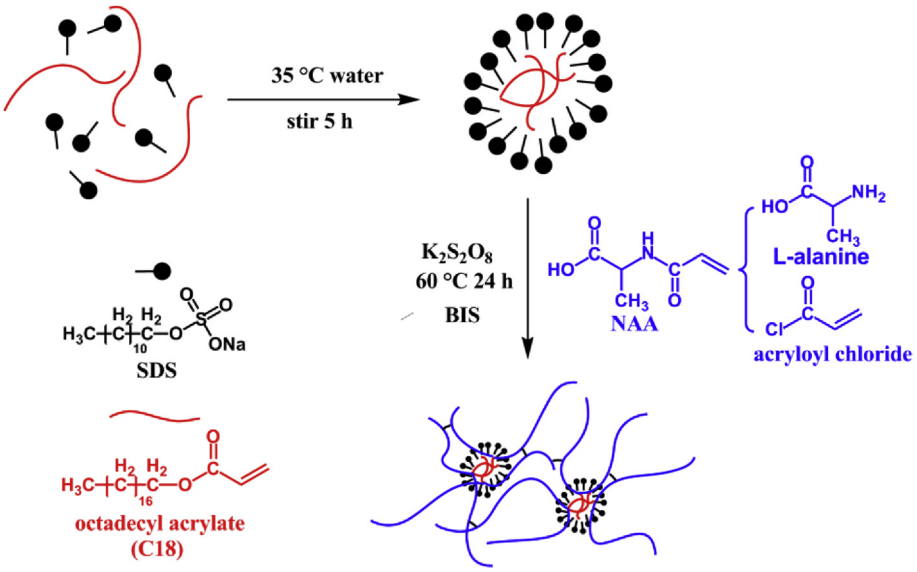

Scheme 1. Schematic strategy for preparing the hydrogels.

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