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A facile preparation of pH-temperature dual stimuli-responsive supramolecular hydrogel and its controllable drug release

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ABSTRACT: A series of pH-temperature dual stimuli-responsive random copolymers poly[*N*,*N*-dimethylaminoethyl methacrylate-*co*-poly(poly(ethylene glycol) methyl ether methacrylate][poly(DMAEMA-*co*-MPEGMA)] were synthesized by free radical polymerization. The supramolecular hydrogel was formed by pseudopolyrotaxane, which was prepared with the host-guest interactions between α-cyclodextrin (α-CD) and poly(ethylene glycol) (PEG) side chains. Fourier transform infrared (FT-IR), nuclear magnetic resonance (^{1}H NMR), and X-ray diffraction (XRD) confirmed the structures of the hydrogels. The pH-temperature dual stimuli responsive properties of the hydrogels were characterized by rheometer. Finally, the controllable drug release behavior of the hydrogel, which was used 5-fluorouracil (5-Fu) as the model drug, was investigated at different temperatures and different pH values. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43279.

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INTRODUCTION

In the past decade, extensive attentions have been garnered by stimuli-responsive hydrogels due to their particular applications in drug delivery, tissue culture, microfluidics, and sensors.[1–6] They can undergo reversible changes in response to external stimuli such as temperature, pH value, electric potential, light, salt, sugar, carbon dioxide, and other environmental factors.[6–11] Among them, the pH-responsive and thermal-responsive hydrogels, which can respond to a dynamic pH or temperature environment, are particular interest for biomedical applications as several locations in the body exhibit pH or temperature changes during either normal function or as part of a disease state.[12,13] These pH variations exist within each part of the body, such as gastrointestinal tract, blood, inflamed tissue/wounds, and tumor tissue.[14–17] While the thermo-responsive hydrogel can be used due to the relatively universal physiological temperature of 37°C and the development of a number of mechanisms to manipulate and control temperature *in vivo*.[18–20]

However, a majority of stimuli-responsive hydrogels reported up to now focus on the types for stimulus responses and tunable response extent. Most of them are difficult to prepare in a large amount. Furthermore, the low drug-loading rate and the laborious drug-loading procedures are the other two reasons that limit their applications. Thus, "facile preparation" and "facile drug-loading" become the new requirements for the hydrogels applied in drug delivery.

In addition to covalently cross-linked hydrogels,[21–24] supramolecular hydrogels based on non-covalent interactions represent another effective strategy of providing rapid response to external stimuli, which offers a novel strategy for the design of drug delivery systems with rapid response abilities. Among numerous types of the supramolecular hydrogels, the hydrogels formed by pseudopolyrotaxane, which was prepared with the host-guest interactions between cyclodextrins (CDs) and poly(ethylene glycol) (PEG), have been intensively studied due to their various advantages, such as easy preparation, self-healing, molecular recognition and selection, and biocompatibility.[25–29]

Herein, we paid great efforts on pH-temperature dual-responsive supramolecular hydrogels, which were facile-preparation and suitable for drug delivery. For this purpose, a random block copolymer consisting of poly[2-(*N*,*N*-dimethylamino)ethyl methacrylate] (PDMAEMA) and poly[poly(ethylene glycol) methyl ether methacrylate] (PMPEGMA) was prepared via free radical copolymerization. PDMAEMA is a typical dual responsive polymer owing to the unique *N*,*N*-dimethylaminoethyl groups, which exhibits a lower critical solution temperature (LCST) in the range of 32–46°C and has a pK_a of 7.0–7.8, depending on its molar mass.[30–35] And PMPEGMA provided

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the long side chain, poly(ethylene glycol), which could thread into the cavity of α-CD at room temperature to form pseudo-polyrotaxane. What's more, the strong hydrogen bonds between α-CDs promoted the formation of hydrogels. The pH-thermo dual responsive properties of the hydrogels were characterized by rheometer. Finally, the controlled drug release behavior of the hydrogels, which was used 5-fluorouracil (5-Fu) as the model drug, was investigated at different temperatures and different pH values.

EXPERIMENTAL

Materials

N,N-dimethylaminoethyl methacrylate (DMAEMA, Aladdin, China) was used after distilled. Azobisisobutyronitrile (AIBN, Aladdin, China) was purified by recrystallization from ethanol twice. 1-(3-Dimethylaminopropyl)−3-ethylcarbodiimide hydrochloride (EDC·HCl), 5-fluorouracil (5-Fu), methoxy-poly(ethylene glycol) (MPEG, $M_n = 5000$), α-cyclodextrin (α-CD), and 4-dimethylamino-pyridine (DMAP), and all other chemical reagents were purchased from Aladdin and used as received without further purification.

Synthesis of Poly(ethylene glycol) Methyl Ether Methacrylate (MPEGMA)

MPEGMA was synthesized as follows. About 5 g MPEG ($M_n = 5000$, 1 mmol), 8.5 mL methacrylic acid (MAA, 100 mmol), 0.37 g DMAP (3 mmol), and 0.58 g EDC·HCl (3 mmol) were dissolved in 30 mL CH_2Cl_2 in order, and the reaction was performed at room temperature for 24 hours. After removing the solvent completely, the residue was dissolved in 50 mL 10% Na_2CO_3 solution. The product was extracted with excess CH_2Cl_2 for three times. The organic layer was combined, washed by brine, and dried with Na_2SO_4. The mixture was filtered and the filtrate was concentrated and added dropwise to cold diethyl ether with stirring. The precipitate was collected by filtration and dried in vacuum until constant weight (yield 84.2%). FT-IR/cm^{-1} (KBr): 2887 (ν_{C-H}), 1718 ($\nu_{C=O}$), and 1651 ($\nu_{C=C}$). Nuclear magnetic resonance (^{1}H NMR)/ppm ($CDCl_3$): 5.69, 6.20 (d, $CH_2C(CH_3)$), 4.35 (t, CH_2CH_2OCO), 3.78 (t, CH_2CH_2OCO), 3.66 (s, $CH_3OCH_2CH_2O$), 3.39 (s, $CH_3OCH_2CH_2O$), and 1.97 (s, $CH_2C(CH_3)$).

Synthesis of Poly(MPEGMA-*co*-DMAEMA) Copolymers

A typical polymerization procedure was as follows. About 1.48 g MPEGMA (0.29 mmol), 3.76 mL DMAEMA (23 mmol), and 53.5 mg AIBN (0.326 mmol) were dissolved in 8 mL *N,N*-dimethylformamide (DMF). The reaction was carried out under the protection of nitrogen at 70°C for 10 hours. The resulting solution was dialyzed against deionized water for 5 days to remove residual monomers. The aimed product was obtained by freeze dehydration (yield 88.6%). FT-IR/cm^{-1} (KBr): 3100–3700 ($\nu_{N(C-H)}$), 2887 (ν_{C-H}), 1718 ($\nu_{C=O}$), 1282 (ν_{C-N}), and 1111 (ν_{C-O-C}). ^{1}H NMR/ppm ($CDCl_3$): 0.78–1.13 (m, $CH_2C(CH_3)$ in PDMAEMA and MPEGMA), 1.73–2.08 (m, $CH_2C(CH_3)$ in PDMAEMA and MPEGMA), 4.12 (t, $COOCH_2CH_2$ in PDMAEMA), 2.36 (s, $CH_2N(CH_3)_2$ in PDMAEMA), 2.62 (t, $CH_2N(CH_3)_2$ in PDMAEMA), 3.39 (s, $CH_3OCH_2CH_2O$ in MPEGMA), and 3.78 (s, CH_2CH_2OCO in MPEGMA).

Formation of Supramolecular Hydrogels

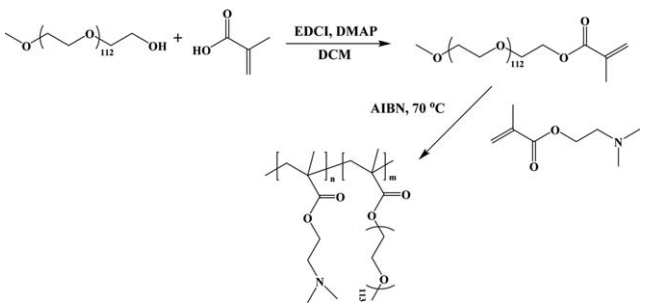
The pH and temperature dual stimuli-responsive hydrogels based on self-assembly were prepared as follows. About 0.4 mL copolymer solution (16.7 wt %) was quickly dropped into 0.8 mL α-CD solution (20.0 wt %) with strongly stirring at room temperature. The mixture rapidly became turbid and turned into gel within a few seconds.

In Vitro Drug Release Study

5-Fu was used as the model drug for confirming the release property. The typical process was as follows. About 0.3 mg 5-Fu was dissolved into 0.8 mL α-CD solution (20.0 wt %) in a glass vial. About 0.4 mL copolymer solution (16.7 wt %) was injected into the vial, mixed strongly and rapidly, and kept overnight for the formation of supramolecular hydrogels. After adding 5.0 mL phosphate buffered solution (PBS) buffer (pH = 7.4, 2.0) as release medium carefully, the vial was inserted into the constant temperature bath oscillator with the oscillation rate of 60 rad/min to test the in vitro release kinetics. About 4.0 mL supernatant was replaced by equal fresh buffer solution at regular intervals. In addition, the concentration of 5-Fu was measured by ultraviolet spectrophotometry. The blank experiment was carried out in the same manner without 5-Fu.

Characterization

Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet 6700 Infrared Spectrophotometer (Thermo Fisher) using KBr sample holder method. ^{1}H NMR spectra were recorded on AVANCE III (Bruker, Switzerland) spectrometer at 500 MHz with $CDCl_3$ as solvent. The number-average molecular weight (M_n), weight-average molecular weight (M_w), and polydispersity index (PDI) of the copolymers were measured by gel permeation chromatography (GPC). GPC was performed on Shimadzu LC-20AD GPC instrument (linear polystyrene calibration) equipped with a refractive index (RI) detector. Tetrahydrofuran (THF) was used as the eluent at a flow rate of 1 mL/min at 25°C. X-ray diffraction (XRD) measurements were obtained on X′ Pert PRO (PANalytical) type X-ray diffractometer using Cu Kα radiation source. The supplied voltage and current were set to 40 kV and 40 mA respectively. The samples were exposed at a scanning rate of $2\theta = 2°$/min over the range from 2° to 50°. The thermostability of the copolymers were characterized by thermogravimetric analyzer (TA Q5000) with a heating rate of 10°C/min from 50°C to 700°C under nitrogen atmosphere. The rheological properties of the supramolecular hydrogels were investigated by a MCR302 rheometer (Anton Paar, Austria) with a parallel plate geometry (diameter: 25 mm). The linear viscoelastic region of hydrogels was determined by dynamic strain sweep experiments at room temperature. Storage modulus (G′) and loss modulus (G″) of the hydrogels, which characterized the gelation process, were measured at 25°C as a function of frequency under oscillatory shear at a strain of 0.1%, which was within the linear viscoelastic region. The temperature responsive of the hydrogels were determined by temperature sweep from 5°C to 70°C at a heating rate of 1°C/min with the same fixed stain $\gamma = 0.1\%$, and a fixed frequency $\omega = 1$ rad/s. Silicone oil with low viscosity of 10 mPa s was used to prevent water evaporating from the hydrogels.



Scheme 1. Synthetic procedure of poly(MPEGMA-*co*-DMAEMA).

RESULTS AND DISCUSSION

The synthetic procedure of the copolymers is presented in Scheme 1. In order to facilely prepare the hydrogels, the long side chain, which means high molecular weight poly(ethylene glycol), should be chosen.

Thus, the macromonomer, poly(ethylene glycol) methyl ether methacrylate (MPEGMA), was synthesized by esterification of methoxypolyethylene glycol (MPEG) and methacrylic acid (MAA). The FT-IR spectrum of the MPEGMA is shown in Figure 1(b). Compared to the spectrum of MPEG [Figure 1(a)], the new absorption peaks at 1718 cm^{-1} and 1651 cm^{-1} were characteristically assigned to the carbonyl band and carbon–carbon double band of methacrylate respectively. Moreover, the ^1H NMR spectrum of MPEGMA is shown in Figure 2(a). The typical peaks of methene protons of methacrylate at 5.69 and 6.20 ppm (peak f) proved the formation of the macromonomer, other signals could be clearly detected. All these demonstrated that the macromonomer was successfully synthesized.

The dual responsive copolymers with MPEGMA and dimethylaminoethyl methacrylate (DMAEMA) were synthesized by free radical copolymerization. According to the FT-IR spectrum shown in Figure 1(c), the wide band at 3100–3700 cm^{-1} was the absorption band of methylamino groups, while the peak at 1282 cm^{-1} was assigned to C–N absorption of DMAEMA units. In addition, the peak at 1729 cm^{-1} corresponded to the carbonyl absorption of methacrylate. The peak assigned to the

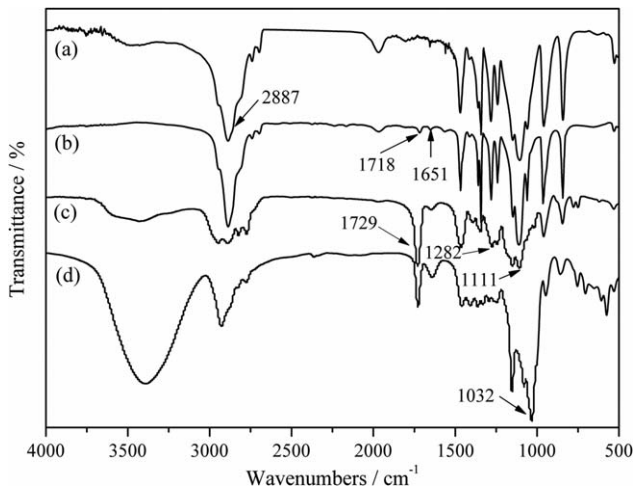


Figure 1. FT-IR spectra of (a) MPEG, (b) MPEGMA, (c) P-3, and (d) H-3.

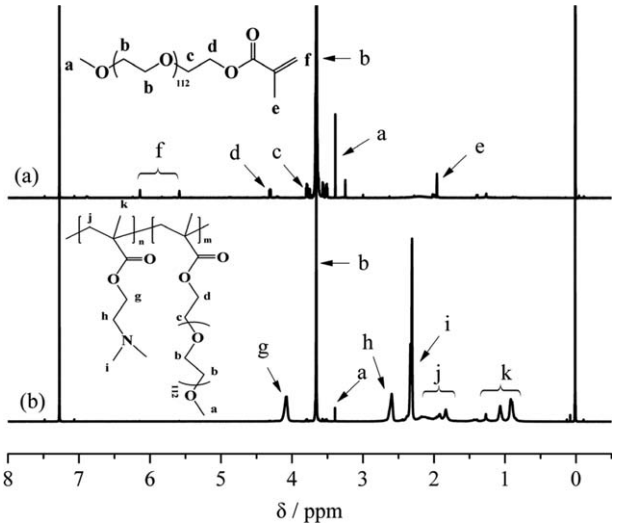


Figure 2. ^1H NMR spectra of (a) MPEGMA and (b) P-3.

ether linkage at 1111 cm^{-1} was important to prove that the MPEG chains existed in the copolymer as a block. The ^1H NMR spectrum of the copolymer is shown in Figure 2(b). All the resonance signals could be attributed to the protons of the copolymer. The virtual molar ratio of DMAEMA and MPEGMA was calculated from ^1H NMR analysis by comparing integration areas of peaks g and b. The results are summarized in Table I. Due to the copolymers without marked end group, the number-average molecular weight and polydispersity index of the copolymers could only be characterized by GPC. As shown in Table I, the number-average molecular weight of all the four samples is very close. That is because the molecular weight of MPEGMA is much higher than DMAEMA, and DMAEMA is more reactive than MPEGMA.

Supramolecular hydrogels can be formed depending on the host-guest inclusion complexation (IC) between α-CD and the side chain of MPEG block in the copolymers in aqueous system. The MPEG block was hydrophilic at room temperature and existed in a random coil conformation in aqueous solutions. After α-CD molecules were added into the copolymer solutions, the MPEG chains were threaded into the cavities of α-CD to form crystalline ICs .The ICs were hydrophobic and they aggregated to form crystalline micro-domains by the strong hydrogen bonds between the adjacent treated α-CD. Through the physical cross-linking of these crystalline microdomains, the supramolecular IC-based hydrogel was formed.[36,37]

The FT-IR spectrum of the lyophilized hydrogel H-3 (prepared by P-3 and α-CD) is shown in Figure 1(d). The broad peak at 3300–3500 cm^{-1} was the characteristic peak of α-CD, while the peak at 1032 cm^{-1} corresponded to the overlap of C–O–C stretching vibration of PEG units and C–O stretching of $–CH_2OH$ group in cyclodextrin as well as the C–H deformation vibration of $–CO–O–CH_2–$ units in MPEGMA and DMAEMA. Compared to Figure 1(c), the significant weakening at 2887 cm^{-1} also improved the formation of pseudopolyrotaxane structure. The thermogravimetric curves of P-3 and the lyophilized hydrogel formed from P-3 and α-CD are shown in

Table I. Results of the Random Copolymers of Poly(MPEGMA-*co*-DMAEMA)

Sample	DMAEMA/MPEGMA (mol/mol)[a]		$M_{n,GPC}$[c] (*10^4g/mol)	M_w/M_n[c]	Conversion (%)[d]
	Feed ratio	Actual ratio[b]			
P-1	80/1	63/1	1.33	1.66	88.6
P-2	85/1	62/1	1.65	1.91	83.1
P-3	90/1	56/1	1.68	2.12	86.2
P-4	95/1	69/1	1.33	1.71	84.1

[a] Reaction condition: [monomer]/[AIBN] = 71/1, polymerization time = 10 hours, polymerization temperature = 70°C, solvent: DMF.
[b] The actual ratio was determined by ^{1}H NMR spectroscopy.
[c] $M_{n,GPC}$ and M_w/M_n were determined by GPC with polystyrene. THF was used as eluent.
[d] Conversion of monomer obtained from gravimetry.

Supporting Information Figure S1. The decomposition process included two stages. The first stage should be ascribed to the decomposition of PEO segments or pseudopolyrotaxane, while the second one should be attributed to the decomposition of PDMAEMA segments. However, the addition of α-CD increased the decomposition temperature of PEO segments slightly, while it decreased the decomposition temperature of PDMAMEA blocks obviously.

The X-ray diffraction (XRD) patterns of α-CD, poly(MPEGMA-*co*-DMAEMA) (P-3), and the matrices of ICs (H-3) formed by α-CD and the copolymer were performed in Figure 3. As shown in Figure 3(a), nonthreaded α-CD cage structure had salient WAXD reflections occurring at $2\theta = 12.0$, 14.4, and 21.7°. Moreover, as shown in Figure 3(b), the diffraction peaks at $2\theta = 19.0$ and 23.0° was assigned to the characteristic crystallization peaks of poly(ethylene glycol) chain segment. Whereas, the ICs showed three intensive peaks located at $2\theta = 11.1$, 13.0, and 19.8°. Among them, the peak at 19.8° was the typical channel-type crystalline structure of PEG. Furthermore, the new peak at $2\theta = 11.1°$ was associated with the microcrystalline areas of α-CD aggregates, which were formed by the strong hydrogen bond interaction between α-CD molecules. This was induced by the formation of ICs and could not be observed in the XRD patterns of pure α-CD and copolymer.[38]

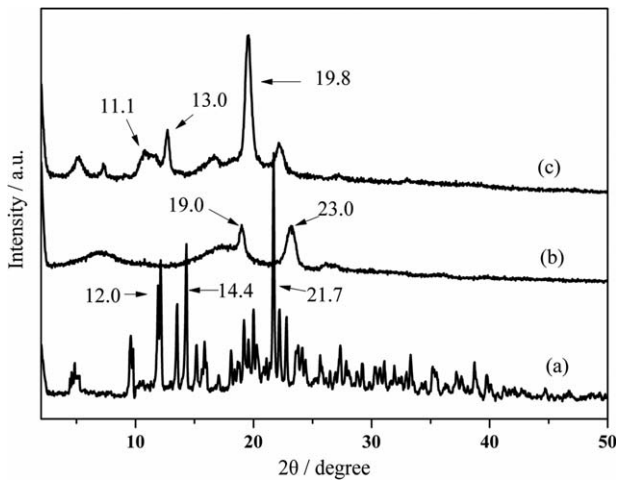


Figure 3. XRD patterns of (a) α-CD (b) P-3, and (c) H-3.

Figure 4 visually indicates the formation of the hydrogel. The solution of the copolymer [Figure 4(a)] eventually became stable physical hydrogel after mixed with α-CD, as shown in Figure 4(b). To get the suitable hydrogel, the concentration of the random copolymer solution must be properly controlled. The gelation time for the four different concentration of the copolymer with α-CD, which P-4 was chosen as the model sample, were studied by rotational rheometer. The mixture of polymer and α-CD solution was placed on a parallel plate rheometer rapidly. By tracking the changes of storage modulus (G′) and loss modulus (G″) with time, we can get their sol-gel transformation kinetics. As shown in Figure 5, the systems were dominated by viscosity at the beginning, with $G'' > G'$. Then we can find a crossing point of G″ and G′, after that G′ increased rapidly became much larger than G″, indicating the formation of the gel network, and the systems were controlled by elasticity. The crossing point of G′ and G″ was defined as the gel point, the corresponding time was the gelation time of the system. We can find from the curves that the gelation time significantly reduced with the increase of the concentration of the copolymer.

The pH and temperature stimuli-responsive properties of the hydrogels were also measured by rotational rheometer (shown in Figures 6 and 7). The thermo-responsive test of the hydrogels, H-3 and H-4, were conducted at a fixed frequency of 1 rad/s with a heating rate of 2°C/min. The results are shown in Figure 6. The storage modulus (G′) of the two samples were risen when the temperature attained 20°C. Until reached to the maximum value around 40°C, G′ decreased rapidly. When

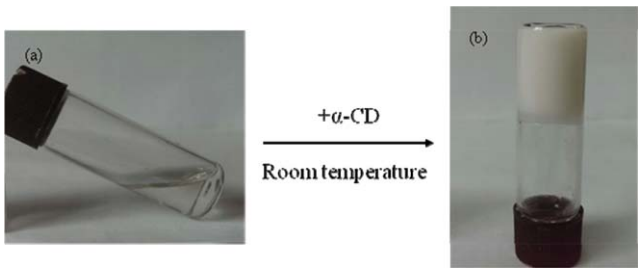


Figure 4. Schematic illustration and the photograph for (a) P-3 solution; and (b) the mixture of P-3 solution and α-CD solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

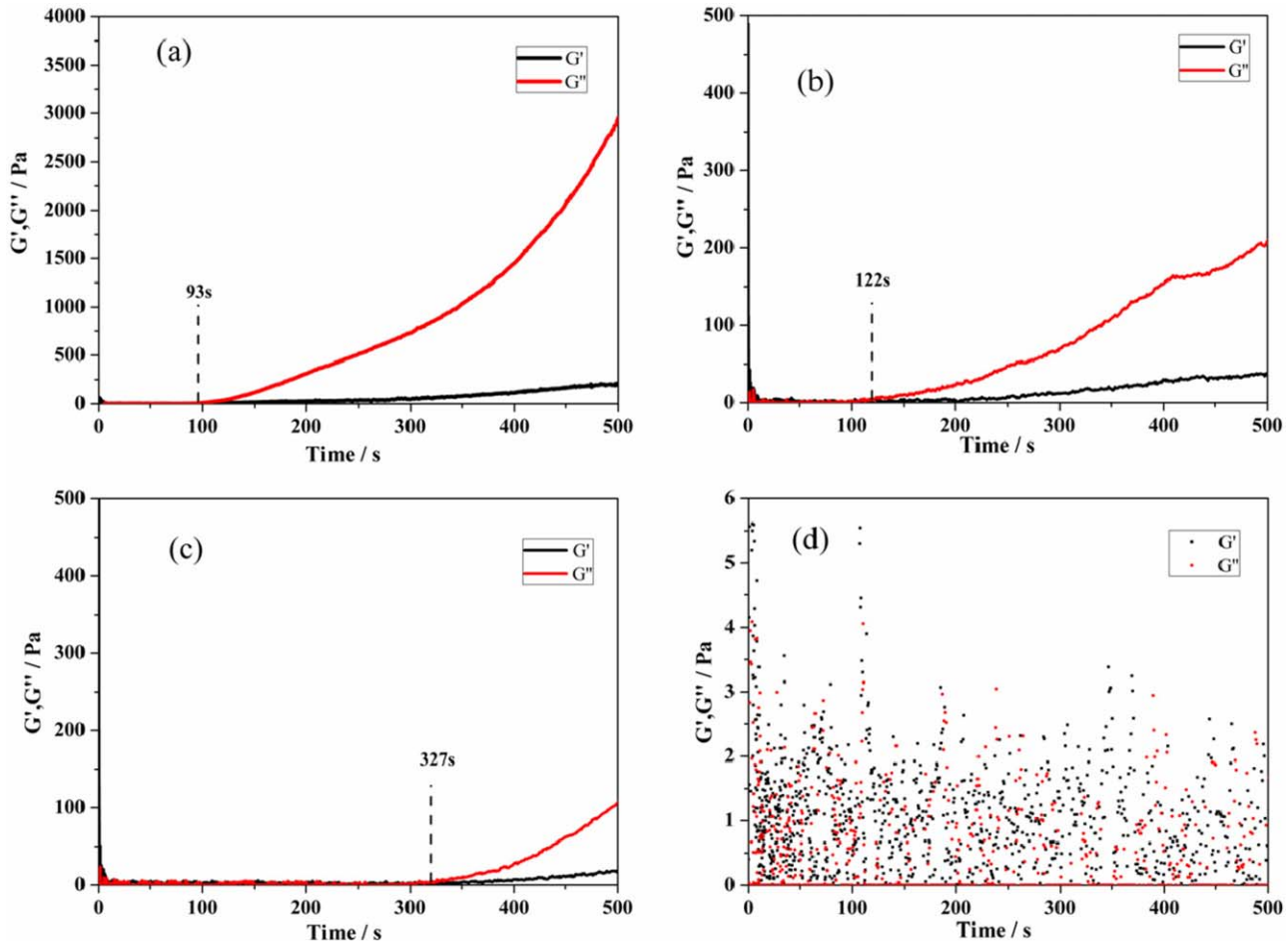


Figure 5. Effect of the concentration of the polymer, P-4, on the gelation time (a) 10 wt %; (b) 5 wt %; (c) 3 wt %; and (d) 0.5 wt %. All the polymer solutions were mixed with 10 wt % α-CD at volume ratio of 1:2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the ambient temperature got about 65°C, the storage modulus became balanced. Thus, the obvious and wide thermo-response interval exceeded 45°C. By contrast, the thermo-sensitivity of the copolymer (P-2 and P-4) and the pseudopolyrotaxane prepared with the copolymer (P-2) and α-CD were characterized by UV transmittance. Supporting Information Figure S2 shows the resulting transmittance curves. The lower critical solution temperature (LCST) regions of the samples P-2 and

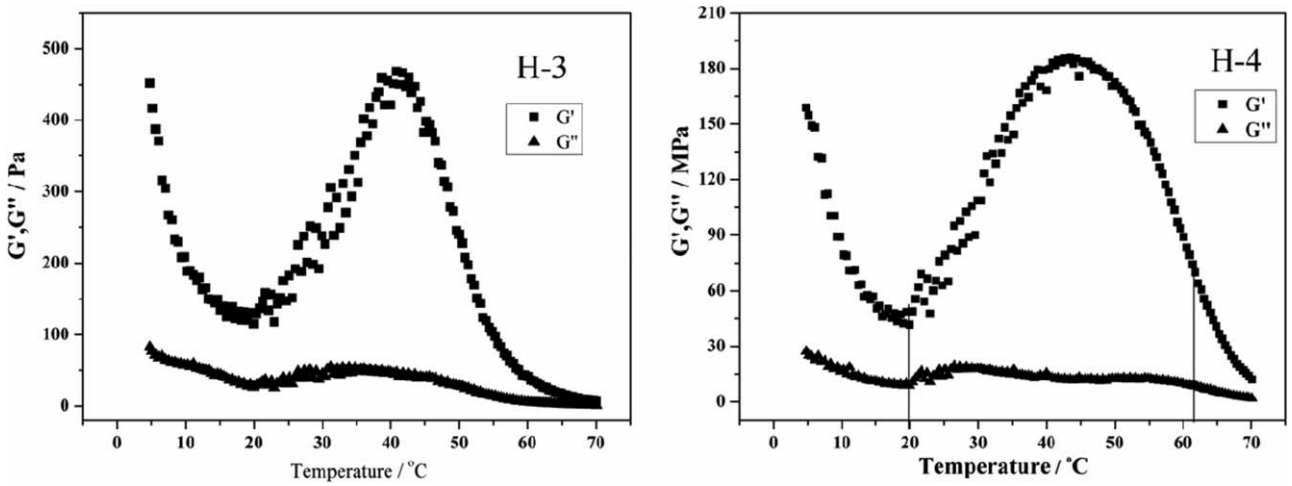


Figure 6. Thermo-response studies with different molar content of DMAEMA (polymer 16.7 wt % and α-CD 20 wt % were mixed at volume ratio of 1:2).

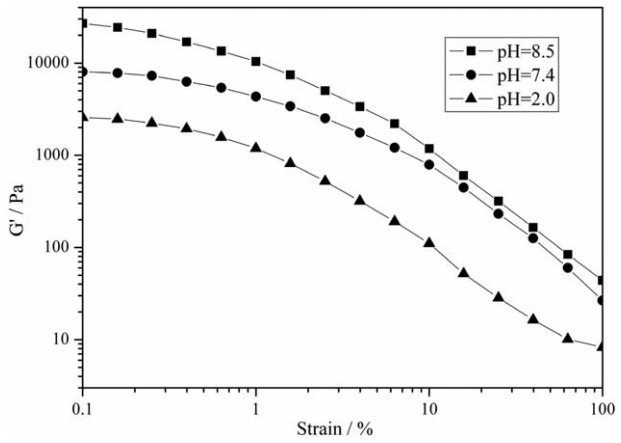


Figure 7. pH-response studies of H-3.

P-4 were from 50°C to 57°C, and from 50°C to 56°C, respectively. While the LCST region of the pseudopolyrotaxane became from 51°C to 60°C, which means the transition of the copolymer was sharper and lower than that of the pseudopolyrotaxane and was similar as that of the hydrogel during heating process. It should be attributed to the changes of hydrogen bonds in these systems. In the polymer solution, the phase transition was considered that the hydrogen-bonding interaction of water molecules and *N,N*-dimethylaminoethyl groups were destroyed at high temperature and the conformation of PDMAEMA chains changed from an expanding shape to a compact coil. While, with the addition of α-CD, the hydrogen-bonding interaction was strengthened, which made the LCST regions became higher and broader. When the hydrogel formed, the hydroxy groups of α-CD were mainly in the microcrystalline areas, and the PDMAEMA segments were similar as these in the copolymer solutions. Thus, the thermo-response of the hydrogel was much similar as the copolymer in aqueous solution.

The storage modulus of the hydrogels with different pH value was characterized by dynamic strain sweep. As shown in Figure 7, the storage modulus (G′) increased in the higher pH

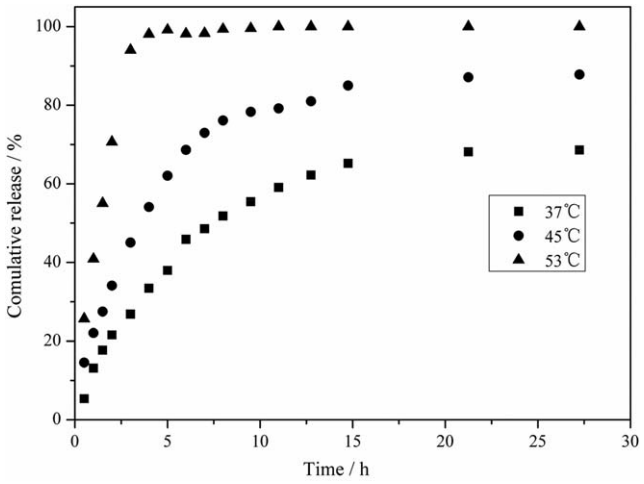


Figure 8. Effect of temperature on the release behaviors of H-3 (pH = 7.4).

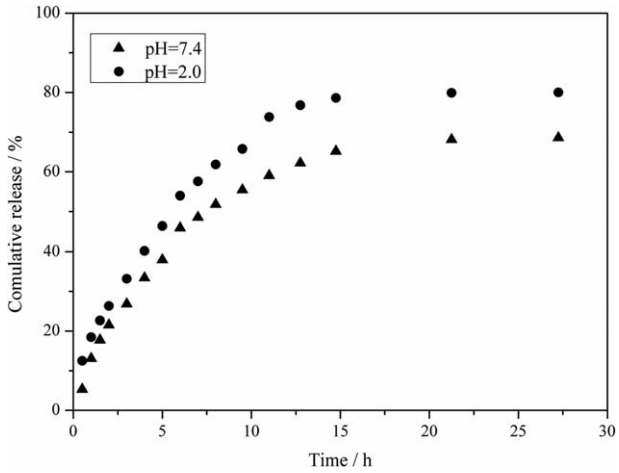


Figure 9. Effect of pH value on the release behaviors of H-3 (temperature = 37°C).

systems due to protonation/deprotonation of *N,N*-dimethylaminoethyl groups in PDMAEMA component. In acidic solution, the PDMAEMA chains were entirely protonated and highly stretched along the radial direction because of the geometrical constraint and the electrostatic repulsion between polymer chains. In addition, this affected the formation of the microcrystalline domain, which means the crosslinking density decrease. Accordingly, in basic environment, G′ increased followed by the growth of the crosslinking density.

Owing to the pH-thermo dual response, biocompatibility, and biodegradability, the IC-based hydrogel could be expected to be used as efficient carriers for drug-controlled release. The anticancer drug 5-fluorouracil (5-Fu) was used as a model water-soluble drug to investigate the feasibility of hydrogels as drug matrixes. Figure 8 shows the time dependency of cumulative 5-Fu release at 37, 45, and 53°C respectively, which were chosen according to the rheology results related to the temperature. The release rate was very fast at 53°C, which may result from the disruption of the hydrogel into aqueous solutions. The temperature had an obvious influence upon the release behavior on 5-Fu. The release rate of 5-Fu at 45°C was higher than that at 37°C. Simultaneously, the release level could reach 87.8% at 45°C, while it was only 68.6% at 37°C, until the release reached the balance after 27 hours. This behavior was mainly due to the thermo-response of the hydrogel, which lead to the change of hydrophilicity inside the hydrogel. Furthermore, the other reason was the hydrogel showed more unstable at higher temperature, which means more α-CD was dissociated from the side chains of PMPEGMA at 43°C than at 37°C.

Figure 9 shows the release behaviors under the conditions of pH 2.0 and 7.4 at 37°C. After 27 hours, the accumulated ratio of drug release reached 80.0% at pH 2.0 and 68.6% at pH 7.4, which means the release rate for 5-Fu from the hydrogel was faster in acid medium. Combined with the rheology results of the hydrogel with different pH values, the release rate of 5-Fu should be changed according to the change of conformation of PDMAEMA block and network formation. In acidic condition, the protonated PDMAEMA block presented expanding

conformation and the formation of the hydrogel became much weaker. Thus, 5-Fu could diffuse out from the hydrogel easily. Furthermore, the samples showed no significant burst release phenomenon in both acidic and neutral conditions. All these demonstrated that the surrounding pH values could effectively control the release rate from the ICs-based hydrogel. The investigation of model drug 5-Fu release indicted that this hydrogel could be expected to become an intelligent carrier in controllable drug release system.

CONCLUSIONS

In summary, a series of pH-thermo dual sensitive hydrogels, which were fabricated via inclusion complexation with α-cyclodextrin (α-CD) and the random copolymers poly(-MPEGMA-*co*-DMAEMA), were prepared successfully. The structures of the copolymers and the hydrogels were confirmed clearly. The rheology behaviors of the hydrogels with the stimulative responsibility of pH and temperature were investigated. The release of model drug could be effectively controlled by altering the temperature and the pH values of the environment. All these indicated that this kind of hydrogels could be expected to be utilized in drug delivery and controllable release.

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