Preparation and Characterization of a Positive Thermoresponsive Hydrogel for Drug Loading and Release

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ABSTRACT: A positive thermoresponsive hydrogel composed of poly(acrylic acid)-*graft*-β-cyclodextrin (PAAc-*g*-β-CD) and polyacrylamide (PAAm) was synthesized with the sequential interpenetrating polymer network (IPN) method for the purpose of improving its loading and release of drugs. The structure and properties of the PAAc-*g*-β-CD/PAAm hydrogel (IPN hydrogel) were characterized with Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and swelling measurements. FTIR studies showed that the IPN hydrogel was primarily composed of an IPN of PAAc-*g*-β-CD and PAAm. The data from DSC and swelling measurements indicated that the phase-transition temperature or upper critical solution temperature (UCST) of the IPN hydrogel was approximately 35°C. Through the measurement of the temperature dependence of the swelling, increases in the UCST and non-sensitivity to changes in the salt concentration were observed for the IPN hydrogel versus the normal IPN hydrogel poly (acrylic acid)/PAAm (without β-cyclodextrin). Furthermore, the swelling/deswelling kinetics of the IPN hydrogel also exhibited an improved controllable response rate versus the normal IPN hydrogel. Ibuprofen (IBU) was chosen as the model drug for examining loading and release from the IPN hydrogel. The experimental data proved that the IPN hydrogel provided a positive drug release pattern; the IBU released faster at 37°C than at 25°C, and improved drug loading and controlled release were achieved by the IPN hydrogel versus the normal IPN hydrogel. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 1417–1425, 2009

Key words: drug delivery systems; FT-IR; functionalization of polymers; hydrogels

INTRODUCTION

Recently, functional hydrogels have been widely investigated,[1–4] and widespread attention has been paid to environmental-stimuli-responsive hydrogels because of their potential applications in numerous fields, including controlled drug delivery,[5–8] chemical separation,[9,10] sensors,[11,12] catalysis,[13] and enzyme immobilization.[14] Because there are many cases in which environmental temperature fluctuations occur naturally and environmental temperature stimuli can be easily designed and artificially controlled, many studies have been focused on thermoresponsive hydrogels.[15–19] Currently, almost all thermoresponsive hydrogels have negative thermoresponse volume phase transition characteristics (i.e., the volume deswells with increasing environmental temperature) because most of them have been prepared with *N*-isopropylacrylamide.[17,20–22] The volume phase transitions of these hydrogels in water are driven by hydrophobic interactions between the macromolecules. In some cases, a positive controlled release pattern, that is, rapid release at an increased temperature and slow release at a decreased temperature, is urgently needed when the drug delivery system is specially designed to respond to an increase in the body temperature resulting from diseases, such as inflammation or cancers. In recent years, another kind of thermoresponsive hydrogel has been reported, and its volume phase transitions are driven by another type of interaction between the macromolecules, that is, hydrogen bonding. This hydrogel is primarily composed of an interpenetrating polymer network (IPN) of poly (acrylic acid) (PAAc) and polyacrylamide (PAAm).[23,24] The PAAc/PAAm hydrogel forms intermolecular complexes via hydrogen bonding at temperatures lower than the upper critical solution temperature (UCST), whereas it dissociates at temperatures higher than the UCST. Driven by hydrogen bonding, the PAAc/PAAm hydrogel shrinks at low temperatures and swells at high temperatures, revealing a positive thermoresponsive volume phase transition behavior that is the opposite of that of the poly(*N*-isopropylacrylamide) hydrogel.

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven glucose units linked with a 1,4-glucosidic bond. This agent has a torus structure

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characterized by a hydrophilic exterior and a hydrophobic cavity.[25,26] Furthermore, β-CD is well known for its ability to bond with suitably sized drugs within their hydrophobic cavity, thereby changing the physicochemical properties of the drug.[27,28] Because of this unique behavior, β-CD and its derivatives, including β-CD-containing polymers, have been studied extensively in many research fields such as drug delivery systems. When β-CD is incorporated into the polymer, the hydrophilic property of β-CD may vary the phase-transition temperature of the polymer;[29–32] the rigid structure and inclusion property of β-CD may adjust the swelling ratio and the drug release ratio of the polymer.[33] It is found that the incorporation of β-CD into polymeric drug delivery systems could improve the drug–carrier interaction, and as a result, the mechanisms of drug release may be modified.[33–37] On the basis of this premise, we examined a hydrogel with a good combination of temperature sensitivity and a capacity for molecular inclusion. When synthesized and used as a drug carrier, the hydrogel allows the manipulation of the drug loading and release kinetics, facilitating the formulation of more advanced drug delivery systems.

In this study, we synthesized a novel IPN hydrogel with a positive volume phase transition component (PAAc/PAAm) and a molecular inclusion component (β-CD units). We systemically characterized its structures and swelling properties. Using ibuprofen (IBU) as a model drug, we investigated the drug loading and release from the IPN hydrogel at the molecular level.

EXPERIMENTAL

Materials

Acrylic acid (AAc), acrylamide (AAm), and β-CD were purchased from Tianjin Bodi Chemical Industry Co. (Tianjin, China). β-CD was purified two times by recrystallization from water before use. All other reagents, including analytical-grade ammonium persulfate (APS), sodium bisulfite (SBS), *N*,*N*-methylenebisacrylamide, and maleic anhydride (MAH), were purchased from Liaoning Chemical Industry Co. (Liaoning, China).

Preparation of poly(acrylic acid)-*graft*-β-cyclodextrin (PAAc-*g*-β-CD)

The molar ratio of β-CD to MAH was 1:10, and a total of 2.0 g of β-CD and MAH was dissolved in 20 mL of dimethylformamide (DMF); the mixture solution was reacted at 80°C for 10 h with stirring.[32] After the reaction was completed, the reactant was allowed to cool to room temperature, and then, 30 mL of trichloromethane was added. The white precipitate that was obtained was filtered, thoroughly washed with acetone, and dried *in vacuo* at room temperature for 24 h. A reactive monomer, β-CD with MAH (MAH–β-CD), was obtained.

PAAc-*g*-β-CD was prepared by the graft copolymerization of MAH–β-CD and AAc in an aqueous solution at 25°C with an APS–SBS redox system as the initiator. A total of 2.0 g of MAH–β-CD (1 mol) and AAc (9 mol) was dissolved in 20 mL of distilled water; after bubbling with nitrogen gas for 15 min to eliminate oxygen, 8.0 mg of SBS and 0.16 mL of an APS solution were added. The reaction was conducted at 25°C for 12 h. After the reaction was completed, the synthesized product was immersed in distilled water at room temperature and kept there until its volume did not change anymore; it was dialyzed with deionized water for 72 h to eliminate residual chemicals and then dried to a constant weight at 40°C.

Preparation of the IPN hydrogel PAAc-*g*-β-CD/PAAm

The IPN hydrogel PAAc-*g*-β-CD/PAAm was finished by a method of sequential IPN synthesis, in which the IPN hydrogel with PAAc-*g*-β-CD and PAAm were synthesized as the initial matrix and the secondary gel, respectively. PAAc-*g*-β-CD (2.0 g) was added with 30 mL of water under conditions of vigorous stirring at 50°C until the polymer was completely swollen. Then, 1.4 g of the monomer AAm, containing the initiator (APS; 0.3 wt % of the total monomer), was added at room temperature in a nitrogen environment. After the monomer AAm was subsequently polymerized within the initial PAAc-*g*-β-CD matrix at 50°C for 24 h, the IPN hydrogel that was obtained was immersed in deionized water at room temperature for 2 days, and the water was changed every several hours. Finally, the IPN hydrogel was dried to a constant weight *in vacuo* at 40°C. The content of β-CD in the IPN hydrogel was 10.7 wt %, which was determined with the phenol–sulfuric acid reaction for carbohydrates, as previously reported.[38]

Instrumental analyses

Fourier transform infrared (FTIR) spectroscopy measurements were performed on a Swiss Bruker (Switzerland) IFS 55 spectrometer with a KBr method and scanned in the wavelength region of 400–4000 cm^{-1}. The differential scanning calorimetry (DSC) curve of the sample was recorded with a differential scanning calorimeter (DSC 60, Shimadzu Co., Tokyo, Japan). The sample was heated in ordinary air at a rate of 10°C/min from 30 to 150°C.

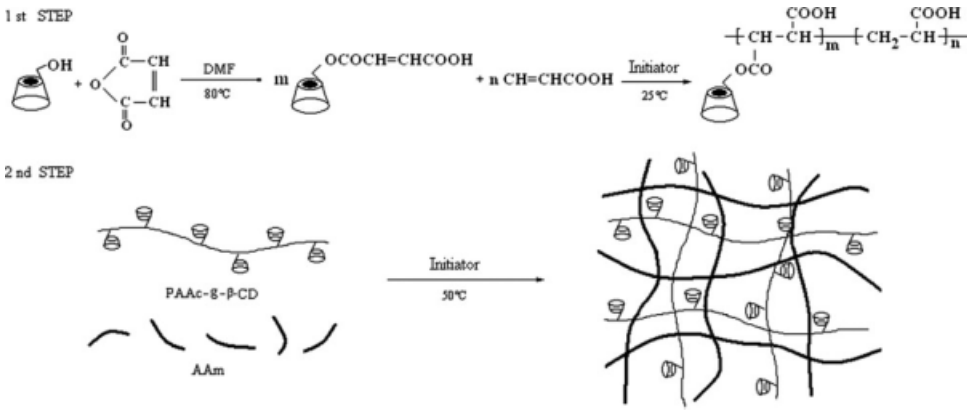

Figure 1 Schematic illustration of the reaction mechanisms of the IPN hydrogel.

Swelling studies

The swelling experiments were performed at different temperatures in a solution of phosphate-buffered saline (PBS; 7.4). The equilibrium swelling ratio (ESR) was measured by the gravimetric method. Briefly, a sample of a certain weight was immersed into solutions of different temperatures until the swelling equilibrium was achieved; excess surface liquid was removed by blotting, and the swollen sample was weighed. The ESR was calculated with the following equation:

$$\mathrm{ESR} = \frac{w_w}{w_d}$$

where w_w and w_d are the sample weights (g) in the swollen and dried states, respectively.

The sample was transferred between identical baths maintained at either 37 or 25°C for swelling/deswelling studies. The sample was briefly removed from the media at certain time intervals and blotted with filter paper to remove any excess surface moisture before being weighed.

Drug loading

Loading was accomplished through the soaking of the dried hydrogel (ca. 0.5 g) in 100 mL of known concentrations of a drug solution in a suitable glass bottle; the temperatures was adjusted at 37°C, and the solution was gently vibrated. Preliminary studies showed that a 24-h period for loading was sufficient. The equilibrium drug concentration in the medium was measured with a UV spectrophotometer (UV-260, Shimadzu) at 225 nm. The amount of drug loaded by the hydrogel was evaluated as the difference between the initial and final quantities in the medium.

Drug release

The drug-loaded hydrogel (ca. 0.5 g) was weighed in triplicate and added to 250 mL of PBS (7.4) as the release medium. The drug release was tested under mechanical shaking (60 rpm). Five millimeters of the solution that was released was collected at predetermined time intervals and then filtered through a 0.45-μm membrane filter. The same volume of fresh medium was replaced. The amount of drug released was analyzed with a spectrophotometer (UV-260, Shimadzu) at 225 nm. The results were presented in terms of the cumulative release as a function of time:

$$\text{Cumulative released } (\%) = \frac{M_t}{M_\infty} \times 100$$

where M_t is the amount of IBU released from the hydrogel at time t and M_∞ is the estimated amount of IBU loaded into the hydrogel.

Drug release in temperature cycling

The drug-loaded hydrogel was placed in a 250-mL solution of PBS (7.4), and the solution temperature was varied between 37 and 25°C. During sampling, 5 mL of the solution that was released was removed and replaced with 5 mL of fresh release solution at the required temperature. The amount of the drug was analyzed with a spectrophotometer (UV-260, Shimadzu).

RESULTS AND DISCUSSION

Design of the IPN hydrogel

An interpenetrating network polymer is a mixture of two or more crosslinked networks that are dispersed or mixed together at a molecular segment level. The preparation of the PAAc-*g*-β-CD/PAAm hydrogel, based on the IPN method, was designed in two steps. In the first step, PAAc-*g*-β-CD was prepared. First, a reactive MAH–β-CD monomer with a vinyl carboxylic acid group was synthesized with MAH for β-CD. Then, PAAc-*g*-β-CD was obtained via graft

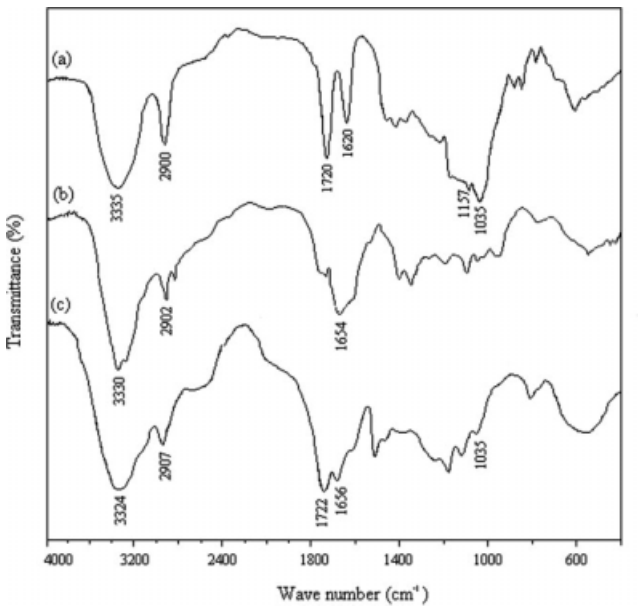

Figure 2 FTIR spectra of (a) PAAc-*g*-β-CD, (b) PAAm, and (c) the IPN hydrogel.

copolymerization of the monomer with AAc in an aqueous solution, with APS and SBS as the initiating agent to polymerize MAH–β-CD with AAc.[32] In the second step, the IPN hydrogel PAAc-*g*-β-CD/PAAm was prepared with a method of sequential IPN technology. The PAAm network was produced in a swelling PAAc-*g*-β-CD network during crosslinking and interpenetrating polymerization. The total reaction mechanism is shown in Figure 1.

It is known that FTIR spectroscopy measurements can give some useful information on the structure of a hydrogel. FTIR spectra of PAAc-*g*-β-CD, PAAm, and the PAAc-*g*-β-CD/PAAm hydrogel are shown in Figure 2.

For PAAc-*g*-β-CD [Fig. 2(a)], a band around 3335 cm^{-1} was assigned to the characteristic stretching vibration of C—OH. The peak at 2900 cm^{-1} corresponded to the —CH_2 asymmetric vibration. The peaks at 1157 and 1035 cm^{-1} demonstrated the stretching vibrations of C—O and C—O—C of β-CD.[39] The stretching vibration of C=O of AAc could be seen at 1720 cm^{-1} and confirmed the grafted copolymer reaction between PAAc and β-CD. For PAAm [Fig. 2(b)], the band for the stretching vibration of N—H appeared around 3330 cm^{-1}, and the peak for the stretching vibration of amide C=O appeared at 1654 cm^{-1}. Comparing the two kinds of complexes, we found that the FTIR spectrum of the PAAc-*g*-β-CD/PAAm hydrogel [Fig. 2(c)] resembled the FTIR spectra of PAAc-*g*-β-CD and PAAm. No new peaks, which might indicate chemical polymerization, appeared for the PAAc-*g*-β-CD/PAAm hydrogel based on IPN.

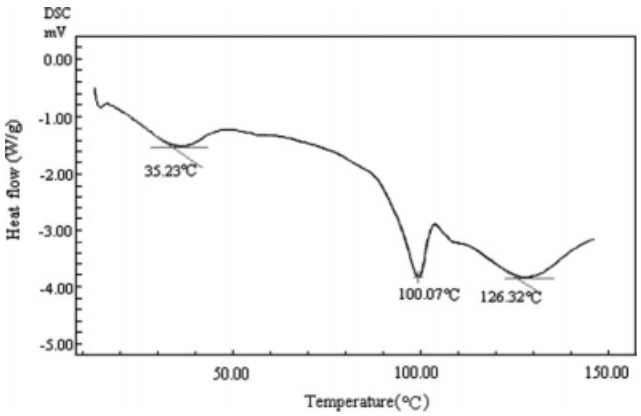

Figure 3 DSC thermogram of the IPN hydrogel.

DSC

The DSC analysis was performed to understand the thermal behavior of the IPN hydrogel from 10 to 150°C. The results are shown in Figure 3.

As shown in Figure 3, three heat absorption peaks were observed in the DSC curve of the IPN hydrogel. The data exhibited a phase transition around 35.23°C, and the swelling experiment also proved a great volume phase transition under this temperature (see Fig. 4). The endothermic peak of free water around 100.07°C indicated the existence of free water in the IPN hydrogel. The glass-transformation temperature appeared around 126.32°C.

Effect of the temperature on the swelling of the IPN hydrogel

The structure of a polymer plays an important role in its swelling process. To investigate the effect of

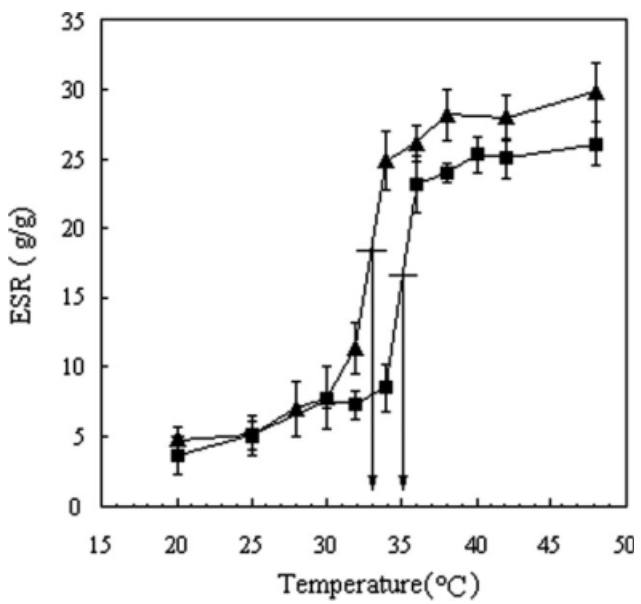

Figure 4 ESRs of the IPN hydrogels from 20 to 50°C: (■) PAAc-*g*-β-CD/PAAm and (▲) PAAc/PAAm.

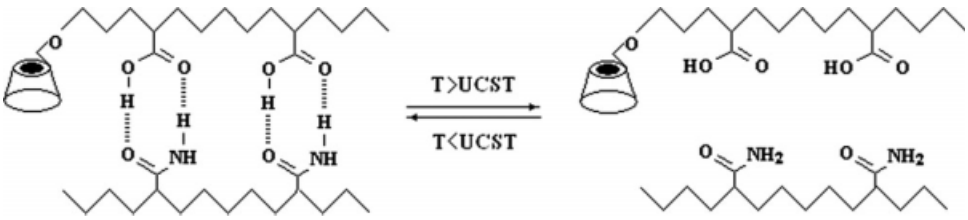

Figure 5 Schematic illustration of cooperative hydrogen bonding in the positive thermoresponsive IPN hydrogel.

introducing β-CD on the swelling behavior of the IPN hydrogel PAAc-*g*-β-CD/PAAm, the ESR of the IPN hydrogel was determined. The preliminary experiment was conducted with the normal IPN hydrogel PAAc/PAAm as a control (the preparation of PAAc/PAAm was based on the method described in ref. 40), and it was performed in the temperature range of 20–50°C. The results obtained from these swelling studies are presented in Figure 4.

Figure 4 shows the swelling behavior of the IPN hydrogel from 20 to 50°C. A considerable increase in ESR was observed and appeared to be a marked transition in the IPN hydrogel. The results indicated that the synthesized IPN hydrogel was indeed a positive thermoresponsive polymer. For reasons discussed, in the IPN hydrogel, the hydrogen bonding between AAc and AAm along with electrostatic repulsion between ionized groups coexisted; the IPN hydrogel was in the swollen or deswollen state according to which force was dominant. The IPN hydrogel was in the deswollen state, and this indicated that the hydrogen bonding was dominant at the lower temperature. As the temperature increased, the hydrogen bonding between AAc and AAm was destroyed, and an ionic bonding network between ionized carboxyl groups and ionized amine groups was formed; the electrostatic repulsion made the IPN hydrogel swell at the higher temperature.[24] A schematic illustration of the principle of the thermoresponsive volume phase transition in the IPN hydrogel driven by hydrogen bonding is shown in Figure 5.

It was also found that swelling abruptly increased at temperatures around 35°C for the IPN hydrogel and around 33°C for the normal IPN hydrogel. The temperature at which the hydrogel showed a sharp increase in swelling was determined to be the UCST, which is approximately the midpoint of the swelling change. In addition, as clearly reflected in Figure 4, there is a difference between the IPN hydrogel and normal IPN hydrogel, indicating that incorporating β-CD into the IPN hydrogel resulted in a simultaneous shift of UCST (ca. 2°C) and reduction of ESR. That is, the effect of the temperature change on swelling also depended heavily on the composition of the IPN hydrogel and the UCST of the IPN hydrogel, which could be adjusted by the incorporation of β-CD into the IPN hydrogel.

Swelling/deswelling cycle

The swelling/deswelling cycle was performed to determine the reversibility of the swelling behavior of the IPN hydrogel upon temperature cycling above and below its UCST. The effect of oscillatory cycling on the thermoresponsive property of the IPN hydrogels at 37 and 25°C is shown in Figure 6.

The data suggest that the thermoresponsive property of the IPN hydrogels was recoverable after two temperature cycles; this indicated that the IPN hydrogels had thermoreversibility with little loss of thermosensitivity. For example, after the first swelling/deswelling cycle, the maximum swelling ratios of the IPN hydrogel and normal IPN hydrogel were 22.5 and 25.6, respectively. After the second swelling/deswelling cycle, the maximum swelling ratios of the IPN hydrogel and normal IPN hydrogel were 19.2 and 22.4, respectively. Figure 6 also shows that the extent of the swelling/deswelling upon oscillatory temperature cycling depended on the composition of the IPN hydrogels (with β-CD or without β-CD). When β-CD was incorporated into the IPN hydrogel, the swelling ratio was smaller than that of the normal IPN hydrogel. From the swelling/

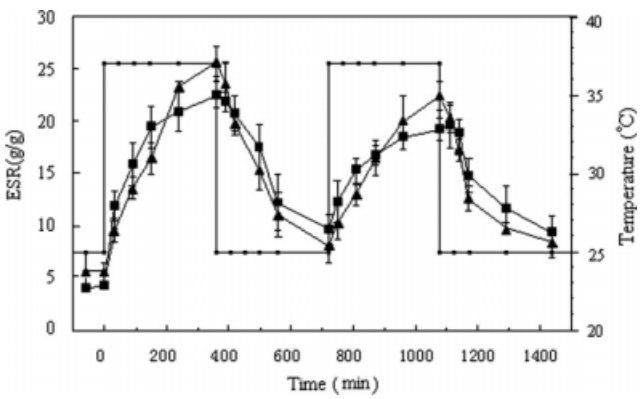

Figure 6 Curves of swelling/deswelling of the IPN hydrogels in response to alternation changes between 37 and 25°C: (■) PAAc-*g*-β-CD/PAAm and (▲) PAAc/PAAm.

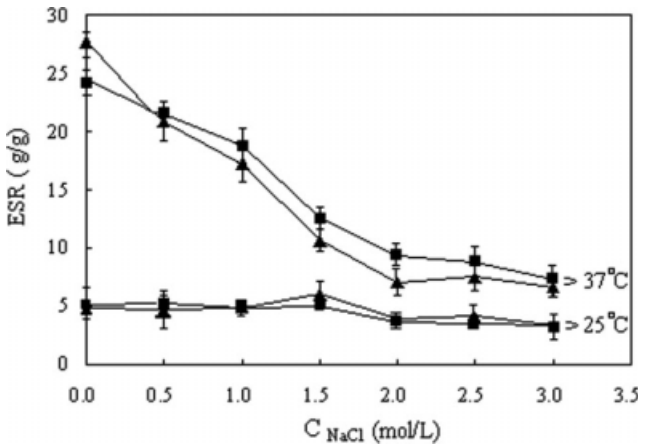

Figure 7 Effect of the salt concentration (C_{NaCl}) on ESRs of the IPN hydrogels at 25 and 37°C: (■) PAAc-*g*-β-CD/PAAm and (▲) PAAc/PAAm.

deswelling kinetic data observed, we found that the incorporation of β-CD played a negative role in the expansion of the IPN hydrogel network because of its rigidity and large volume, which reduced the flexibility of the network.[25,30] We concluded that the controllable thermoresponsive property was retained after the cycle of swelling/deswelling, and this was an indication of the structural stability of the IPN hydrogel, which is vital for future practical applications.

Effect of salt on the swelling of the IPN hydrogel

The salt concentration of the medium also affected the swelling behavior of the ionizable IPN hydrogel.[30] Figure 7 shows the relationship between ESR of the IPN hydrogel and various salt concentrations at 25 and 37°C.

As shown in Figure 7, the ESRs of the IPN hydrogel and normal IPN hydrogel were appreciably decreased at 37°C versus those at 25°C; the values were measured in solutions of various salt concentrations. This phenomenon, commonly observed in the swelling of ionizable hydrogels, has often been attributed to the salt-out effect.[41] The reason is that, at temperatures below the UCST, the intermolecular complexes formed by hydrogen bonding between —COOH and —CONH and the chain–chain zipper effect make the hydrated layers shrink. As a result, the mean hydrodynamic diameter is small. Therefore, the ESR cannot be influenced by the salt. In contrast, the IPN hydrogel was in a swollen state at temperatures above the UCST because of intermolecular complex dissociation by the breakage of hydrogen bonding. Free —COOH and —CONH formed the hydrated layer with water, which resulted in a larger hydrodynamic diameter. The added salt caused the hydrated layer to be broken, with the concomitant release of water of hydration, leading to phase separation. The results indicated that the influence of salt on the ESR of the IPN hydrogel depended on the temperature, and this meant that the swelling of the IPN hydrogel was due to changes in the salt concentration.

Furthermore, as clearly reflected in Figure 7, when the temperature was 37°C, although the salt concentration of the medium obviously affected the swelling behavior of the IPN hydrogels, there were differences between the IPN hydrogel and normal IPN hydrogel at the same salt concentrations. For instance, at 1.0 mol/L NaCl, the ESRs of the IPN hydrogel and normal IPN hydrogel were 18.8 and 17.2, respectively; at 2.0 mol/L NaCl, the corresponding ESRs were 9.4 and 7.0, respectively; and at 3.0 mol/L NaCl, the corresponding ESRs were 7.3 and 6.6, respectively. These data indicated that the ESR of the IPN hydrogel was higher than that of the normal IPN hydrogel at any salt concentration. This meant that the IPN hydrogel might not be sensitive to a change in the NaCl concentration in comparison with the normal IPN hydrogel. This might be attributed to effects caused by the cavity structure of β-CD and its larger volume, which reduced the free —COOH and —CONH that combined with water to form the hydrated layer.

Drug loading and release kinetics

β-CD has been successfully used to modify the release features of polymeric systems, primarily because of its ability to form noncovalent complexes with drugs (i.e., to have different solubility and/or diffusion rates).[42,43] For a better understanding of the mechanisms by which the incorporation of β-CD into the IPN hydrogel affects drug loading and release, experiments were conducted with IBU as a model molecule and the normal IPN hydrogel as a control to elucidate the role of β-CD in the IPN hydrogel during the drug loading and release process.

In the process of drug loading, a temperature above the UCST of IPN hydrogels was selected so that a quick change in the volume or drug loaded could be attained within a short time. Loading was accomplished in solutions of various drug concentrations at 37°C.

As shown in Figure 8, initially the loading quantities of IBU remarkably increased, and the loading exhibited similarly increased rates when concentrations were below 0.6 g/L for both IPN hydrogels. Subsequently, the loading exhibited a difference when the concentrations were above 0.6 g/L. The loading for the normal IPN hydrogel was stable, and it increased continuously for the IPN hydrogel. As IBU was loaded into the IPN hydrogel, it formed a

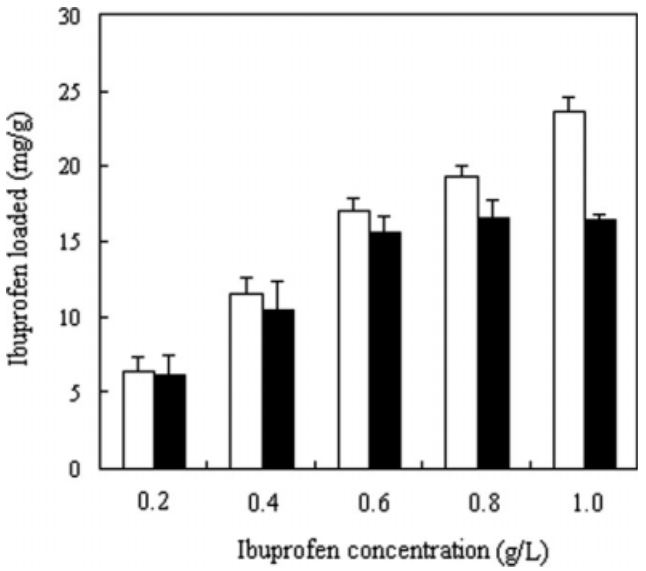

Figure 8 Amounts of IBU loaded into the IPN hydrogels at 37°C: (□) PAAc-*g*-β-CD/PAAm and (■) PAAc/PAAm.

complex with β-CD in the IPN hydrogel, which facilitated drug solubility. Thus, a higher drug loading was obtained versus the normal IPN hydrogel. This result indicated that the drug loading was successfully modulated with β-CD as a component of the IPN hydrogel.

Next, we attempted to determine a mechanism explaining how β-CD affects the release of IBU from IPN hydrogels. We believe that this experiment may provide useful information for designing a drug carrier with a desired release rate from an IPN hydrogel by modification of the content. The release profiles of IBU from IPN hydrogels at 37 and 25°C are shown in Figure 9(a,b).

First, as shown in Figure 9, the release of IBU from IPN hydrogels increased with an increase in temperature. This indicated that the release of IBU from IPN hydrogels can be manipulated by temperature; second, different release amounts of IBU were observed from the IPN hydrogel and normal IPN hydrogel at both 37 and 25°C. For instance, the amounts of IBU released from the IPN hydrogel and normal IPN hydrogel at 37°C were 38.9% and 49.2% at 4 h, 74.6% and 81.7% at 8 h, and 79.4% and 84.2% at 12 h, respectively. In contrast, the amounts of IBU released from the IPN hydrogel and normal IPN hydrogel at 25°C were 9.5% and 17.4% at 4 h, 19.9% and 23.0% at 8 h, and 25.2% and 28.4% at 12 h, respectively. The data suggest that the release of IBU from IPN hydrogels was dependent on the presence of β-CD; the amount of IBU released from the IPN hydrogel was lower than that from the normal IPN hydrogel at both 37 and 25°C. That is, the incorporation of β-CD led to a delayed release of IBU from the IPN hydrogel. In fact, matrix swelling, drug dissolution, and diffusion were affected by the presence of β-CD in the IPN hydrogel and could occur simultaneously.[44,45] For the normal IPN hydrogel, the release of the drug was essentially controlled by hydrogel swelling. As β-CD was present in the IPN hydrogel, drug release was not completed when the swelling was over. This may due to that fact β-CD has a hydrophobic cavity and can bond to a hydrophobic drug to form a stable inclusion complex. For the IPN hydrogel, the release of the drug should change it from an inclusion complex to a free form, and β-CD plays a role in decreasing drug mobility through the polymeric matrix. Therefore, because of the formation of an IBU/β-CD complex retarding the diffusion rate of IBU, a delayed release of IBU from the IPN hydrogel could be obtained versus the normal IPN hydrogel without β-CD. We concluded that a hypothesis about the mechanism by which

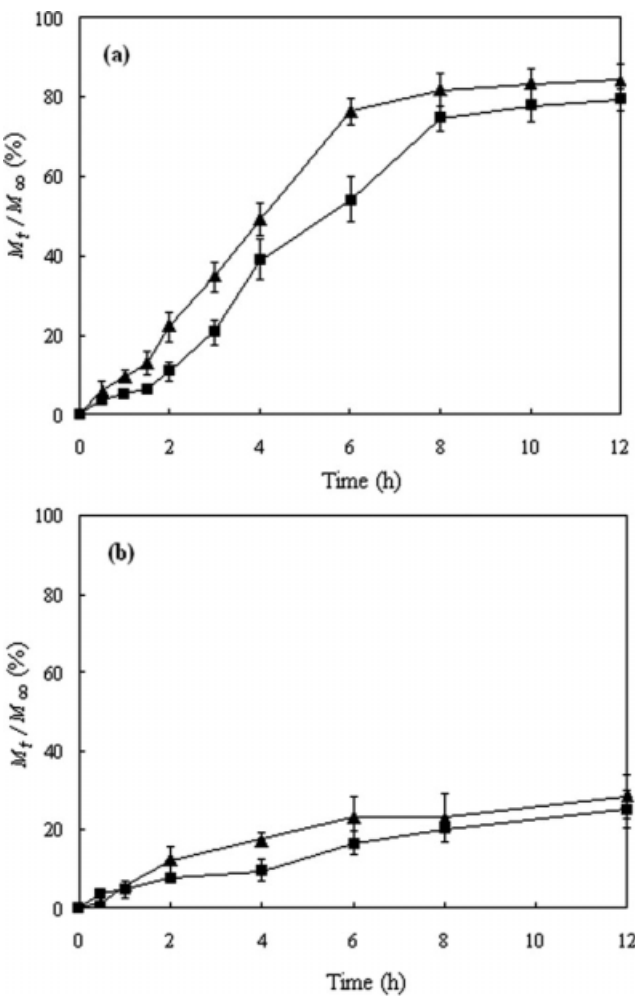

Figure 9 Cumulative release of IBU from the IPN hydrogels, including (■) PAAc-*g*-β-CD/PAAm and (▲) PAAc/PAAm, at (a) 37 and (b) 25°C in buffer solutions of pH 7.4 (the IBU load was 16.63 mg/g for PAAc-*g*-β-CD/PAAm and 15.90 mg/g for PAAc/PAAm).

β-CD modulates the release rate can be justifiably proposed.

The release of a drug from a hydrogel is generally known to follow the Higuchi relationship,[46] in which release kinetics can be expressed as follows:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t and M_∞ express the amounts of the drug at time t and time ∞, respectively; k is a constant characteristic of the system; and n is an exponent that characterizes the release kinetic mechanism. If $n = 0.5$, the drug releases from the hydrogel matrix following Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian drug diffusion occurs. If $n > 1$, case II release kinetics are operative.[47,48] By plotting $\log \frac{M_t}{M_\infty}$ versus $\log t$, we obtained n directly from the linear portion of the slope.

Figure 9(a) illustrates that drug release kinetics from the IPN hydrogel at various times at 37°C. The results showed that almost 80% of the loaded IBU was released from the IPN hydrogel within 8 h. On the basis of the previously described method, the transparent exponent n was determined to be 0.8148, which indicated that the release of IBU from the IPN hydrogel was suitable for the non-Fickian mechanism.

Effect of temperature cycling on drug release

The effect of temperature cycling on drug release may reflect a response rate to various environments. Figure 10 shows the IBU release profile and release rate from the IPN hydrogel as a function of temperature cycling.

An IBU-loaded sample was first exposed to a temperature of 25°C followed by 37°C. After each temperature cycling, a higher release amount and a higher release rate were generally observed at 37°C versus 25°C. The results clearly showed the pulsatile release of IBU from the IPN hydrogel when the temperature was either increased or decreased. Pulsatile drug release of the IPN hydrogel meant that an effective modulation of the drug release rate was achieved. That conclusion is vital for future practical applications.

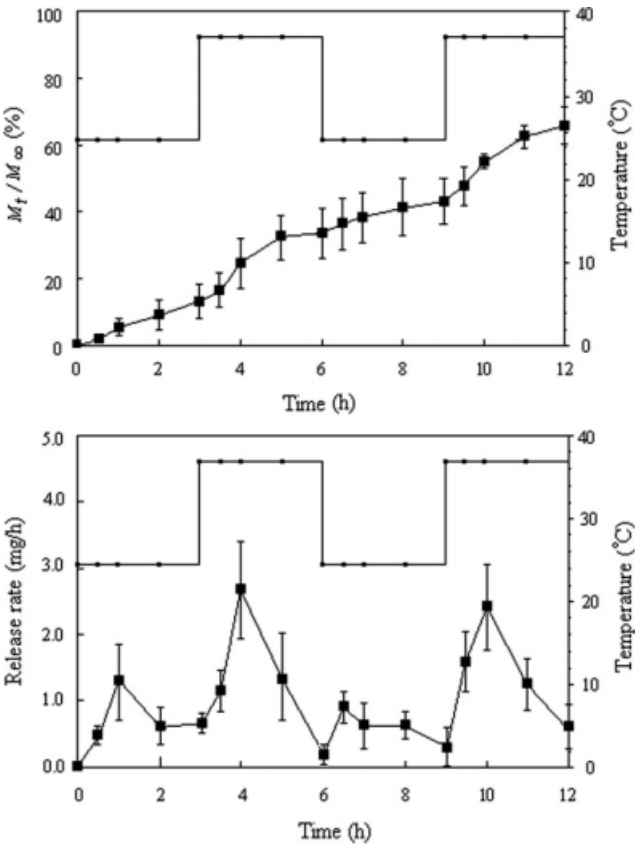

Figure 10 IBU release profiles when the hydrogel was subjected to temperature cycling: (a) cumulative release profile and (b) release rate versus time (the IBU load was 16.63 mg/g for the IPN hydrogel).

CONCLUSIONS

Employing β-CD as a modified group, we have examined the synthesis of a novel positive thermoresponsive IPN hydrogel consisting of IPNs between PAAc-*g*-β-CD and PAAm chains. The IPN hydrogel showed a positive thermoresponsive volume phase transition. The swelling of the IPN hydrogel exhibited a high sensitivity to external temperature stimuli. IBU was used as a model drug to examine the loading and release behavior from the IPN hydrogel at two different temperatures (25 and 37°C). The experimental data confirmed our hypothesis that the IPN hydrogel could provide a positive drug release pattern, that is, a rapid drug release rate at a high temperature and a slow drug release rate at a low temperature. The IPN hydrogel also exhibited improved multidimensional characteristics, such as enhanced loading, delayed release of the drug, and an enhanced controllable response rate in comparison with the normal IPN hydrogel. Therefore, we employed the IPN hydrogel modified by β-CD instead of the normal IPN hydrogel to further control the drug loading and release. This novel IPN hydrogel has potential and promising applications in cases in which positive drug control release is required.

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