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Click synthesis of the thermo- and pH-sensitive hydrogels containing β-cyclodextrins

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Abstract Novel intelligent hydrogels containing β-cyclodextrins were prepared by tandem physical and chemical crosslinking method based on Diels–Alder reaction. First, dienophile-functionalized cyclodextrins (HCD–AMI) were synthesized by the coupling reaction of hydroxyethyl-β-cyclodextrins and *N*-maleoyl alanine (AMI); diene-functionalized polymers (PFMIPA) were synthesized by free radical copolymerization of *N*-isopropylacrylamide and furfuryl amine maleic acid monoamide, a novel monomer synthesized in our lab. Then, the LCSTs of the PFMIPA were estimated by transmittance measurements of copolymer solutions. After the as-synthesized PFMIPA and HCD–AMI were dissolved separately in water and mixed, the hydrogels with physical crosslinks formed quickly within 10 s at 37 °C. Subsequently, chemical crosslinks came into being gradually due to Diels–Alder reaction. Therefore, there are both physical crosslinks and chemical crosslinks in as-prepared hydrogels, resulting in the improvement of the mechanical strength of the hydrogels. And the in vitro degradation behaviors of the resultant hydrogels were given a pilot study. A general gravimetric method was used to study the swelling behavior of the hydrogels. It was found that the hydrogels showed good pH/temperature-sensitivity. The strategy described here has several advantages for preparing intelligent hydrogels including tunable gelation rate, mild reaction conditions, no initiator or catalyzer, and no organic solvent. We believe that this novel, potentially biocompatible hydrogels could have biomedical applications, especially in the area of tissue engineering and drug-controlled release carriers.

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Introduction

Cyclodextrins (CDs) are a series of cyclic oligosaccharides consisting of six or more α-l,4-linked D-glucopyranose units. Among them, the most abundant are α-, β-, and γ-cyclodextrins, containing 6, 7, and 8 D-(+)-glucopyranose units, respectively [1–3]. CDs are able to form host–guest complexes with hydrophobic molecules and polymers due to the unique cyclodextrin structure [4–7]. As a result, cyclodextrins have a number of applications in a wide range of fields, including fluorescence enhancement, pharmaceutical applications, and solubility enhancement by forming inclusion complex [8–10]. Therefore, cyclodextrins are often introduced into hydrogels in order to improve the properties of hydrogels [11, 12].

As is well-known, considerable research attention has been focused on hydrogel materials over the past decades, especially smart hydrogels or intelligent hydrogels, which can response to the external environmental stimuli including temperature, light, pH, and electric field [13–17]. At the same time, injectable hydrogels are highly desirable in clinical applications. Injectable precursor solutions can be introduced into the body in a minimally invasive manner before gelling within the desired tissue, organ or body cavity, which may be more suitable for treating irregularly shaped defects than rigid scaffolds. Moreover, the procedure is simpler, more cost-effective and time-saving than open surgery [18–20]. Therefore, intelligent hydrogels with in situ gel-forming capability have recently attracted increasing attention in the development of therapeutic implants and drug delivery systems [21–24].

Poly(*N*-isopropylacrylamide) (PNIPA) is one of the most popular polymers used in the preparation of intelligent and injectable hydrogels since it exhibits a sharp phase transition close to 32 °C [25, 26]. The temperature at which this transition occurs is called the lower critical solution temperature (LCST). The quality of hydrogels based on PNIPA can be improved by finding the right balance of hydrophobic and hydrophilic comonomers or changing LCST to a desired temperature range by copolymerization with a more hydrophilic comonomer (which increases the LCST) or a more hydrophobic comonomer (which decreases the LCST) [27]. In addition, these hydrogels can possess pH-sensitivity by copolymerizing N-isopropylacrylamide with acidic or basic comonomers. Of course, changes in pH values also affect the ionization state and hydrophilic/hydrophobic balance in these hydrogels, resulting in an adjustment of the LSCT [28]. So far, there are many reports on the preparation of the thermo- and pH-sensitive hydrogels based on *N*-isopropylacrylamide [29]. A variety of methods for in situ formation have also been explored, such as free radical polymerization and conjugate chemical reaction [30, 31]. On the basis of the advantages of Diels–Alder reaction, we think it is an ideal reaction for preparing intelligent and injectable hydrogels [32]. Recently, our group has developed a system based on copolymer of *N*-isopropylacrylamide and furfuryl methacrylate, and the hydrogels were formed by Diels–Alder reaction [33]. More recently, thermosensitive and injectable hydrogels were prepared by means of tandem physical and chemical crosslinking based on Diels–Alder reaction between diene-functionalized terpolymers and dienophile-functionalized terpolymers [34], but the hydrogels neither possess pH-sensitivity nor contain cyclodextrins, a host compound of supramolecular chemistry.

Based on the above consideration, in this study, our objective is to prepare pH/temperature dually sensitive and injectable hydrogels containing cyclodextrins by Diels–Alder reaction. For this purpose, the cyclodextrins were modified by dienophile groups. And diene-functionalized polymers were prepared by copolymerization of *N*-isopropylacrylamide and furfuryl amine maleic acid monoamide (FM), a novel monomer designed for our purpose. Afterward, the thermo- and pH-sensitive hydrogels were prepared by tandem crosslinking. To the best of our knowledge, there is no report on preparing thermo- and pH-sensitive hydrogels in this way.

Experimental part

Materials

Furfurylamine, *N*-isopropylacrylamide (NIPA), *N*,*N*′-dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino)pyridine (DMAP) were purchased from Sigma-Aldrich (Shanghai) Trading Co., Ltd., China. L-Alanine (AR) and maleic anhydride (AR) were obtained from Sinopharm Chemical Reagent Co., Ltd, China. 2,2′-azobisisobutyronitrile (AIBN) (AR) was produced by Shanghai Shanpu Chemical Co., Ltd, China. Hydroxyethyl-*β*-cyclodextrin (Mean degree of substitution = 6) was provided by Zibo Qianhui Fine Chemical Co., Ltd, China. *N*-maleoyl alanine (AMI) was synthesized according to our previous paper [35]. The buffer solution with different pH was prepared according to reference and ionic intensity was adjusted to 0.1 mol/L with NaCl.

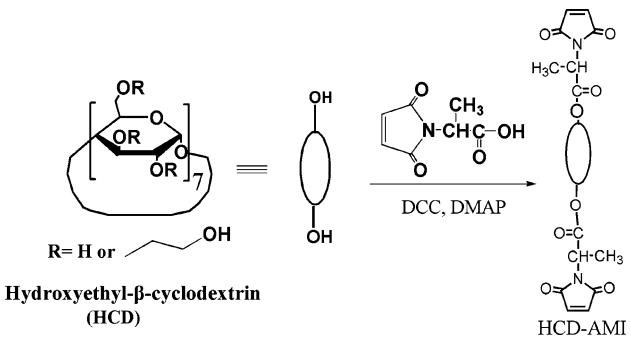
2,2′-Azobisisobutyronitrile (AIBN) was purified by crystallization from methanol. 1,4-Dioxane was distilled and then dried over molecular sieve for 2 days. Tetrahydrofuran, *N*,*N*-dimethyl formamide (DMF) and toluene were distilled and dried over anhydrous magnesium sulfate for 2 days. Triethylamine was distilled and then dried over plate-shaped KOH. All other reagents used were of analytical grade and used without further purification.

Synthesis of dienophile-functionalized *β*-cyclodextrin (HCD–AMI)

Dienophile-functionalized *β*-cyclodextrin (HCD–AMI) was synthesized by the coupling reaction of hydroxyethyl-*β*-cyclodextrin and AMI. As a typical example, synthesis process of HCD–AMI was conducted as follows (Scheme 1). Hydroxyethyl-*β*-cyclodextrin (1.00 g, 0.72 mmol) and AMI (0.60 g, 3.6 mmol) was dissolved in dry DMF (12 mL). After being cooled to −2 °C, 6 mL of DMF solution of DCC (0.90 g, 4.4 mmol) and DMAP (0.04 g, 0.6 mmol) was added dropwise, and the mixture was stirred at −2 °C for 8 h. The resulting mixture was filtered, and the filtrate was precipitated in about 400 mL of diethyl ether. The precipitate was filtered out and dried under vacuum to constant weight. Yield: 65%.

Synthesis of poly(furfuryl amine maleic acid monoamide-co-*N*-isopropyl-acrylamide) (PFMIPA)

Diene-functionalized polymer was synthesized by the following steps. First, a polymerizable monomer containing



Scheme 1 Synthetic route of HCD–AMI

both diene group and pH-sensitive group was designed to synthesize from furfuryl amine and maleic anhydride. Typically, furfurylamine (0.5000 g, 5.15 mmol) and maleic anhydride (0.5048 g, 5.15 mmol) were charged into 50 mL round-bottom flask containing 20 mL of toluene with a magnetic stirrer under high pure nitrogen. The flask was immersed in a water bath held at 30 °C for 12 h. Afterward, the flask was removed from the bath and dropped into about 20 mL of diethyl ether to present white precipitate. The precipitated sample was washed with diethyl ether and purified by reprecipitation from methanol, dried under vacuum until constant weight was attained. The product here was denoted as FM. Yield: 62.5%. mp. 113–114 °C.

^{1}H NMR(400 MHz, DMSO-d_6):δ = 14.31(s, 1H, –COO*H*), 9.30–9.33 (t, 1H, –CO–N*H*–CH_2–), 7.61 (d, 1H, –O–C*H*=CH–CH=CCO), 6.41–6.42 (q, 1H, O–CH=C*H*–CH=CCO), 6.37–6.40 (d, 1H, –NHCOC*H*=CHCOOH), 6.34–6.35 (d, 1H, O–CH=CH–C*H*=CCO), 6.25–6.28 (d, 1H, –NHCOCH=C*H*COOH), 4.38–4.39 (d, 2H, CCH_2NHCO). ^{13}C NMR (400 NMR, DMSO-d_6): δ = 166 (*C*OOH), 165 (NH–*C*=O), 151(NH–*C*=C), 142 (O–*C*=C), 133(O=C–*C*=C), 131 (C=*C*–COOH), 111 (C=*C*–C=C–CH_2–NH), 108 (C=C–*C*=C–CH_2–NH), 36 (C=C–*C*H_2–NH).

Second, PFMIPA was synthesized by copolymerization of FM and NIPA, as shown in Scheme 2. The copolymers prepared here were denoted as PFMIPA-n, where n standed for a feed molar ratio of NIPA to FM. Typically, PFMIPA-5 was synthesized by the following steps. FM (0.3267 g, 1.6754 mmol) and NIPA (0.9428 g, 8.4179 mmol) were charged into a 100 mL of round-bottom flask containing 30 mL of 1,4-dioxane with a magnetic stirrer under high pure nitrogen, then adding 0.0246 g of AIBN. The flask was immersed in an oil bath held at 70 °C for 24 h. Afterward, the flask was removed from the bath and the content was dropped into about 50 mL of mixture solution of diethyl ether and petroleum ether (1:1 by volume) to present the precipitate. The precipitated sample was washed with the as-prepared mixture solution (20 mL) and then ethylacetate (30 mL), and dried under vacuum until constant weight was attained. Yield: 81%.

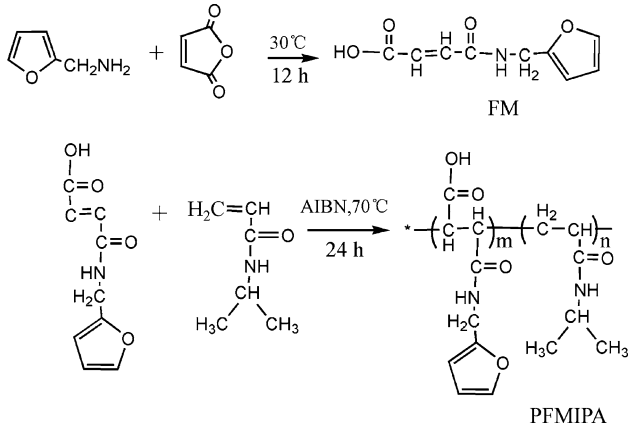
Screening of PFMIPA by LCST

LCST of the as-prepared copolymer solutions was measured by transmittance measurements using a TU-1900 dual-beam UV–Visible spectrophotometer (Beijing purkinje general instrument Co., Ltd., China) fitted up with a temperature controller. The samples for the UV–Vis experiments were prepared in quartz colorimetric cell (10 mm in thickness) with a concentration of 1 g/L.

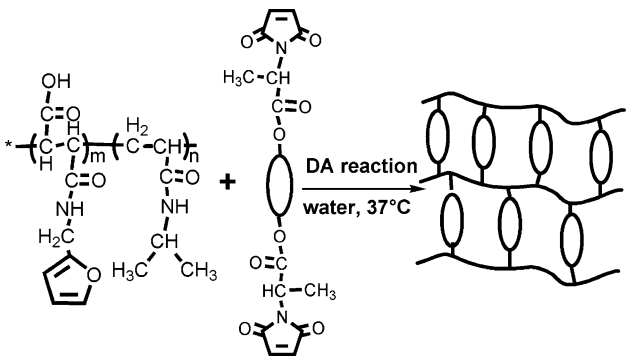
A colorimetric cell filled with doubly distilled water was used as a reference. All extinction measurements were performed at a wavelength of 500 nm. The transmittance of the copolymer solutions was recorded as a function of temperature. The temperature was varied at a step width of 0.5 K/10 min. LCST of the polymer solutions was defined as the temperature at which the optical transmittance of the solution reduced to 10% of its original value. Because our purpose is to prepare injectable hydrogels, the PFMIPA whose LCST was near body temperature was chosen as a diene-functionalized copolymer to carry out the following experiment.

Preparation of hydrogels by Diels–Alder reaction

The hydrogels were prepared by tandem physical and chemical crosslinking based on Diels–Alder reaction (Scheme 3). A determined amount of the screened copolymer and HCD–AMI were put into a tube and dissolved in distilled water, respectively, then mixed, making the total mass concentration of the mixture 25%. After the resulting mixture was dissloved fully, the tube was put into a thermostatic bath of 37 °C, and view the gelation process.



Scheme 2 Synthetic route of PFMIPA



Scheme 3 Chemical structure of hydrogels formed by DA

Hydrolytic degradation study

Aqueous solutions of pH = 2, 7.4, and 9 were used as degradation media and the as-prepared tandem hydrogels were chosen as model samples. The detailed degradation process was as follows. The dried tandem crosslinked gels were weighed and immersed in 100 mL of buffer solutions with pH = 2, 7.4, and 9, respectively, then incubated in a water bath at 37 °C under a mild shaking motion (60 rpm). The medium was refreshed every day. At specified time intervals, three disks were removed from the degradation medium, washed thoroughly with deionized water, and dried at room temperature for 1 day and dried under vacuum for another 3 days at 50 °C. The percent weight loss of each sample was determined by the following equation:

$$\text{Weight loss } (\%) = [(W_0 - W_t)/W_0] \times 100$$

where W_0 denotes the weight of the initial dried gels and W_t the weight of the final dried gels after complete drying in a vacuum oven.

Characterization

The FTIR spectral analysis was carried out on a Nicolet NEXUS 470 infrared spectrophotometer at room temperature, in the range from 4000 to 500 cm^{-1}. Samples were prepared by well dispersing the complexes in KBr and compressing the mixtures to form disks. The ^1H NMR spectra were recorded on a Bruker DPX-400 NMR instrument at room temperature with tetramethylsilane as internal standard. Gel permeation chromatography (GPC) analysis was carried out with a SHIMADZU LC-10AVP chromatographic system equipped with a (SHIMADZU) shim-pack GPC-803 chromatographic column. THF was used as eluent at a flow rate of 1.0 mL/min. Monodispersed polystyrene standards were used to obtain a calibration curve. The microstructures of the hydrogels after freeze-drying were observed using a JSM-6360 LV scanning electron microscope (SEM).

The swelling behavior of dried hydrogels was measured by a general gravimetric method. About 0.5 g of dry hydrogels were incubated in distilled water at 20 °C, and the swollen weight for each sample was recorded at regular time intervals after excess surface water was blotted carefully with filter paper. The procedure was repeated until there was no further weight increase. While the temperature increased gradually the swollen hydrogels began to shrink. The temperature was maintained constant for 12 h after increased by each 5 °C, and then shrunk hydrogels were weighed. To characterize the pH-sensitivity of the hydrogels, we took turns to put the hydrogels into the buffer solutions of pH = 2, 3.6, 6, 8, 9, and 10, and weighed the hydrogels after 12 h in each buffer solution. The oscillatory shrinking/swelling dynamics of the as-prepared hydrogels was also studied between pH = 2 and 8. The hydrogels were incubated in the butter solution of pH = 2 for 12 h, alternating with being incubated in the butter solution of pH = 8 for 12 h.

The swelling ratio (SR) was calculated by the following equation:

$$\text{SR} = (m_1 - m_0)/m_0$$

Herein, m_0 stands for the initial weight of dried gel and m_1 the weight of the swelling gel at a particular temperature and a prescribed time interval.

Results and discussion

Synthesis of HCD–AMI

To obtain a water-soluble dienophile-functionalized cyclodextrins, HCD, which have more solubility in water than β-cyclodextrin do, were chosen after some experiments. It was found that when the feed molar ratio of AMI to HCD was more than 5, the sample obtained did not dissolve well in water. Therefore, the feed molar ratio was 5 during the synthesis process in order to insure at least two dienophile groups in each cyclodextrin molecule. With respect to the synthesis of dienophile-functionalized hydroxyethyl-β-cyclodextrins, the coupling reaction between carboxyl and hydroxyl group was utilized. As exhibited in Fig. 1, after the coupling reaction, the absorbent peaks appearing at 3101 cm^{-1} (=C–H vibration in AMI), 1744 and 1713 cm^{-1} (C=O stretch in AMI) revealed the existence of dienophile groups. In addition, from the ^1H NMR spectra of dienophile-functionalized HCD (b) and HCD (a) in Fig. 2, the chemical shifts appearing at 1.48 ppm (the proton b in methyl) and

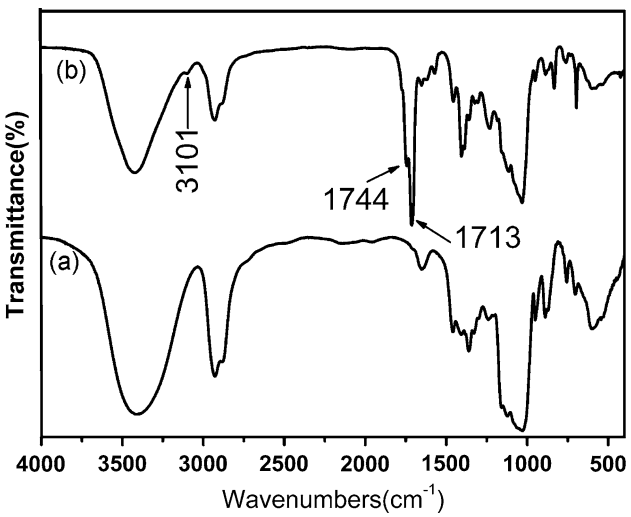


Fig. 1 The FTIR spectra of HCD (*a*) and HCD–AMI (*b*)

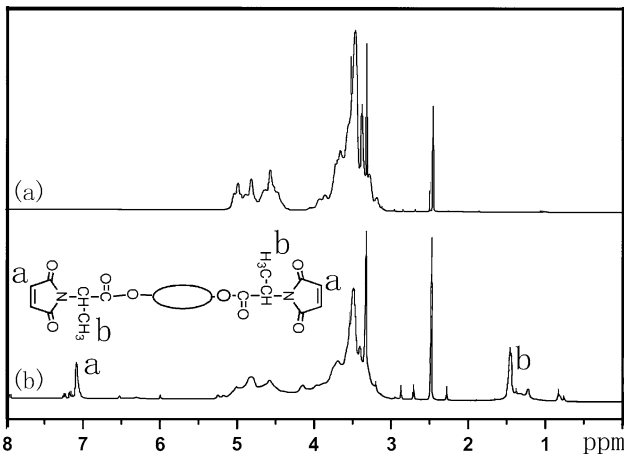


Fig. 2 The ^{1}H NMR spectra of HCD (*a*) and HCD–AMI (*b*) in DMSO-d_6

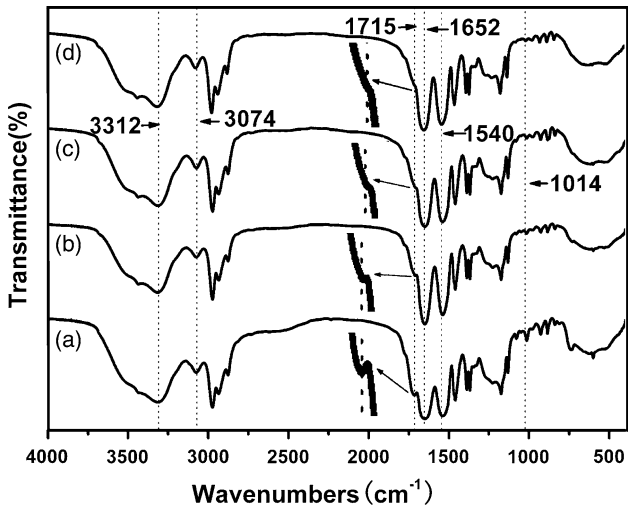


Fig. 3 The FTIR spectra of PFMIPA-5 (*a*); PFMIPA-10 (*b*); PFMIPA-15 (*c*); PFMIPA-20 (*d*) (The bands at 1715 cm^{-1} were enlarged and inserted)

7.17 ppm (the proton a in maleimide group) also demonstrated the existence of dienophile groups. Therefore, dienophile-functionalized cyclodextrins were obtained. Of course, it is more desirable to modify cyclodextrins with exact degree of substitution, and we are devoted to the study on this aspect.

Synthesis of PFMIPA

Herein, the initial total concentration of monomers was reduced to 0.3 mol/L to prevent the gelation, which may be attributed to lability of the carbon-5 of the furan ring during polymerization of furan derivatives, which is obtained from the reference and our experiment results [32–35]. The GPC data showed that all the obtained macromers had a unimodal peak with a polydispersity index (PDI) around 3 (Table 1).

FTIR spectra of PFMIPA-n were shown in Fig. 3. The band at 1715 cm^{-1} was assigned to the C=O stretching mode in FM, and the amide I band (C=O stretch) emerges at 1652 cm^{-1}, the amide II band (N–H vibration) at 1540 cm^{-1}, and the methyl groups (in isopropyl group) at 1367 and 1387 cm^{-1}. The band at 1014 cm^{-1} was due to C–H deformation vibration in furan ring, and the band at 3074 cm^{-1} belonged to =C–H stretching mode in furan ring. The broad peak at 3312 cm^{-1} was assigned to the N–H vibration. It could be seen that the intensity of the peak at 1715 cm^{-1} became weaker from curve a to curve d as the NIPA to FM molar ratio increased.

^{1}H NMR spectrum of PFMIPA-5 was presented in DMSO at room temperature (Fig. 4). The copolymer compositions were estimated by comparison of the integrated intensities of resonance signals at 6.37 ppm (the protons d, e in furan group) and 1.04 ppm (the protons in methyl of NIPA), which varied in accordance with the feed molar ratio (Table 1). Molar feed ratio was different from calculated molar ratio in copolymer, which have something to do with reactivity ratios of NIPA and FM and detailed research on this aspect need be done further.

The LCSTs of the polymers were estimated in water by measuring transmittance measurements of the aqueous copolymer solutions. It could be seen from Fig. 5 that all the copolymer solutions showed sensitive and discontinuous transmittance change in a distinctly narrow temperature range. If LCST of the polymer solutions was defined as the temperature at which the optical transmittance of the solution reduced to 10% of its original value, the LCSTs of copolymers for PFMIPA-5, PFMIPA-10, PFMIPA-15, and PFMIPA-20 were 25, 31, 37, and 32 °C, respectively. Therefore, we chose PFMIPA-15 for tandem crosslinking. Moreover, on the basis of the results in Fig. 5, it was revealed that the LCSTs of the copolymers could be

Table 1 Characterization of some copolymers

Copolymer	NIPA/FM molar feed	NIPA/FM molar ratio in copolymer[a]	Yield (%)	$\overline{Mn}$	PDI	LCST[b] (°C)
PFMIPA-5	5	3.4	81	52470	2.92	25
PFMIPA-10	10	7.6	88	40470	3.07	31
PFMIPA-15	15	10.8	86	58420	2.98	37
PIPAFM-20	20	16.3	82	49400	2.88	32

[a] Estimated by ^{1}H NMR

[b] Measurements using a UV–Visible spectrophotometer in water

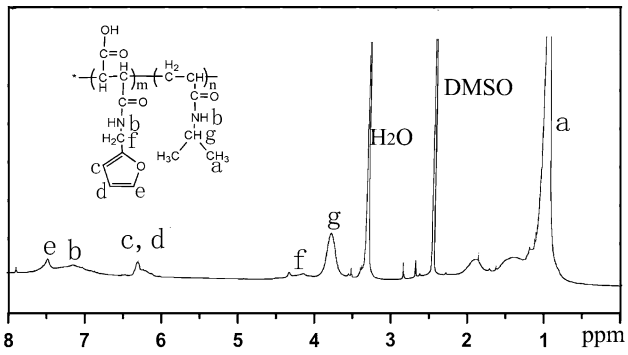


Fig. 4 ^{1}H NMR spectrum of PFMIPA-5 in DMSO-d_6 at room temperature

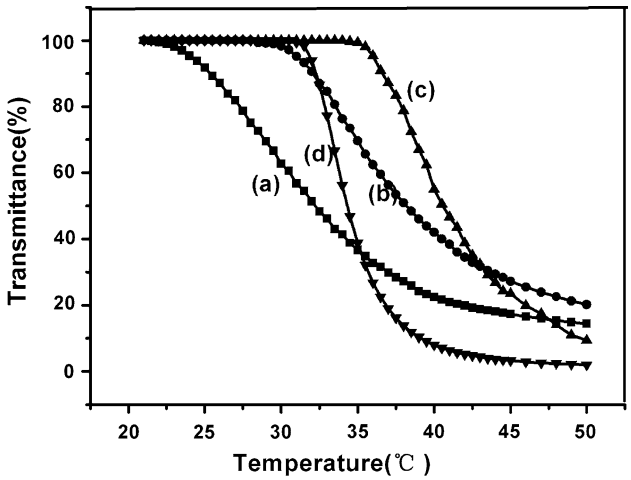


Fig. 5 Transmittance changes with temperature of aqueous solutions of copolymers: PFMIPA-5 (*a*), PFMIPA-10 (*b*), PFMIPA-15 (*c*), PFMIPA-20 (*d*)

controlled by varying the feed ratio of the comonomers. As is well-known, phase transition temperature control is a very important aspect in some biomedical applications.

Preparation of hydrogels by DA reaction

A determined amount of PFMIPA-15 and HCD–AMI was separately charged into a tube and dissolved in distilled water so that the total mass concentration of the mixture became 25% after mixing. Subsequently, the tube was put into a thermostatic bath of 37 °C, white and opaque

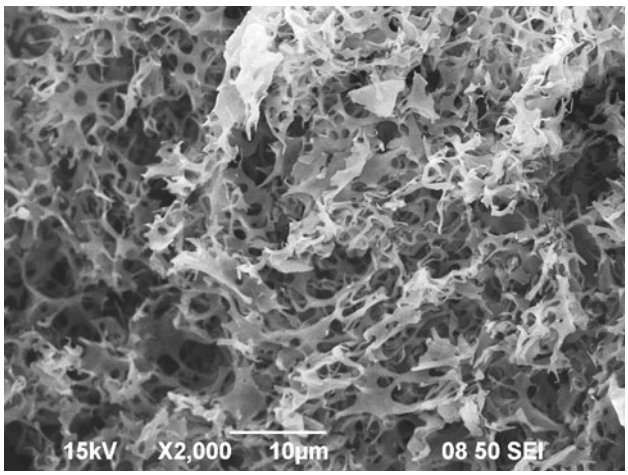


Fig. 7 SEM image of the hydrogel from PFMIPA-15 and HCD–AMI

physical gel was observed within 10 s. At this stage, the gel could turn into sol easily when decreasing temperature. Continuing putting the tube in thermostatic bath of 37 °C for 60 min, the physical gel changed into chemical gel gradually due to carrying out Diels–Alder reaction. At this stage, the gel could not turn into sol again even if the tube was kept at a low temperature for a fair long time. Figure 6 shows the solution states before and after transition. SEM image of freeze-dried hydrogel by means of tandem crosslinking of PFMIPA-15 and HCD–AMI are shown in Fig. 7 and porous structure are observed. As is well-known, a highly inter-connected porous structure is required when used as a drug carrier and scaffold in tissue engineering [36, 37].

The FTIR spectra of HCD–AMI (a), PFMIPA-15 (b) and the corresponding gel formed by DA reaction (c) are shown in Fig. 8. It can be seen that curve c is the overlapping of curve a and curve b excluding the change in peak intensity and a little shift because of less content of diene group and dienophile groups in copolymer.

Swelling behavior

The SRs of the as-prepared hydrogels were measured in distilled water at 15 °C. After reaching the swelling equilibrium, these hydrogels were left at 20, 25, 30, 35, 40, 45, 50, and 55 °C in turn in the thermostatic water bath for 12 h before measuring the SR changes. As depicted in Fig. 9

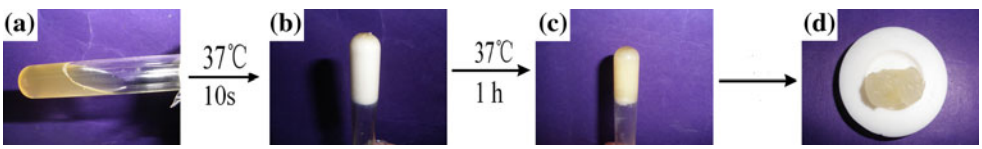


Fig. 6 Photographs in the process of gel formation: **a** gel precursor solution; **b** the gel obtained by physical crosslinking after 10 s; **c** the gel obtained by tandem crosslinking after 60 min; and **d** the state of the hydrogel drawn out of the tube

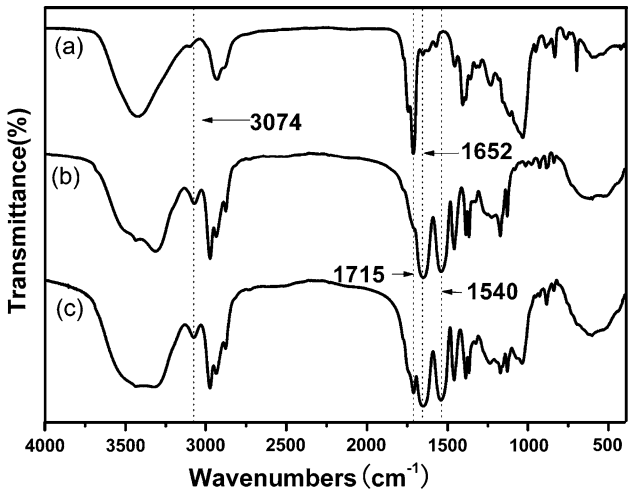


Fig. 8 The FTIR spectra of HCD–AMI (*a*), PFMIPA-15 (*b*), and the corresponding gel formed by DA reaction (*c*)

(Left), the hydrogels had high SRs in water at 15 °C, and the SRs grew faster at the beginning and then augmented gradually after 1 h. It was found that the SRs of the hydrogels possessed temperature-sensitivity, just as expected. As shown in Fig. 9 (Right), when temperature increased from 15 to 50 °C, the SR of the hydrogels decreased. This is because there existed poly(*N*-isopropylacrylamide) segments, which could become hydrophobic with increasing temperature [38, 39]. Polyelectrolyte hydrogels showed pH-sensitivity due to the ionic reaction. In this study, the pH value of the external buffer solution had been varied in the range from 2 to 10. The SR of the hydrogels changing with pH was shown in Fig. 10 (Left). The SRs of the hydrogels increased as the pH value of buffer solution increased from 2 to 10. The SRs of the hydrogels were extremely low at low pH solutions. When the pH of the solution was higher than 4, the SRs of the hydrogels increased rapidly. However, when the pH of the solution was higher than 9, the SRs of the hydrogels increased slightly with the increasing pH of the solution. As a weak acid, the ionization of PFMIPA was suppressed at low pH, and the electrostatic repulsion among the polymer chains was weakened, as a result, the hydrogels were kept at a shrinking state at low pH. When the pH of the solution was higher than 4, H^+ in hydrogel was replaced by Na^+. Because –COONa could ionize completely, the electrostatic repulsion among the polymer chains increased significantly, and the hydrogel swelled. However, when the pH of the solution was higher than 9, H^+ in hydrogel was already replaced by Na^+ completely, therefore, the electrostatic repulsion among the polymer chains achieved its maximum, consequently, the SRs of the hydrogels increased slightly with the increasing pH of the solution. Considering applications, especially in actuators for drug release regulation or artificial muscle,

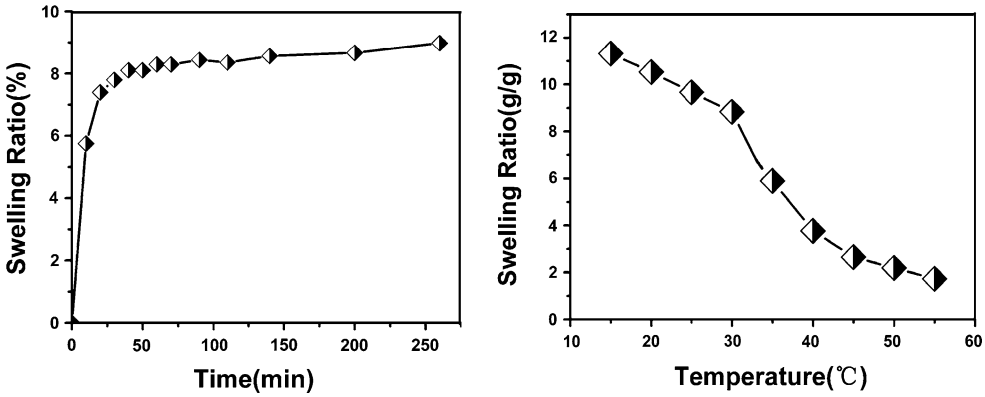


Fig. 9 The swelling behavior of the hydrogel as a function of time at 15 °C (*left*) and as a function of temperature from 15 to 60 °C (*right*)

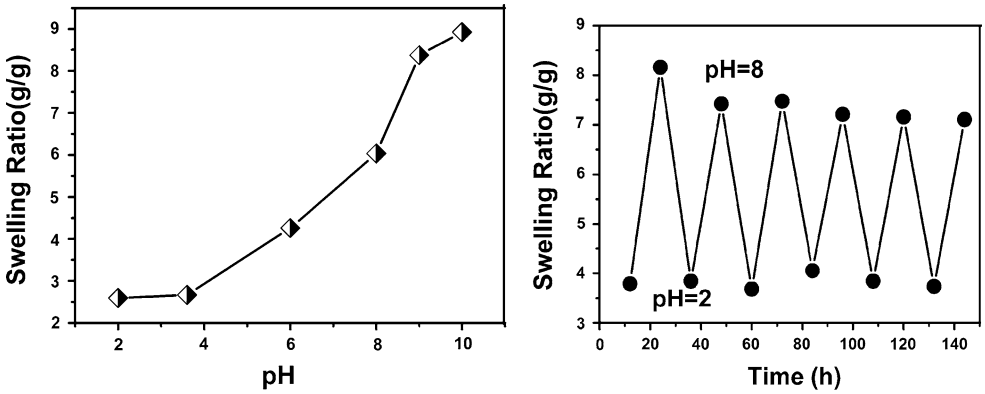


Fig. 10 The swelling behavior of the hydrogel as a function of pH from 2 to 10 (*left*), and the pH-stimulating swelling–deswelling kinetics of the hydrogel between pH = 2 and 8 (*right*)

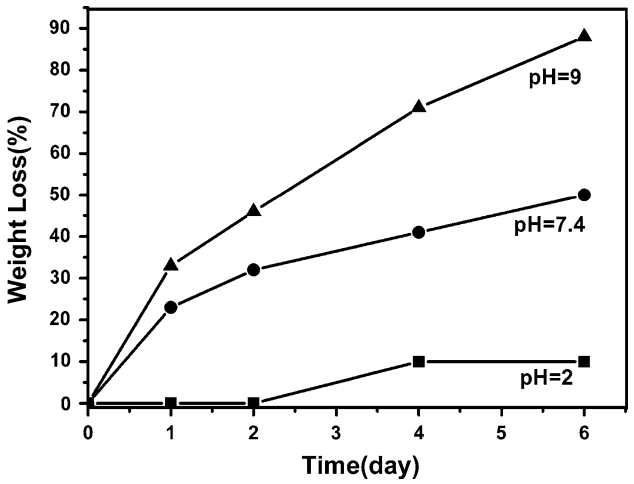


Fig. 11 The hydrolytic degradation behavior of the hydrogels in different pH solutions at 37 °C

recurrent response is an important property [40]. Figure 10 (Right) shows the pH-stimulating swelling-deswelling kinetics of the hydrogel from PFMIPA-15 and HCD–AMI between pH = 2 and 8. The hydrogel deswelled at pH = 2 and swelled at pH = 8, and the SR of the hydrogel changed slightly after five cycles. This also indicates that the hydrogels have reversible pH response properties.

In vitro hydrolytic degradation of the hydrogels

Injectable hydrogels for biomedical applications should be degraded from the body after completing their mission. The as-prepared hydrogels contain the hydrolytically labile ester bonds that provide the network with degradable characteristics. The cleavage of ester bonds within the polymer networks results in the weight loss of the hydrogels. The hydrolysis of the hydrogels was related with the pH of the medium. The hydrolytic degradation rate of the hydrogels increased when increasing pH of the medium. As shown in Fig. 11, at pH = 2, the hydrogel degradation rate was slow, and ten percent mass loss was observed in 6 days. Whereas at pH = 9, the hydrogel degradation rate was faster, exhibiting 88% mass loss in 6 days.

Conclusion

A novel type of injectable hydrogels both containing β-cyclodextrins and possessing pH/temperature dually responsive properties were prepared by tandem physical and chemical crosslinking. Their SRs decreased with the increase of temperature and the hydrogels deswelled at low pH value but swelled at high pH value. This kind of hydrogels could be decomposed via hydrolysis in acid or basic media, and the degradation rate could be controlled by the pH of the solution. Tandem crosslinking method has a potential application in the synthesis of injectable hydrogels, due to its combining the advantages of physically crosslinked hydrogels and chemically crosslinked hydrogels. In view of mild and environmental-friendly reaction conditions, the strategy described here will have a promising application in the preparation of biomaterials. In addition, it may show unique drug-controlled properties due to the presence of β-cyclodextrins, which is the focus of our ongoing investigations.

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