pH–Temperature Responsive Poly(HPA-Co-AMHS) Hydrogel as A Potential Drug-Release Carrier

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ABSTRACT: In this study, a novel pH–temperature-responsive copolymer was first synthesized by the radical copolymerization between HPA (2-hydroxypropyl acrylate and 2-hydroxyisopropyl acrylate) and AMHS (aminoethyl methacrylate hydrochloric salt). The molecular structure of the corresponding copolymer has been confirmed by ^{1}H-NMR and FTIR. The lower critical solution temperature of the resulting copolymer exhibited a considerable dependence upon the ratio of monomers and pH value in the medium. On the basis of the copolymer, a hydrogel as drug release carrier was prepared via the introduction of a crosslinker, *N*,*N*′-methylenebisacrylamide. The swelling behaviors of hydrogel in the different pH value, temperature, and NaCl concentration have indicated that the hydrogel showed a remarkable phase transition at 31.5°C. The swelling ratio was increased with an increasing of pH value, especially in the greater pH values. By the use of caffeine as a model drug, we investigated the caffeine-controlled release from hydrogel systematically as a function of pH value, temperature, and crosslinker content. The caffeine release was sensitive to the temperature. Only 55% caffeine was released from the hydrogel at room temperature, whereas ~ 92% caffeine diffused into the medium at 37°C. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 114: 176–184, 2009

Key words: pH–temperature responsive hydrogel; lower critical solution temperature (LCST); drug release; swelling

INTRODUCTION

Hydrogel, as a promising material, is defined as three-dimensional network of hydrophilic polymers that do not dissolve but can swell in water.[1] There are some hydrogels that undergo a dramatic change in their network structure, swelling behaviors, and mechanical strength in response to the external stimuli such as temperature, pH value, electric field, and ion strength.[2–5] These so-called responsive hydrogel or intelligent materials have drawn considerable interests in the design of novel drug-release system,[6–9] artificial organs,[10] as well as gene carriers.[11]

In recent years, the most extensive investigation about responsive hydrogel has been focused on the drug-release system and some applications of biomedical materials. Generally speaking, on the basis of the pH–temperature-sensitive polymers, the preparation of hydrogels often is performed by the homopolymerization in the presence of a crosslinker, the copolymerization with other monomers, or the introduction of some natural products, including chitosan, alginate, and starch. For example, Zhang et al.[12] described the synthesis of a novel thermo-sensitive copolymer composed of *N*-isopropylacrylamide, ε-caprolactone, and 2-hydroxyethyl methacrylate and found an improvement in the drug release behaviors due to the special structure of the copolymer. In poly(*N*-isopropylacrylamide) and cyclodextrin-grafted polyethylenimine system, the prolonged release time of propanolol from the polymeric gel has been observed because of the formation of inclusion complex between drug molecule and cyclodextrin groups.[13] Also, Gao et al.[14] combined the natural chitosan with poly (*N*-isopropylacrylamide) to get a pH–temperature responsive copolymer, and the results showed that the copolymer seemed to be a promising candidate for the drug controlled-release system.

For the temperature or pH–temperature-responsive hydrogels, an appropriate balance between hydrophobicity and hydrophilicity in polymer chains is required for the reversible phase transition to occur.[15] Moreover, the promising hydrogels with different lower critical solution temperature (LCSTs), especially close to body temperature, can be obtained by modulating hydrophobicity and hydrophilicity of the repeating units in polymer chain. No

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thermo-responsiveness was observed in the aqueous solution of the homopolymer from both HPA and AMHS under our experiment conditions. Meanwhile, the copolymer between HPA and AMHS, as a potential temperature-responsive polymer, has not yet been reported. In the copolymerization of HPA and AMHS, the balance between hydrophobicity and hydrophilicity on the copolymer chain can be effectively controlled by varying the monomer ratio. Here, the HPA monomer units on the copolymer chains serve as the hydrophobic moieties and AMHS units function as the hydrophilic groups. So, the corresponding copolymer and its hydrogel may theoretically exhibit the temperature-responsive property. Because AMHS is a kind of weak-base/strong-acid salt, the incorporation of AMHS into the macromolecular chain may produce a copolymer which is also responsive to the pH and inorganic ions stimuli. Furthermore, such a copolymer and its hydrogel are expected to use as a new precursor in exploiting the drug controlled-release carrier or the pH–temperature switching device.

In this work, we tried to combine HPA with AMHS to synthesize a novel temperature-sensitive copolymer and its hydrogel as a potential drug release carrier. The molecular structures of the resulting copolymer and the monomer were confirmed by ^{1}H-NMR and FTIR measurements. By varying the ratio of HPA to AMHS, the hydrophilic and hydrophobic balance of the resulting copolymer was adjusted. When the ratio of HPA to AMHS was fixed at 2, 3, and 4, the LCSTs of copolymers in the aqueous solution were found to be 36.5°C, 28.2°C, and 17.8°C, respectively. To illustrate the pH–temperature sensitivity of hydrogels, the swelling ratio of hydrogel was evaluated as a function of pH value, ion strength and temperature. Using caffeine as a model drug, we found that the copolymer hydrogels have shown a good pH–temperature release-controlled behavior, suggesting a potential application of the resulting copolymer as the drug carrier.

EXPERIMENTAL

Materials

2-Aminoethanol, propylene oxide, and benzoyl chloride were purchased from Dongfang Health Materials Factory (Tianjin, China) and Huadong Chemical Factory (Tianjin, China), respectively. Acrylic acid and methacrylic acid were purified by vacuum distillation. HPA were synthesized from propylene oxide and acrylic acid in our investigation. The molar ratio of 2-hydroxypropyl acrylate and 2-hydroxyisopropyl acrylate in HPA was 1.7 : 1. Potassium persulfate (KPS) was recrystallized from water before use. Phosphate-buffered saline (PBS) with different pH value was made according to the standard method, and the ion strength in PBS solution was adjusted to the same value ($I = 0.6$) with NaCl. Caffeine from tea was recrystallized twice with acetone and petroleum ether. The crosslinker, *N*,*N*-methylenebisacrylamide (MBA) and other chemicals were analytical grade and used without any further treatment.

Measurements

Fourier-transform infrared spectrum (FTIR) was recorded on a Vector22 FTIR spectrophotometer with KBr pellet in the range of 400–4000 cm^{-1}. ^{1}H-NMR spectra of the monomers and the corresponding copolymers were measured with the use of a Bruker Avance-400 (400 MHz). The thermo-sensitivities of the copolymer in the solution were detected by monitoring the optical transmittance at 500 nm on a Shimadzu UV-120-02 spectrophotometer with a thermally controlled cuvette holder. The temperature at which the transmittance of the copolymer solution decreased to half of the initial value during heating was defined as LCST for the copolymers in our study.

Synthesis of HPA and AMHS

2-Aminoethanol hydrochloride was prepared via the neutralization of 2-aminoethanol with the calculated amount of hydrochloride solution and complete drying under vacuum at 70°C. Methacryloyl chloride was synthesized by reacting methacrylic acid with benzoyl chloride according to the literature.[16] The mixture of 2-aminoethanol hydrochloride and methacryloyl chloride (an excess of 10%) was heated up to 75°C and maintained for 2 h. Then, it was cooled and dissolved in tetrahydrofuran. The solution of the crude AMHS was poured into ethyl ether to remove the unreacted methacryloyl chloride. The pure AMHS, a white powder, was obtained after filtration with a yield of 81%.

FTIR (cm^{-1}): 3381, 3044 (broad v_{N-H}), 2974–2887 (strong v_{C-H}), 1720 (strong $v_{C=O}$), 1622 (weak $\nu_{-HC=CH-}$), 1494 (median δ_{N-H}), 1163 (strong $v_{O-C=O}$), 1064 (strong v_{C-O-C}).

Then, 0.2 mol acrylic acid, 0.28 mol propylene oxide, a trace amount of CuCl as inhibitor, and pyridine as catalyst were added into the round flask with a condenser. The mixture was heated to 90°C and kept for 4 h. Finally, the isomers (HPA) containing 2-hydroxypropyl acrylate and 2-hydroxyisopropyl acrylate were obtained after vacuum distillation with a yield of 63%. From ^{1}H-NMR measurement, HPA was composed of pure 2-hydroxypropyl acrylate and

2-hydroxyisopropyl acrylate, and the molar ratio of two isomers was about 1.7 : 1.

FTIR (cm^{-1}): 3420 (broad ν_{O-H}), 2977–2885 (strong ν_{C-H}), 1720 (strong $\nu_{C=O}$), 1617 (weak $\nu_{-HC=CH-}$), 1194 (strong $\nu_{O-C=O}$), 1080 (strong ν_{C-O-C}).

Synthesis of the copolymers from HPA and AMHS

A series of the copolymers with various feed ratios of HPA to AMHS were synthesized by the conventional radical copolymerization using $K_2S_2O_8$-$NaHSO_3$ as the redox initiator. In the polymerization, the molar ratio of monomers to initiator was fixed at 100 : 1, and the total monomer concentration was 0.3 mol/L in the deionized water. The Schlenk tube was added with the required amount of $K_2S_2O_8$-$NaHSO_3$ initiator, HPA, AMHS and deionized water. After degassing with dry nitrogen, the reaction mixture was magnetically stirred for 10 h at room temperature. Finally, the resulting mixture was precipitated into cold sodium chloride solution to remove the residual HPA, AMHS and un-reacted initiator. After several washing with hot water, the titled copolymer was obtained via filtration and dried under vacuum at 60°C for 48 h. When the ratio of HPA to AMHS was fixed at 1, 2, 3, and 4, the corresponding copolymers were designated as PHA1, PHA2, PHA3, and PHA4, respectively.

Preparation of copolymer hydrogel

The caffeine-loaded copolymer hydrogel (CLCH) in this investigation was prepared according to the following procedure.[17,18] Herein, caffeine was selected as a model drug and MBA was used as crosslinker. In a tube, the required amount of MBA, 0.452 g of HPA, and 0.211 g of AMHS were dissolved in 10 mL of deionized water. The initiator, $K_2S_2O_8$/$NaHSO_3$ and caffeine were fixed at 1.0% and 5.0% with respect to the weight of monomers. The solution was bubbled with nitrogen gas for 3 min in order to remove oxygen gas. Then, the tube was maintained at room temperature for 8 h. After the polymerization was completed, the drug-loaded gels were pushed out. According to the aforementioned procedure, the caffeine-free hydrogel used for swelling study was synthesized by the same method.

Swelling behavior measurement

To characterize the swelling behaviors of hydrogel, the swelling tests were performed at various pH value, NaCl concentration (ion strength), and temperature. The hydrogels were immersed in 20 mL of medium at the predetermined temperature, pH value, and NaCl concentration for 24 h to get the swelling equilibrium. After reaching the swelling equilibrium, the wet hydrogel was taken out. Then, the surface water on the wet hydrogel was removed by blotting with filter paper, and the weight of wet hydrogel was determined. The swelling ratio (SR) for the hydrogel was calculated as the following equation.

$$SR = (W_w - W_d)/W_d$$

Here, W_w and W_d are designated as the weight of wet hydrogel and dried hydrogel, respectively.

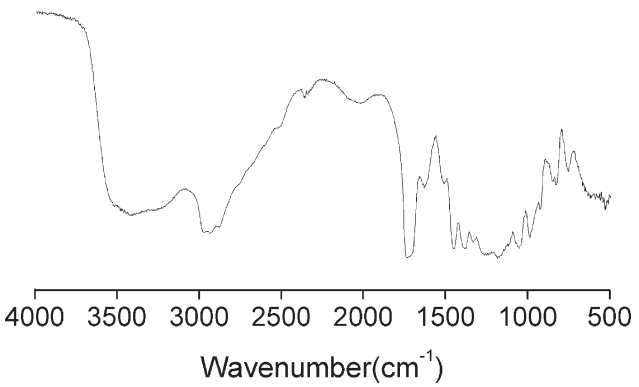

Figure 1 FTIR spectrum of PHA4.

Drug release investigation

The CLCH were immersed into 30 mL of deionized water or the buffer solution with the same ion strength in a separate beaker. At predetermined time intervals, 3 mL of caffeine solution was extracted from the release system. At the same time, 3 mL of fresh release medium with the same ion strength and pH was added into the beaker to maintain the fixed volume. The caffeine released from the system was measured by the absorption at 272 nm using a UV spectrometer. The caffeine concentration was calculated according to the calibration curve constructed from a series of caffeine solution with standard concentration.

RESULTS AND DISCUSSION

Characterization of the copolymer from HPA and AMHS

To confirm the structure of the copolymer from HPA and AMHS, the FTIR spectrum and the ^{1}H-NMR spectrum of PHA4 was recorded. As shown in Figure 1, the broad peaks at about 3600 and 3350 cm^{-1} in the spectrum of PHA4 implied the presence of the —OH and —NH_2·HCl groups. Also, the strong characteristic absorption at 1735.8 cm^{-1} was observed, which corresponded to the characteristics stretching vibration of C=O group from HPA and

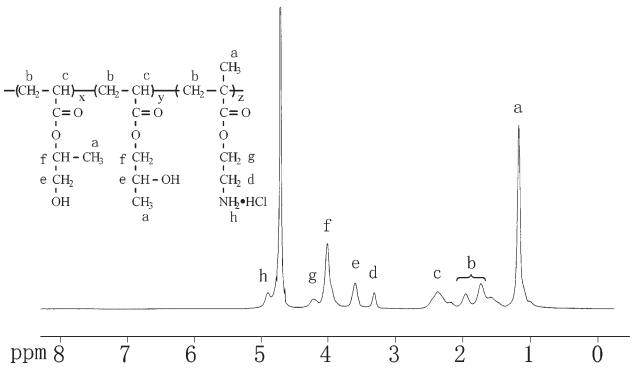

Figure 2 ^{1}H-NMR spectrum of PHA4 using D_2O as solvent.

AMHS repeating units. The absorption bands at 1176.2 cm^{-1} could be ascribed to the C—O—C stretching vibration. In the ^{1}H-NMR spectrum of PHA4 shown in Figure 2, the main peaks of the copolymer PHA4 were found. For example, the peaks at 4.06 and 3.61 ppm were ascribed to methylene and methine groups in [—O*C*H_2*C*H(OH)CH_3] repeating unit. The chemical shift of methylene and methine groups in [—O*C*H(CH_3)*C*H_2(OH)] repeating unit was also observed at 3.61 and 4.06 ppm due to the similar structure. The peaks for the two methylene groups close to oxygen and nitrogen atom [—O*C*H_2*C*$H_2$$NH_2$·HCl] in AMHS unit were recorded at 4.21 and 3.32 ppm, respectively. The peak at 4.9 ppm may be attributed to the existence of —NH_2 groups in the AMHS repeating unit. It is necessary to state that no peaks for the active hydrogen atoms on —OH group were observed in the measurement using D_2O as solvent.

Investigation of pH–temperature sensitivity for copolymer

The temperature-responsiveness of the titled copolymer was confirmed by monitoring transmittance in a 3% (wt) aqueous solution as a function of temperature. As usual, the temperature at which the transmittance decreased to half of the initial value was defined as the LCST. As shown in Figure 3, the LCSTs of copolymer were 36.5°C, 28.2°C, and 17.8°C, respectively, when the ratios of HPA to AMHS were fixed at 2, 3, and 4. This result suggested that the LCST of copolymer was increased with increasing content of hydrophilic AMHS units. Compared with AMHS units, HPA factually exhibits a slight hydrophobicity to some extent in the copolymer chain. The similar tendency has been reported that the LCST of *N*-isopropylacrylamides-based copolymer was increased by the incorporation of more hydrophilic acrylic acid.[19] In general, the responsiveness of polymeric materials depends on a delicate balance between two interactions in aqueous solution. The two interactions in nature related to the hydrophobic interaction among polymers and the hydrophilic interaction (hydrogen bonding) between hydrophilic groups on polymer and water molecules.[15] The changing HPA/AMHS ratio means a modulation of hydrophobic/hydrophilic interaction, leading to formation of the copolymer with different LCST values. LCST values of the copolymers prepared in this study, especially for PHA2, are very close to the physiological temperature. Accordingly, these copolymers are suitable to the application in the biomedical fields. In addition, the more sensitive responsivity was found with increasing the hydrophobic HPA content in copolymer chains. The temperature span in the phase transition for PHA2 was about 28°C (from 27 to 55°C), whereas the range during the phase transition for PHA4 reached about 12°C (from 13 to 25°C), respectively.

Figure 4 has demonstrated the effect of pH on LCST of PHA3 copolymer. Herein, NaOH and HCl were used as a pH-adjustor to modulate the corresponding pH value in the medium. From these figures, it is seen that the phase transition behaviors are considerably dependent on the pH value in the solution, namely, increasing pH leads to greater LCST value in the range of pH 2.1–7.2. This effect is related to the dissociate behaviors of the aminoethyl hydrochloric salt moiety on AMHS units. The ionization degree of aminoethyl hydrochloric salt was increased with increasing pH value due to its weak-base/strong-acid salt nature. Therefore, the hydrophilicity of copolymer increases with pH value, resulting in a higher LCST value. This result is consistent with the reported phase transition behaviors of poly(*N*,*N*-diethylacrylamide-*co*-methacrylic acid) in different pH solution.[20] At too high pH, however,

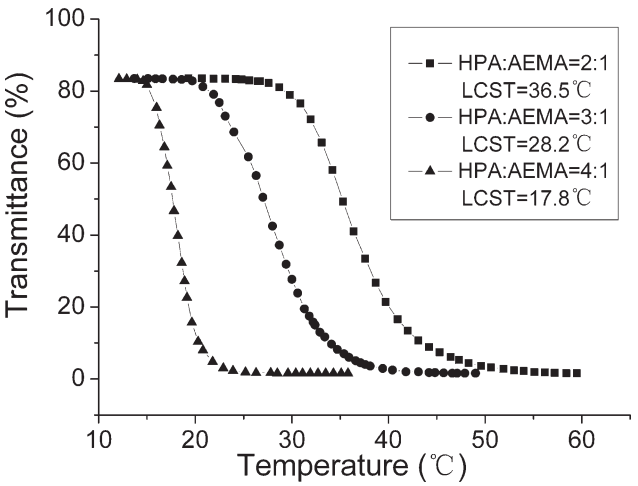

Figure 3 Transmittance as a function of temperature for the copolymers in aqueous solution solvent: deionized water; pH = 6.5; wavelength = 500 nm.

the LCST sharply decreased with increasing pH value. For instance, when pH values were adjusted to 7.2, 8.8, and 10.3, the LCSTs were 20.6°C, 18.0°C, and 15.0°C, respectively. In the alkaline medium, AMHS units were converted to the amino form, and some inorganic salts simultaneously formed, such as NaCl in this system. NaCl served as "salting-out" effect and induced LCST to decrease.[21] The "salting-out" effect from NaCl overtook the action of the dissociate behaviors of AMHS in higher pH range. Therefore, the higher pH value in the medium is, the more NaCl formed in the system is, resulting in the lower LCST. This observation is in a good agreement with the effect of NaCl and KCl on the LCST of poly(organophosphazenes) with methoxypoly (ethylene glycol) and amino acid esters as side groups.[22] In conclusion, the sensitivity of copolymer to pH value is originated from the following fact that AMHS unit belongs to a kind of organic amino hydrochloric salt.

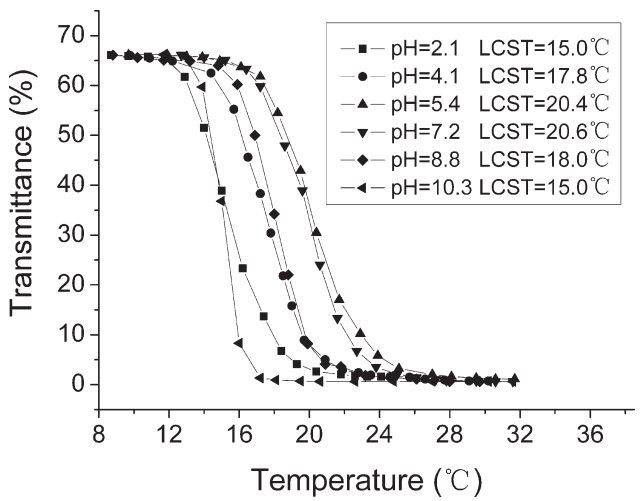

Figure 4 Effect of pH value on LCST for PHA4 in aqueous solution solvent: deionized water; wavelength = 500 nm.

Swelling behavior of hydrogel

Effect of ion strength on the swelling ratio of hydrogel

The swelling behaviors of the hydrogel are considered as an important factor, influencing the drug-releasing rate and the cumulative drug release. Considering the practical application of hydrogel, the study on swelling behavior of hydrogel in salt solution seems to be more significant. In this investigation, the aqueous medium with different ion strength value was adjusted by adding the various amount of NaCl. The Figure 5 has shown the effect of ion strength on the swelling ratio of the prepared hydrogel. It can be seen that the swelling ratio

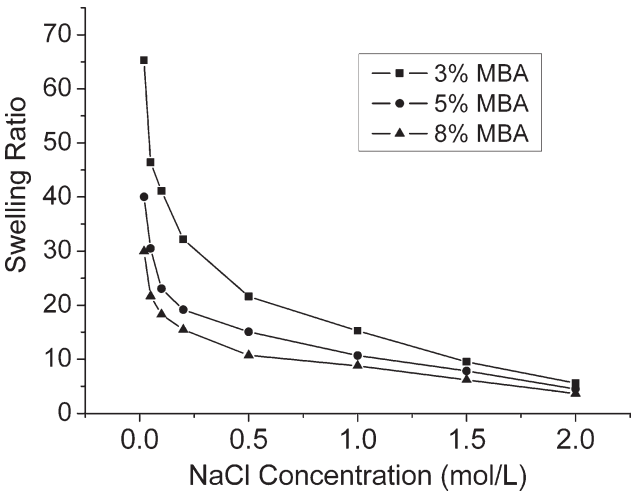

Figure 5 Effect of ion strength on the swelling ratio of hydrogel. Time = 7 h; temperature = 18.0°C; pH = 6.5.

exhibited a considerable dependence on the ion strength, especially in the lower ion strength range. With increasing the ion strength, the swelling ratio of hydrogel decreased sharply. For instance, when NaCl concentrations were controlled at 0.02, 0.05, 0.10, and 0.20 mol/L, The swelling ratio for the hydrogel with 5% MBA was 40.0, 30.5, 23.1, and 19.2, respectively. In the hydrogel of PNIPA,[23] and PNEPAM,[24] the similar observation that the swelling ratio decreased with an increase of ion strength was also found. On the other hand, the swelling ratio was not significantly sensitive to the ion strength at greater NaCl concentration. NaCl in the medium, as a "salt-out" agent, factually decrease the H-bonding (hydrophilic interaction) between water molecules and polymeric chains, leading to a decrease of swelling ratio.

Effect of temperature on the swelling ratio of hydrogel

For the hydrogel used as drug-releasing system, the swelling behavior in the different temperature is an important parameter to evaluate a hydrogel. As Figure 6 shown, the swelling behaviors for the three hydrogels with 3, 5, and 8% MBA have been investigated as temperature was changed. For all hydrogels, a remarkable change in the swelling ratio occurred at about 31.5°C, suggesting their phase transition temperatures (LCST). Here, the sample with 3% MBA was not suitable to the drug-releasing carrier because of its poor mechanical property, although it has shown a good sensitivity to the temperature. The average swelling ratios for the samples with 5 and 8% MBA were about 130 and 70 in the range of 24–31°C, whereas the swelling ratio decreased to about 85 and 60 greater than the LCST, respectively. The sensitivity of hydrogel to the

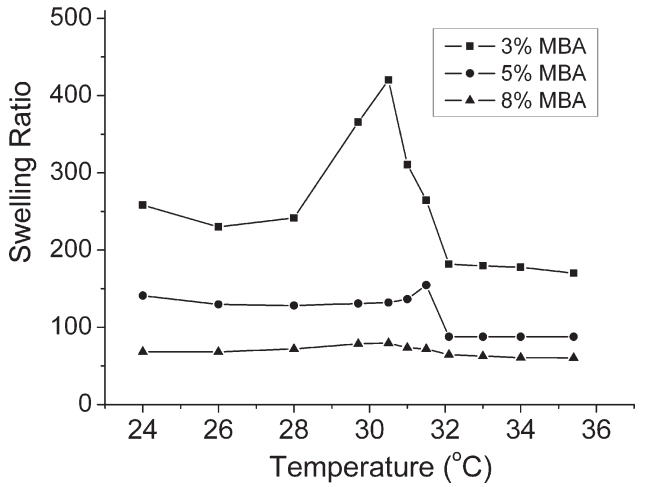

Figure 6 Effect of temperature on the swelling ratio of hydrogel. Time = 7 h; medium: deionized water; pH = 6.5.

temperature can be explained as the following facts. There is a hydrophilic/hydrophobic balance in the hydrogel network because of the existence of hydrophilic —OH/—NH_2 groups and hydrophobic —CH_3/—CH_2/—CH groups. At temperatures less than LCST, the polymeric chains swell well in water owing to the H-bonding interaction between water and the hydrophilic groups. As the temperature was increased, the H-bonding weakened and the interaction among the hydrophobic groups began to act as a dominant role. Therefore, the hydrogel network collapsed at greater temperatures, and the entrapped water molecules were squeezed out to the medium, which finally led to the decrease of swelling ratio. In addition, the equilibrium swelling ratio decreased with an increase of MBA content at the same temperature. The higher MBA content allowed the polymeric chains to outspread in a limited space due to the higher crosslinking density. Aiming at the better drug release and good mechanical nature, an appropriate MBA content should be required in the preparation of hydrogel.

Effect of pH value on the swelling ratio of hydrogel

Figure 7 illustrates the effect of pH value in the medium on the swelling ratio for the hydrogel. Because the swelling ratio was of dependence on the ion strength, the medium used for the pH-swelling ratio investigation were adjusted to the same ion strength (I = 0.6). In the present work, the pH value in the external buffer solution was varied in the range of 1.69–12.11. As shown in Figure 7, the swelling ratio was significantly influenced by changing pH value, especially in the alkaline medium. From pH 1.69 to 4.83, the swelling ratio decreased slightly with an increase of pH value. At acidic condition, amine groups on the AMHS repeating unit are protonated as the format of —NH_3^+. The electrostatic repulsion among —NH_3^+ groups caused the polymeric chain to outspread to some extent. As a result, the amount of —NH_3^+ inside the hydrogel decreased along with increasing pH value, leading to a decrease of swelling ratio. In the *N*-coboxyehtyl chitosan/poly(-HEMA)[1], and chitosan-EPI hydrogels,[25] the swelling ratio also increased with a decrease of pH value, especially for the hydrogel with high-content electrostatic segment. In the range of pH = 7–10, no obvious effect of pH value on the swelling ratio was seen at the same ion strength. Beyond pH = 10, however, the swelling behaviors had a considerable dependence on pH value in the medium. When pH was adjusted to 10.15, 11.10, and 12.11, the swelling ratio of hydrogel with 5% MBA reaches to 16, 19 and 39, respectively. All —NH_2·HCl segments in AMHS repeating units reacted with OH^- to form —NH_2 groups. The hydrophilic H-bondings of —NH_2 group between water molecules were constructed, which makes for an increase of hydrophilicity of hydrogels. So, the swelling ratio of hydrogel was increased with increasing pH value. Seen from this case, it seems that the hydrophilic H-bonding of —NH_2 groups acted as the main function in determining swelling ratio, compared with the electrostatic repulsion.

Caffeine release investigation

Effect of temperature on caffeine release

In general, the drug release character from hydrogel is related to the swelling behaviors of polymeric hydrogel in the medium. Besides, the various interactions between drug molecules and polymeric

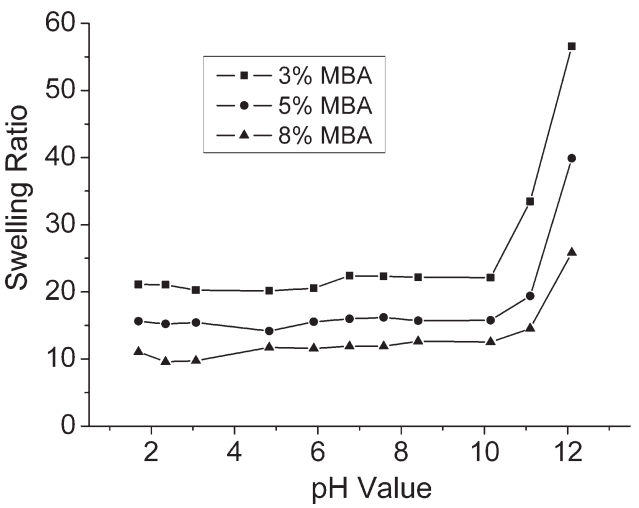

Figure 7 Effect of pH value on the swelling ratio of hydrogel. Time = 7 h; medium: PBS; temperature = 18.0°C.

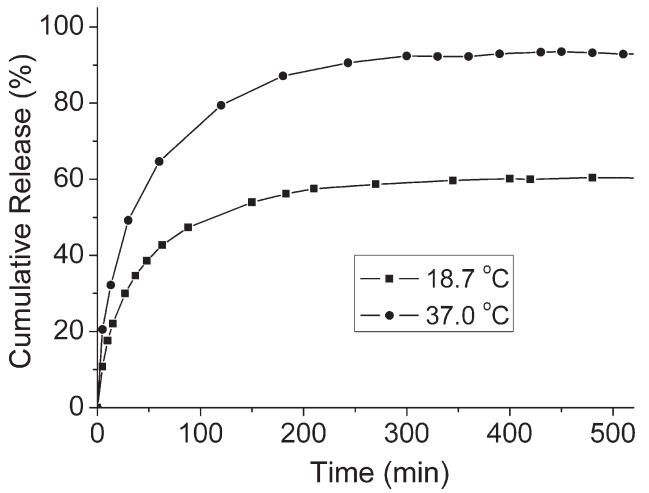

Figure 8 Cumulative release of caffeine from copolymeric hydrogels at various temperatures. Medium: deionized water; pH = 6.5; MBA = 5%.

network, water molecules also play a key role in the drug release behaviors.[26] To investigate the effect of temperature on caffeine release behaviors, the release experiments were performed at 18.7°C (room temperature), and 37.0°C in deionized water (pH = 6.5).

From Figure 8, it is seen that the greater temperature leads to both rapid release and higher cumulative release. For example, the cumulative caffeine release reached about 56%, and 91%, respectively, after 200-min release, when the temperature was fixed at 18.7°C and 37°C. The caffeine release behaviors in this system can be explained with the following facts. Firstly, when the ratio of HPA to AMHS in the CLCH was 2 : 1, the phase transition temperature for hydrogel was about 31.5°C according to Figure 6. As well known, the copolymer chains were solvated with water molecules and outspreaded to some extent at the temperature less than LCST, whereas they became collapsed/aggregated near or greater than LCST. Thus, as the temperature approached to its LCST, the effective density of CLCH network is remarkably decreased because of the precipitation of copolymer chains. The porous size of the channel for caffeine release would be enlarged via aggregation of copolymer chains as temperature increased. Accordingly, the higher temperature (37°C) led to the rapid rate of caffeine release and higher cumulative release compared to the room temperature (18.7°C). Second, H-bonding interaction is formed between —N=, —C=O groups in caffeine with ester and hydroxyl groups on copolymer chains. And when the temperature increases, the H-bonding interactions between them will become weak or disappear. So, caffeine-releasing rate at 37°C is faster than that at 18.7°C. The similar results about effect of temperature on the release rate were found in the other drug release systems.[13,27,28] Thirdly, drug release from hydrogels to outside medium is also a molecular diffusion progress. At the greater temperatures, the molecular movement become intensive, which cause the molecule to effectively diffuse. In this case, the rate of caffeine diffusion from gel to water is quickened at the higher temperature, leading to the rapid release rate and high cumulative release at 37°C.

Effect of crosslinker content on caffeine release

Figure 9 has shown the effect of crosslinker content on caffeine release behaviors in deionized water at room temperature. Both the rate and cumulative caffeine release are increased as the crosslinker content increased in CLCH. For example, when the MBA content was controlled at 8% and 5%, the cumulative release reached about 78% and 56%, within 150 min, respectively. Apparently, the lower MBA content certainly resulted in a lower crosslinking density in CLCH. As Figure 6 shown, the swelling ratio of CLCH reached about 70 and 140 in the deionized water at room temperature as MBA was fixed at 8% and 5%. Below the LCST value, the polymeric chain were solvated by water molecules and outspreaded in hydrogel. In the hydrogel with larger swelling ratio, the larger porous size in hydrogel seems to be propitious to the rapid caffeine release. The experimental results in this study, however, showed that the lower caffeine release was observed in the larger SR hydrogel with 5% MBA. This observation suggested diffusion-controlled release behavior existed in this hydrogel system. In other words, the resistance from hydrogel network in caffeine release seems to be a main factor in the case. During the drug release, caffeine has to overcome the

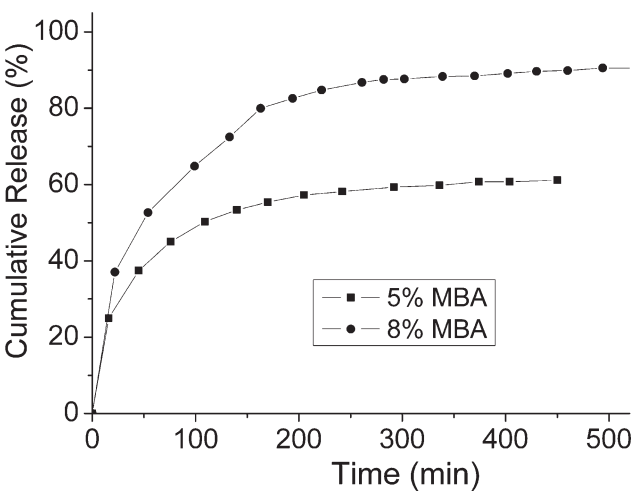

Figure 9 Cumulative release of caffeine from copolymeric hydrogels in different MBA content. Medium: deionized water; pH = 6.5; temperature = 18.0°C.

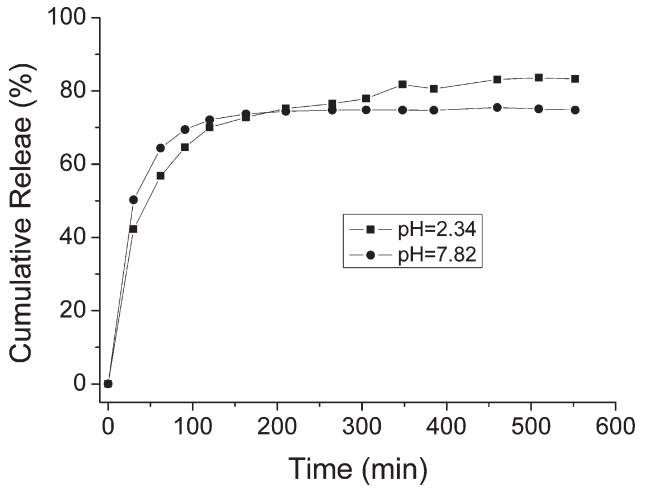

Figure 10 Cumulative release of caffeine from copolymeric hydrogels in various pH medium. Medium: PBS; temperature = 18.0°C; MBA = 5%.

intermolecular interaction such as H-bonding, Vander Walls forces and so on. As a result, the larger SR of hydrogel means a longer path and more hinders for caffeine to encounter, leading to the lower release in hydrogel with 5% MBA. In this case, a typical diffusion-controlled release was observed.

Effect of pH on caffeine release

The effect of pH value on caffeine release behaviors at room temperature was depicted in Figure 10, when MBA content was 5%. A tendency for an increase of caffeine cumulative release with pH increasing was observed in the prophase of release. When the release experiments were conducted at pH value 2.34 and 7.82, the cumulative release was found to be about 56% and 63% after 60 min, respectively. The similar effect of pH value on drug release also has been observed in other pH-sensitive hydrogel system.[6] As mentioned in Figure 7, the swelling ratio of the polymer hydrogel with 5% MBA reached to 15 and 16 when pH value was controlled at 2.34 and 7.82. According to the diffusion-controlled mode mentioned previously, the caffeine release in acidic and basic medium should show the same releasing behavior because of their close swelling ratios. In this case, however, the lower release rate of caffeine was observed in the acidic medium. This result may be ascribed to the different format of amine groups attached to caffeine as pH value changed. The interactions between caffeine molecules and water, polymeric network affect the drug releasing behavior. In the acidic medium, as the hydrogel swelled, the more salts of caffeine with charge were formed because caffeine is an organic base. Also, the amino groups attached to AMHS unit existed dominantly in the form of hydrochloric salts. Compared to the pure caffeine molecule, the caffeine diffusion in acidic medium was hindered because of its bulky salt as well as the interaction between caffeine with copolymer chains and water. In the medium of pH 7.82, caffeine was in the form of amine, and AMHS still existed in the hydrochloric salt form. Unexpectedly, in the anaphase of release (after 200 min), the cumulative release of caffeine became much higher in strong acidic medium than in neutral medium. This observation can be explained as following facts which the degradation of polymeric hydrogel occurred in the acidic condition over a long time.

CONCLUSIONS

In this study, the pH–temperature responsive copolymers were prepared by modulating the ratio of HPA to AMHS monomers. The LCSTs of the resulting copolymers rapidly increased as the content of hydrophilic monomer AMHS was increased. Also, the copolymer exhibited a complicated phase transition behavior in the different pH medium, namely, its LCST first increased and thereafter decreased with an increase in pH. The hydrogel exhibited a rapid phase transition at 31.5°C with temperature change. Moreover, the swelling ratio had a remarkable dependence on the ion strength and pH value, particularly in lower NaCl concentration and higher pH value. Additionally, the caffeine release behaviors from the copolymer gels were found to be dependent on the temperature, pH and content of crosslinker. The caffeine release is in inverse proportion to the swelling ratio when investigating the effect of temperature and MBA content. In the different pH release medium, the format of drug and amine groups on AMHS served as a main factor to influence the drug release rate. The copolymer hydrogel seems to be a potential material for drug-controlled release modulated by temperature.

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