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A Temperature-Responsive Copolymer Hydrogel in Controlled Drug Delivery

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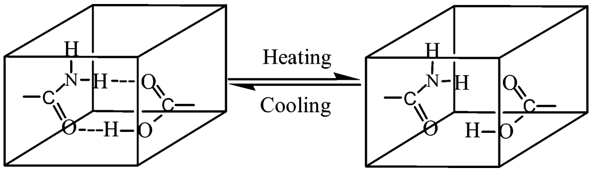
ABSTRACT: A novel optical transition for a hydrogel of polyacrylamide and poly(acrylic acid) random copolymer was observed. The poly(acrylamide-*co*-acrylic acid) hydrogel is opaque white at low temperature, while it will become transparent gradually or sharply on a fast or slow increase of temperature. Meanwhile, the hydrogel can swell or collapse with changing temperature. Both optical transition and volume swelling are reversible responding to temperature stimuli. The FT-IR, laser Raman, and ^{1}H NMR spectroscopy demonstrated the driving force of optical and volume transition: formation and dissociation of hydrogen bonds in the hydrogel. The heterogeneity of the network results in these reversible transition responding to temperature stimuli. The effects of monomer, initiator, and cross-linker on the optical transition of the hydrogel were studied in detail. The formation and dissociation of hydrogen bonds in the limited domain of the hydrogel is related to the network structure. Because of the property of swelling or collapse, the P(AAm-*co*-AAc) hydrogel has potential value of application in drug controlled release.

Introduction

Hydrogel, a kind of polymer network system holding a large amount of water in the interspaces of the network, is increasingly attracting the academic and industrial interests.[1−5] Some hydrogels can undergo drastic volume changes, volume phase transition, in response to minute environmental stimuli, such as solvents,[6,7] temperature,[8−11] pH,[11,12] ionic concentration,[13] electric field,[14,15] and light irradiation.[16] Numerous investigations have been reported on the volume phase transition of different hydrogel systems, especially poly(*N*-isopropylacrylamide), in response to different environmental stimuli,[6−16] and hydrogels with these properties have potential application in controlled drug delivery.[17−19] It has been proved that the volume phase transition of hydrogel is the result of the sole or combination of four kinds of molecular interactions:[20,21] ionic interaction, hydrophobic interaction, hydrogen bonding, and van der Waals force.

It is known that poly(acrylic acid) (PAAc) forms intermolecular hydrogen bonds with poly(acrylamide) (PAAm), as well as other polymers having amide groups as a side group, only at low temperature, while it dissociates at a certain temperature.[22−28] This phenomenon, which is the so-called “zipper effect”, also exists in the copolymer poly(acrylamide-*co*-acrylic acid) (Scheme 1). Some research results had related with the interaction induced by hydrogen bonds for interpenetration network (IPN) or mixture solution of linear PAAc and linear PAAm.[21,29] In addition, some works were about the properties of random copolymer P(AAm-*co*-AAc), such as absorption property,[30] size-dependent surface properties,[31−33] mechanisms of mucoadhesion to gastric mucus layer,[34] and swelling behavior in response to pH and temperature changing.[34,35] However, few studies paid attention to the optical properties of poly(AAm-*co*-AAc) hydrogel. A detailed understanding of the optical properties might be important in order to understand the formation and dissociation of hydrogen bonding.

Scheme 1. Schematic Picture of Cooperative Hydrogen Bonds in P(AAm-*co*-AAc) Network



It was reported that the turbidity of poly(acrylamide) (PAAm) gel increased with an increasing content of monomer or cross-linker, *N,N*′-methylenebis(acrylamide) (MBAAm), until the gel became totally opaque.[36] This irreversible optical change was considered a phase separation due to the agglomerations of the polymer chains, which resulted in the scattering of visible light. Recently, we found that the hydrogel of polyacrylamide and poly(acrylic acid) copolymer exhibited dramatic optical transparency changes with changing the environmental temperature. The present paper reports a hydrogel, containing a random copolymer of acrylamide, acrylic acid, and cross-linker, that undergoes reversible optical transition and swelling behavior driven by the formation and dissociation of hydrogen bonds. Furthermore, the gel application in drug controlled release was investigated.

Experimental Section

Materials. The monomers acrylic acid (AAc) and acrylamide (AAm) were AR Reagents provided by Jingyi Chemical Co., Beijing, China. Acrylic acid was frozen and recrystallized three times before use. Acrylamide was recrystallized from the mixed solvent of benzene and chloroform. *N,N*′-Methylenebis(acrylamide) (MBAAm), the cross-linker purchased from Academy of Military Medical Sciences, was recrystallized from alcohol. The photoinitiator, α-ketoglutaric acid (KGA), reagent of Wakolure Chem.

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Inst. Ltd. Japan, was used as received. Ketoprofen was provided by Hefei Institute of Pharmaceutical Industry Co., Ltd., and was used as received. Other regents were all AR.

Preparation of Hydrogels. The poly(acrylamide-*co*-acrylic acid) or P(AAm-*co*-AAc) hydrogel was prepared by free-radical solution polymerization initiated by photoinitiator at 25 °C. Two monomers, cross-linker and photoinitiator, were fed into cells with solvents, redistilled deionized water, and then the mixture was deoxygenated by bubbling nitrogen for about an hour. The total monomer concentration was 1.0 mol/L (n_{AAm}:$n_{\mathrm{AAc}} = 1$:1), the cross-linker was 1.0 mol % ($n_{\text{cross-linker}}$:$n_{\text{total monomer}}$), and the photoinitiator was 0.3 mol % ($n_{\text{photoinitiator}}$:$n_{\text{total monomer}}$). The solution was polymerized under UV lamp (Spectroline model ENF 240 C/J, Spectronics Co., Westbury, NY) at $\lambda = 365$ nm. The hydrogels were characterized by the composition of solution from which they were obtained.

Characterization. Fourier transform infrared (FT-IR) spectroscopy of the hydrogel was measured with Bruker Equinox55 FT-IR with average 200 scans in the resolution of 2 cm^{-1} at room temperature. The P(AAm-*co*-AAc) was granulated and pressed with KBr for test. Laser Raman spectroscopy was obtained with a Bruker FAR 106 at temperature of 25 °C. The planar hydrogel of P(AAm-*co*-AAc) was cut into rectangular pieces for measurements. The power of laser source was 200 mW. The signals were the average results of 200 scans at a resolution of 4 cm^{-1}. The NMR measurements were carried with a Bruker DMX-300 NMR spectrometer at different temperature, which was stabilized by Bruker temperature control units and checked by a substitution method.[37] The resonance frequency for ^{1}H was 300.13 MHz. The hydrogel for NMR measurements was synthesized in the specific NMR tube with deuterium oxide as solvent.

Transparency (%*T*) Measurements. Optical transparency of the hydrogel was quantitatively measured by the transmittance of the sample. The transmittance of 10 mm thick hydrogel was recorded under different conditions with a Unicam 1750 UV−vis spectrophotometer at $\lambda = 520$ nm.

Swelling Measurements. The copolymers of P(AAm-*co*-AAc) were cut into disks to use. After immersion in deionized water at a desired temperature, diameters and thickness of the copolymers were measured by a micrometer to calculate the volume. The copolymers were repeatedly measured and reimmersed in deionized water at a fixed temperature until the volume reached a constant value. After equilibration at one temperature, the copolymers were then reequilibrated at a higher temperature. The volume ratio, V_s/V_0, was used to evaluate the swelling ratio, where V_s is equilibration swelling volume and V_0 is the initial volume equilibrating at 1 °C.[38]

Drug Loading and Release. The copolymers of P(AAm-*co*-AAc) were cut into square pieces and then immersed in ketoprofen ethanol−water (50:50 v/v) solutions for 24 h at 25 °C,[28,39] and the drug was entrapped in the P(AAm-*co*-AAc) hydrogel. After removal of the drug from the surface by washing with ethanol, the copolymers were exposed to air for drying at room temperature for 1 h.

Drug release rate changes with temperature were investigated by using a diffusion cell with stirrer. The medium was redistilled water, and the stir rate was 60 rpm. The drug concentration was monitored with Rayleigh UV-1600 spectrophotometer ($\lambda = 259$ nm). The diffusion cell was put into the water bath to keep the temperature under control.

Results and Discussion

As given in the literature,[21,29] there are strong interactions induced by hydrogen bonds for the interpenetration network (IPN) or complex solution of linear PAAc and linear PAAm. The hydrogen bonds in a random copolymer hydrogel, P(AAm-*co*-AAc), should exist, and the molecular movement of some group in the hydrogel will be influenced. FT-IR is a good method to investigate the intermolecular interaction. Figure 1 contains the FT-IR spectra of PAAc, PAAm, and P(AAm-*co*-AAc) hydrogel. The hydrogen bonds between water and polymer do not mask the difference of the three hydrogels. The carbonyl stretching vibration related to PAAm hydrogel (~1672 cm^{-1}) and PAAc hydrogel (~1716 cm^{-1}) is still observed in the P(AAm-*co*-AAc) hydrogel. However, the deformation vibration of $-\mathrm{NH}_2$ (~1612 cm^{-1}) related to PAAm hydroge1[40] is not observed in P(AAm-*co*-AAc) hydrogel. It means the restriction of the amide group's deformation vibration in P(AAm-*co*-AAc).

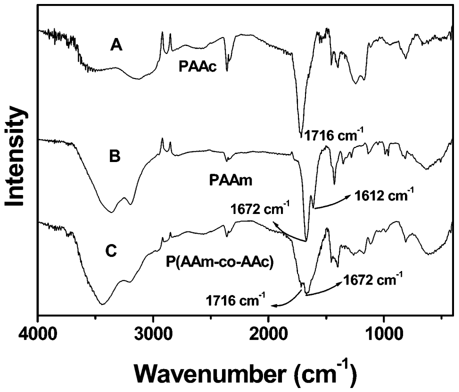

Figure 1. FT-IR spectroscopy of PAAc, PAAm, and P(AAm-*co*-AAc) hydrogels. [AAm + AAc] = 1.0 mol/L, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol %. (A) [AAc] = 100 mol %, (B) [AAm] = 100 mol %, and (C) [AAm] = 50 mol %.

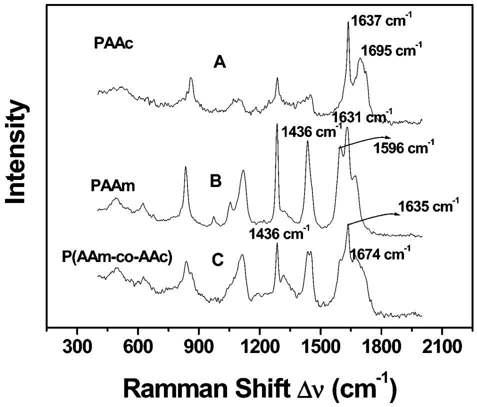

Figure 2. Laser Raman spectroscopy of PAAc, PAAm, and P(AAm-*co*-AAc) hydrogels. [AAm + AAc] = 1.0 mol/L, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol %. (A) [AAc] = 100 mol %, (B) [AAm] = 100 mol %, and (C) [AAm] = 50 mol %.

Because Laser Raman spectroscopy is not affected by water, it is favorable to characterize the difference of samples by this method. Figure 2 shows the expected difference of these three hydrogel samples that are not treated after synthesis. Laser Raman spectroscopy shows that two of the three amide bands are shifted higher. Amide band I (C−O stretching vibration, ~1631 cm^{-1}) in pure PAAm hydrogels[41] is shifted to ~1635 cm^{-1} in P(AAm-*co*-AAc) hydrogels. Sharp peaks of amide band III (C−N stretching vibration, ~1436 cm^{-1}) is split into two equal strength peaks at ~1436 and ~1452 cm^{-1}. The intensity of amide band II (~1596 cm^{-1}) which belongs to the deformation vibration of $-\mathrm{NH}_2$ decreases in P(AAm-*co*-AAc) hydrogels.[31] The results demonstrate the restriction of amide group by the formation of hydrogen bond.

During the formation and dissociation of hydrogen bonds the two hydrogen nuclei of amide group are experienced different chemical environments. Figure 3 gives the NMR of $-\mathrm{NH}_2$ in the hydrogel with different compositions. The chemical shifts are 7.691, 7.627, and 6.909 ppm in traditional scale of TMS corresponding to the hydrogen nuclei in $\mathrm{NH}_2...\mathrm{H}_2\mathrm{O}$ (A peak in Figure 3), $\mathrm{NH}_2...\mathrm{NH}_2$ (B peak in Figure 3), and free $-\mathrm{NH}_2$ (C peak in Figure 3), respectively. With the increase of AAc content in hydrogels, the double peaks of NMR at low field gradually

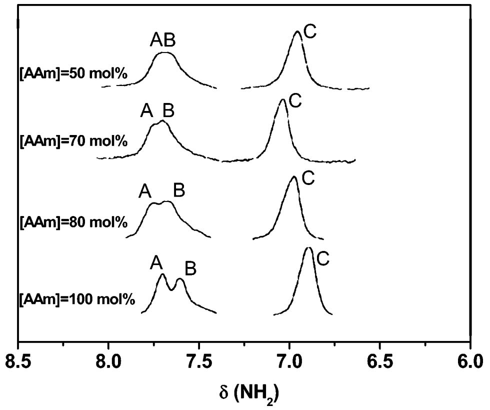

Figure 3. ^{1}H NMR chemical shifts of $-NH_2$ group in different copolymer hydrogels. [AAm + AAc] = 1.00 mol/L, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol %.

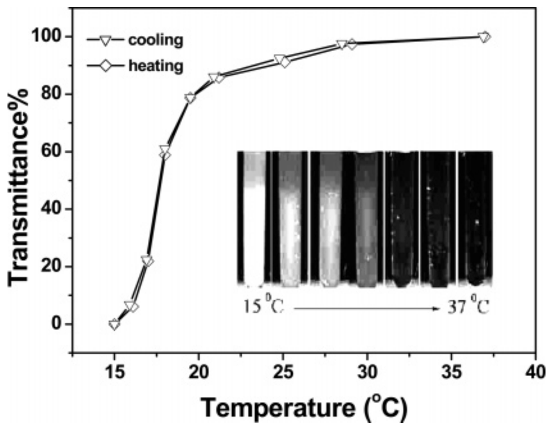

Figure 4. Transmittance transition of P(AAm-*co*-AAc) hydrogel with temperature. [AAm + AAc] = 1.0 mol/L, [AAm] = 50 mol %, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol %.

approach each other and become one peak. The formation of hydrogen bond between hydrogen of amide group in PAAm and oxygen of carboxyl group in PAAc makes the nuclei shift down compared with the hydrogen bond among amide groups of PAAm.

The random copolymer hydrogel, poly(acrylamide-*co*-acrylic acid), P(AAm-*co*-AAc), was found to undergo a reversible optical transparency transition with temperature change. Figure 4 illustrates the recorded transmittance transition of the hydrogel with temperature and the related photos.

The P(AAm-*co*-AAc) hydrogel is transparent at about 37.0 °C, while it is white opaque at low temperature of about 15.0 °C. There is little difference in the temperature dependence of the transition with increasing and decreasing temperature. The maximum (or minimum) transmittance is defined as 100% (or 0%), and all values are relative. The temperatures are defined as lower (T_{lower}) and upper transition temperature (T_{upper}) at T = 10% and 90%, respectively. The optical transition region for the hydrogel is defined as the temperature span from T = 10% to T = 90%.

On the basis of above discussion, the results demonstrate that there are large amounts of hydrogen bonds between carboxyl group ($-COOH$) and amide group ($-CONH_2$) in the P(AAm-*co*-AAc) hydrogel network at low temperature. Such molecular interaction favored the agglomeration of polymer chains. If the agglomeration domains are comparable to 1/2 wavelength of visible light, the hydrogel can scatter the visible light. This results in the white opaque hydrogel at the low temperature. When the hydrogel is heated, the formed hydrogen bonds within the polymer networks are cleaved, and these agglomeration domains disappear so that the hydrogel becomes gradually transparent with increasing temperature.

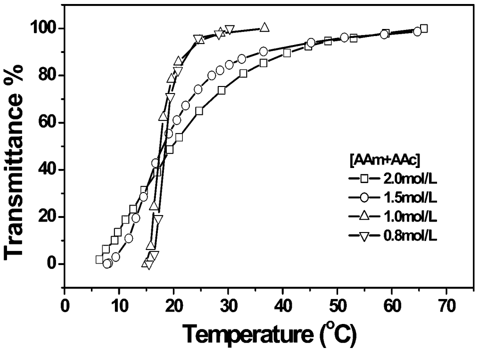

Figure 5. Phase transition of hydrogel at different monomer concentrations. [AAm] = 50 mol %, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol %.

Table 1. T_{lower} and T_{upper} of Hydrogel at Different Monomer Concentrations

[AAm + AAc]^a (mol/L)	T_{lower} (°C)	T_{upper} (°C)	transition region (°C)
2.0	9.2	41.0	31.8
1.5	11.8	36.0	24.2
1.0	16.0	22.5	6.5
0.8	16.7	22.8	6.1

^{a} [AAm] = 50 mol %, [MBAAm] = 1.0 mol %, and [KGA] = 0.3 mol %.

This optical transition of hydrogel, induced by the formation and dissociation of hydrogen bonds, depends on the hydrogen bonds density, network structure, and temperature change. Obviously, the density of hydrogen bonds is related to macromolecular chain concentration and composition ratio in the hydrogel. The network structure of the hydrogel is mainly influenced by the content of the cross-linker and photoinitiator.

Monomer Concentration. The macromolecular chain content in hydrogel, which is determined by the concentration of monomer, determines the number of hydrogen bonds formed in the limited network space. Figure 5 shows the influence of monomer concentration on the optical phase transition of the hydrogel.

The four hydrogels in Figure 5 are opaque white, translucent white, almost transparent, and transparent of the given concentration of monomer at room temperature. As the numbers of macromolecular chains in a specified volume increase, so does the probability for acrylamide and acrylic acid molecules to form hydrogen bonds. Since the dissociation of hydrogen bonds is endothermic, the energy needed to cleave these hydrogen bonds increases with the number, so that a higher polymer concentration in the hydrogel became transparent at higher temperature. The hydrogels with total monomer (AAm + AAc) concentration of 2.0 and 1.5 mol/L became transparent at about 70 °C or higher, whereas the hydrogels of 1.0 and 0.8 mol/L became transparent at about 40 and 30 °C, respectively. The higher monomer concentration leads to the higher network density in the hydrogel, which leads to the dissociation of hydrogen bonds more difficult. All these factors cause the gradual dissociation of hydrogen bonds in hydrogel and a wider transition region with the temperature change. Table 1 lists the T_{lower}, T_{upper}, and transition region for the four hydrogels.

Monomer Ratio. The optical transition of the hydrogel depends on ratios of acrylamide to acrylic acid. Figure 6 illustrates the influence of the composition on the hydrogel. The

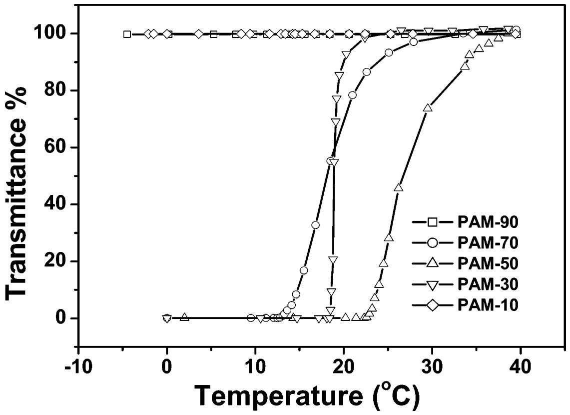

Figure 6. Influence of monomer ratio on the optical transition. The designation *X* in PAM-*X* denotes the AAm mole percentage in P(AAm-*co*-AAc) hydrogel. [AAm + AAc] = 1.0 mol/L, [MBAAm] = 0.1 mol %, [KGA] = 0.1 mol %.

designation *X* in PAM-*X* denotes the AAm mole percentage in P(AAm-*co*-AAc) hydrogel.

PAM-10 and PAM-90 give transparent hydrogels during the temperature change from −4.5 to 40 °C, indicating a weak hydrogen bond interaction in these two hydrogels. The other three samples exhibit an obvious optical transition during the temperature change. PAM-70 is opaque white at temperatures lower than 12.8 °C. The transition region of this hydrogel is from temperature of 14.8 to 23.2 °C. PAM-50 is opaque white at the temperature lower than 23.2 °C. The transition region of PAM-50 is from temperature of 25.0 to 35.0 °C. At temperatures higher than 40 °C the hydrogel is always transparent. The closer the mole ratio of acrylamide approaches 50%, the higher is T_{lower} and the more general is the transition.

The difference can be attributed to a balance between the hydrogen bonds interaction and the elastic force at different temperatures in the P(AAm-*co*-AAc) hydrogel. At equal mole ratio of acylamide and acrylic acid the number of possibly formed hydrogen bonds reaches a maximum, and hydrogel becomes transparent at highest temperature. There is also a wider transition region for the optical transition. When one of the monomers is in excess, as in PAM-10 and PAM-90, few hydrogen bonds form so that the hydrogel cannot become opaque even at temperature below 0 °C. The hydrogel is always transparent during the temperature change. The hydrogel sample PAM-30 has the shortest transition region responding to temperature change. Sample PAM-70 has a large excess of acrylamide and is more elastic than PAM-30 containing more of the AAc component in the hydrogel. Therefore, the transition region of the PAM-70 sample is also wider than that of PAM-30.

Cross-Linker Concentration. The cross-linking density is responsible for the elastic stress, which limits the swelling of the hydrogels. The structure of the hydrogel network will surely contribute to the phase transition. The effect of cross-linker concentration on the hydrogel transparency transition is shown in Figure 7. The three hydrogels are transparent at about 70, 50, and 45 °C for 1.00, 0.50, and 0.30 mol % cross-linker concentration, respectively. Under our experimental conditions the system with low cross-linker concentration changes more sharply with changing temperature.

Lower amounts of cross-linker give lower T_{upper} and a narrower transition region. The retracting force of the elastic network becomes the main factor influencing the phase transition. A lower density of cross-links gives a smaller elastic retracting force, so that the hydrogen bonds can be easily cleaved at lower temperature. At the same time polymer chains are more flexible to form hydrogen bonds more easily during the equilibration.

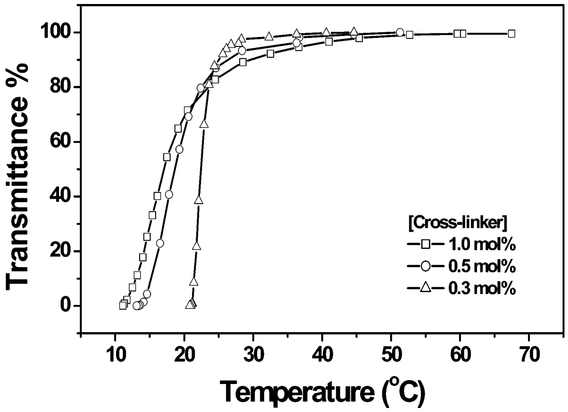

Figure 7. Effect of cross-linker on hydrogel transmittance transition. [AAm + AAc] = 1.0 mol/L, [AAm] = 50 mol %, [KGA] = 0.3 mol %.

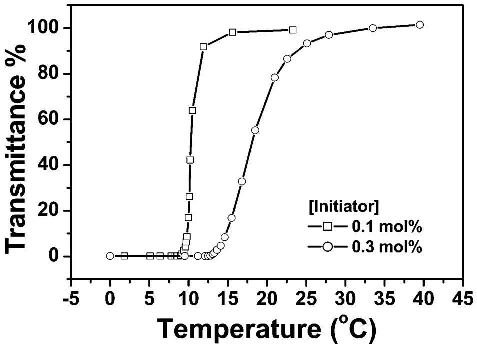

Figure 8. Effect of initiator concentration on hydrogel optical transition. [AAm + AAc] = 1.0 mol/L, [AAm] = 70 mol %, [MBAAm] = 0.1 mol %.

Initiator Concentration. The initiator concentration influences not only the polymerization speed but also the structure or the uniformity of the hydrogel. A lower initiator concentration leads to a smooth free radical reaction and a homogeneous hydrogel, while a higher initiator concentration will cause the inhomogeneity of the hydrogel due to the accumulation of polymerization heat. Figure 8 gives the system of PAM-70 at two different initiator levels. PAM-70 with 0.1 mol % initiator concentration becomes transparent gradually above 7.4 °C, while that with 0.3 mo1% initiator concentration become transparent above 12.8 °C. The hydrogel with higher initiator concentration also has higher T_{lower}. On the other hand, the hydrogel has wider transition region at 0.3 mol % initiator concentration. This hydrogel has a denser network, which can only be expanded at higher temperature.

Swelling Ratio. Bouillot et al. reported the swelling behavior of random P(AAm-*co*-AAc) nanoparticles.^{35} By contrast, the swelling behavior of the copolymer disks is illustrated in Figure 9. The volume of copolymer gradually gets larger with increasing temperature. In addition, the swelling ratio of P(AAm-*co*-AAc) hydrogel is much higher with lower cross-linker content. However, instead of decreasing right away, the swelling ratio keeps high when temperature declines from 40 to 30 °C. The copolymer disks collapse slowly with temperature continuously decreasing, until almost reaching the initial volume. This reversible volume transition is based on the fact that hydrogen bonds can dissociate and recombine in response to the changing temperature. However, the copolymer containing low cross-linker consumed more time to return to the original state.

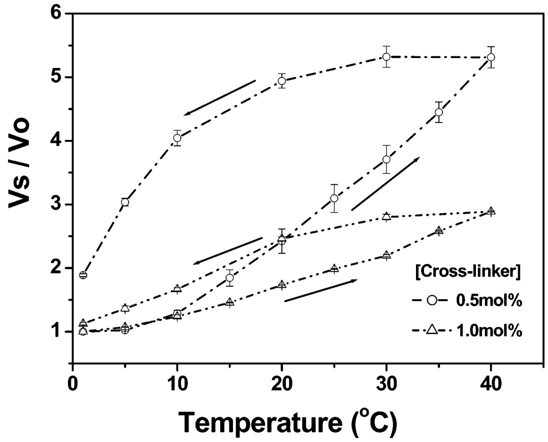

Figure 9. Swelling ratio of P(AAm-*co*-AAc) under different temperature. [AAm + AAc] = 2.0 mol/L, [AAm] = 50 mol %, [KGA] = 0.3 mol % (mean ± S.D.; *n* = 2).

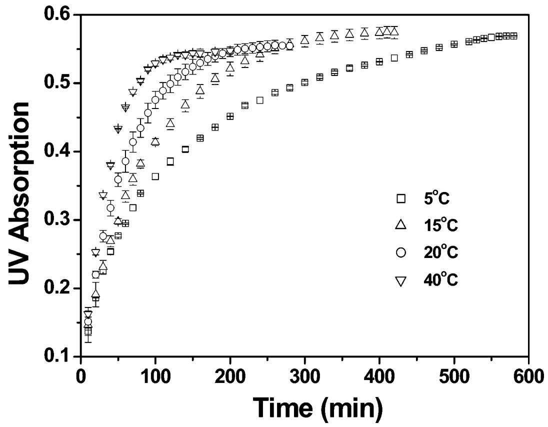

Figure 10. Release curves of Ketoprofen in P(AAm-*co*-AAc) under different temperature. [AAm + AAc] = 2.0 mol/L, [AAm] = 50 mol %, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol % (mean ± S.D.; *n* = 2).

Drug Release. Since the ketoprofen solution has UV absorption at 259 nm, the drug concentration can be indicated by the absorption value. The release curve, setting the absorption value as a function of the time, is measured every 5 °C from 5 to 40 °C. The results show that the lower temperature makes the longer equilibration time, and some curves are shown in Figure 10. Although the equilibration time is different, every release process confirms to the first-order exponential decay, and the relationship between absorption (A) and time (t) can be indicated by the following equation:

$$A = a - b\mathrm{e}^{-kt}$$

where k is the decay rate and a and b are constants. The decay rate can be figured out by fitting the data to the equation described above. The decay rate, as a function of temperature, increases with the temperature increasing, which is illustrated in Figure 11. The curve almost accords with that of optical transition and swelling behavior. As hydrogen bonds dissociate with the temperature increasing, higher temperature results in less restriction to drug molecules.

Conclusion

The reversible optical transparency transition of poly(acrylamide-*co*-acrylic acid) hydrogel is the result of the formation and dissociation of hydrogen bonds with changing temperature. The FT-IR, laser Raman, and ^{1}H NMR spectroscopy demonstrated the driving force of this optical transition: formation and dissociation of hydrogen bonds in the hydrogel. Monomer, initiator, cross-linker, and the change of environmental temperature influence the optical transparency transition. The formation and dissociation of hydrogen bonds in the limited domain of the hydrogel is related to the network structure. With increasing monomer, initiator, cross-linker concentration, the networks of the hydrogel become denser or more elastic so that the hydrogen bonds cleave with greater difficultly, the phase transition temperature is higher and the transition region wider. The formation and dissociation of hydrogen bonds result in swelling and collapse of copolymer hydrogel, and this special property can be used to control the delivery of drugs or other active molecules.

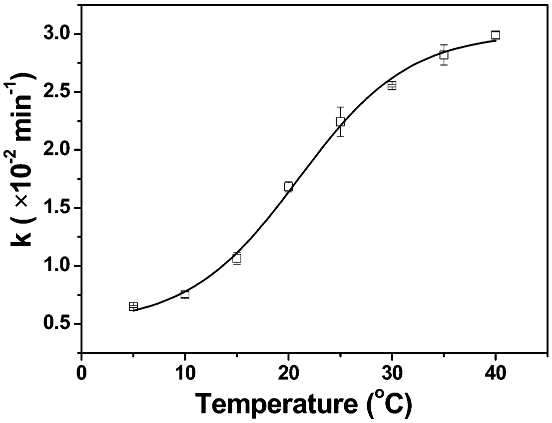

Figure 11. Decay rate of release curve under different temperature. [AAm + AAc] = 2.0 mol/L, [AAm] = 50 mol %, [MBAAm] = 1.0 mol %, [KGA] = 0.3 mol % (mean ± S.D.; *n* = 2).

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