Preparation and Characterization of pH and Temperature Dual Responsive-, Poly(*N*-isopropylacrylamide-*co*-itaconic acid) Hydrogels Using DMF and Water as Mixed Solvents

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In this paper, pH and temperature dual responsive poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogels were synthesized using DMF and water as mixed solvents. The surface morphologies and network structures of the newly synthesized hydrogels were characterized by scanning electron microscopy (SEM) and found gels prepared in the mixture exhibited porous structures. Temperature and pH sensitivities of the resultant hydrogels were examined through swelling ratios, deswelling/reswelling kinetics and deswelling-reswelling cycles experiments. The data obtained demonstrated that these hydrogels had improved pH and thermosensitive characteristics in terms of high equilibrium swelling ratio as well as excellent response dynamics upon external conditions due to changed chain conformations and their porous structures.

KEY WORDS: *N*-Isopropylacrylamide / Itaconic Acid / pH / Temperature / Phase Separation / Chain Conformations /

Hydrogels are defined as lightly crosslinked, three-dimensional hydrophilic polymer networks capable of imbibing large volumes of water while remaining insoluble in water. Intelligent hydrogels can undergo abrupt volume transition reversibly in response to small external stimuli changes, such as temperature,^{1–6} pH,^{7–9} solvent composition,^{10,11} ionic strength,¹² light¹³ and antigen.¹⁴

It is well-known that poly(*N*-isopropylacrylamide)-(*N*IPAAm) hydrogel is a typical thermo-sensitive hydrogel for its exhibiting volume phase transition at a lower critical solution temperature (LCST) around 32–34 °C. Below LCST, PNIPAAm hydrogel swells while dehydrates to collapse when heated above the LCST.¹⁵

Comparatively, polyelectrolyte gel such as poly(acrylic acid)(PAAc) is an ionizable hydrophilic polymer network that can swell to high degrees in basic solutions and collapse in acidic solutions in response to changes of pH.

So, temperature and pH dual responsive hydrogels can be attained by means of copolymerizing these sensitive monomers, such as *N*-isopropylacrylamide and acrylic acid. Very recently, a number of pH and temperature-sensitive materials^{16–20} have been developed for use as drug delivery systems (DDS), separation operations in biotechnology, and processing of agricultural products.

To date, a lot of efforts have been made to improve the properties of hydrogels, especially the response rate, such as employing phase separation techniques,^{21,22} introducing the dangly comb-chains,^{23,24} forming macro-porous^{25,26} or super-porous^{27,28} structures, using mixed solvents,^{29,30} adding particles in gel networks,^{31,32} cold-treating^{33,34} or freezing polymerization.^{35,36} However, in some applications, large water

retention is also needed, specially, in the applications of DDS, large drug load is desired and for the purpose, more hydrophilic polyelectrolyte monomer was often needed to be incorporated. Unfortunately, introduction of too many hydrophilic monomers would result in the hydrogels losing thermo-sensitivities and exhibiting low mechanical strength in a highly swollen state, as revealed by several reporters.^{37,38}

This paper was therefore aimed at developing hydrogels to overcome these problems, getting higher swelling ratios without weakening thermo-sensitivities. A strategy of using mixed solvents DMF and water was introduced to control the conformations of the polymer chains during its growth. Itaconic acid was adopted to introduce pH sensitivity which had two carboxylic acid groups with different p*K*_a (3.85, 5.45) leading to form more hydrogen bonds than acrylic or methacrylic acid to show more hydrophilic. In addition, itaconic acid obtained by fermentation of renewable resources, such as carbohydrates (sugarcane molasses or starch), is expected to show better biocompatibility than acrylic acid or methacrylic acid.^{39,40}

The newly synthesized P(*N*IPAAm-*co*-IA) hydrogels were characterized by scanning electron microscopy to investigate their surface morphologies and network structures. The properties of the hydrogels, such as temperature-sensitivity, pH-sensitivity, were also examined through swelling ratios, deswelling/reswelling kinetics and deswelling-reswelling cycles.

EXPERIMENT

Materials

N-isopropylacrylamide (NIPAAm, Acros) purified by recrystallization from a mixture of toluene and *n*-hexane

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Table I. Feed composition, resulted massive weight and PIA percent of P(NIPAAm-*co*-IA) Hydrogels (G80-G35) synthesized in DMF and water mixed solvents at 15 °C

RUN ^a SampleID	NIPAAm (g)	IA (g)	BIS (g)	H ₂ O (ml)	DMF (ml)	W _t ^b (g)	Conver sion(%)	Mol % of PIA
1. (G80)	0.5000	0.0150	0.0250	8	0	0.5297	96.3	2.401
2. (G71)	0.5000	0.0150	0.0250	7	1	0.5233	95.1	2.399
3. (G62)	0.5000	0.0150	0.0250	6	2	0.5179	94.2	2.398
4. (G53)	0.5000	0.0150	0.0250	5	3	0.5109	92.9	2.401
5. (G44)	0.5000	0.0150	0.0250	4	4	0.5068	92.1	2.402
6. (G35)	0.5000	0.0150	0.0250	3	5	0.5007	91.0	2.398

a: KPS: 0.0125 g, TEMED: 10 uL. b: W_t: the weight of the resultant dry gel.

(v:v = 3:2) and itaconic acid (IA, purity > 99%) purchased from Aldrich were used as monomers. *N,N'*-methylenebisacrylamide (BIS) purified by recrystallization from methanol was used as a crosslinking agent, potassium persulfate (KPS), *N,N,N',N'*-tetramethylethylenediamine (TEMED) were used as the polymerization initiator and accelerator. Dimethylformamide (DMF) was analytical grade and was used as received without further purification.

Potassium tetroxalate dehydrate (KH₃(C₂O₄)₂·2H₂O), Potassium hydrogen tartrate (KHC₄H₄O₆), Potassium hydrogen phthalate (C₆H₄CO₂HCO₂K), Disodium hydrogenorthophosphate (Na₂HPO₄), Potassium dihydrogen phosphate (KH₂PO₄), Sodium tetraborate decahydrate (Na₂B₄O₇·10H₂O) and Sodium chloride (NaCl) were analytical grade and used to prepare pH buffer solutions.

Preparation of Hydrogel

Monomers NIPAAm, IA, and crosslinker (BIS) at fixed molar ratios were fully dissolved in premixed water and DMF solvents at 15 °C. Then the initiator KPS and accelerator TEMED were added. The mixtures were allowed to copolymerize for 24 h at this temperature. The resultant hydrogels were cut into discs (10 mm in diameter, 1 mm in thickness) and immersed in distilled water at 5 °C to extract DMF, unreacted monomers and linear polymers. During the purification period, the distilled water was replaced every day for a week. The resulting P(NIPAAm-*co*-IA) hydrogels were labeled as G80, G71, G62, G53, G44 and G35, respectively. And the feed compositions of the monomers, crosslinker and mixed solvents were listed in Table I.

Preparation of pH Buffer Solutions

Standard pH buffer solutions were prepared according to IUPAC STANDARDS AND PROCEDURES.⁴¹ The pH and compounding way were listed in Table II. The ionic strength of pH buffer solutions were adjusted to uniform (I = 0.05 mol·Kg⁻¹) using NaCl.

Instrumentation

Optical Images. All the optical images were recorded using Canon A510 cameras.

Surface Morphology Observation. Scanning electron microscopy (SEM, JSM-5910, Japan) was used to study the surface morphologies of the hydrogels. To prepare samples for

Table II. The standard pH buffer solutions with different molarities (C) and ionic strengths (I) and the compounding ways

pH	C (mol·L ⁻¹)	I (mol·kg ⁻¹)	Compounding Way
1 1.68	0.05	0.05	12.71 g KH ₃ (C ₂ O ₄) ₂ ·2H ₂ O in 1 L H ₂ O
2 3.56	0.034	0.034	7 g KHC ₄ H ₄ O ₆ in 1 L H ₂ O overnight, filtrated
3 4.01	0.05	0.05	10.21 g C ₆ H ₄ CO ₂ HCO ₂ K in 1000 mL H ₂ O
4 6.86	0.025	0.01	3.53 g Na ₂ HPO ₄ and 3.39 g KH ₂ PO ₄ in 1 L H ₂ O
5 9.18	0.01	0.03	3.80 g Na ₂ B ₄ O ₇ ·10H ₂ O in 1 L H ₂ O

SEM, the swollen hydrogels were freeze-dried and then sputter coated with gold.

Temperature Dependence of the Swelling Ratio

The temperature dependence of swelling ratio of hydrogels was measured gravimetrically after carefully blotting surface water with moistened filter paper in the temperature range from 25 to 60 °C. Hydrogel samples were immersed in distilled water for at least 24 h at each predetermined temperature. The average value of three measurements was taken for each sample, and the equilibrium swelling ratio (ESR) is defined as follows:

$$\text{Equilibrium Swelling Ratio: ESR} = (W_s - W_d)/W_d;$$

where W_s is the weight of swollen hydrogel at the particular temperature and W_d is the dry weight of the hydrogel.

The Equilibrium Swelling Ratio in pH Buffer Solutions

The swelling ratio of hydrogels was measured gravimetrically at ambient temperature (25 °C). Hydrogel samples were immersed in various pH buffer solutions for at least 24 h. The average value of three measurements was taken for each sample, and the swelling ratio (SR_{pH}) is defined as follows:

$$\text{Swelling ratio: SR}_{\text{pH}} = (W_s - W_d)/W_d;$$

where W_s is the weight of swollen hydrogel at ambient temperature and W_d is the dry weight of the hydrogel.

Measurement of Deswelling Kinetics

The deswelling kinetics of hydrogels was measured gravimetrically at 60 °C. The hydrogel samples were first immersed in distilled water at 25 °C until equilibrium was reached. Then, the equilibrated hydrogels were quickly transferred to various pH buffers of 60 °C. At specified time intervals, the samples

were removed from the hot pH buffers and weighted after wiping off the excess surface water with moistened filter paper. The average value of three measurements was taken for each sample, and the swelling ratio (SR_d) is defined as follows:

$$\text{Swelling ratio: } SR_d = (W_t - W_d)/W_d;$$

where W_t is the weight of hydrogel at regular time intervals, W_d is the weight of the dry gel.

Measurement of Reswelling Kinetics

The kinetics of reswelling of gels was measured gravimetrically at 25 °C. Before the measurement, the hydrogel samples were freeze-dried for 24 h. The weight changes of gels were recorded during the course of reswelling in distilled water after blotting the excess surface water at regular time intervals. The swelling ratio (SR_r) is defined as follows:

$$\text{Swelling ratio: } SR_r = (W_t - W_d)/W_d;$$

where W_t is the weight of hydrogel at regular time intervals, W_d is the weight of the dry gel.

Deswelling-Reswelling Cycles

In order to investigate the structure stability of the gels, the oscillatory deswelling–reswelling behavior was studied. Samples which swelled below the LCST were transferred into pH 6.86 buffer solutions at 60 °C. At specified time intervals, the samples were removed from the hot water and weighted after wiping off the excess surface water with moistened filter paper. After reaching equilibrium, the sample was transferred to a cold distilled water (25 °C) to swell. In the same way, the samples were removed from the cold water and weighted at specified time intervals. After reaching equilibrium, the samples were transferred to pH 6.86 buffer solutions at 60 °C again. The average value of three measurements was taken for each sample and the deswelling–reswelling measurements were repeated three times. And the swelling ratio (SR_c) is defined as follows:

$$\text{Swelling ratio: } SR_c = (W_t - W_d)/W_d;$$

where W_t is the weight of hydrogel at regular time intervals, W_d is the weight of the dry gel.

RESULTS AND DISCUSSION

Preparation of Hydrogel

The chemical structures and the preparation procedures of the hydrogels are shown in Figure 1. It is worth noting that the polymerization tubes need to be immersed in an ice/water bath to avoid any pre-polymerization of NIPAAm due to the strong exothermic behavior when DMF and water were mixed together. For the same reason TEMED was added only at the final stage, otherwise, the hydrogels obtained would be opaque and soft. As shown in the Table I, in the all runs, the amount of commoners (NIPAAm, IA), crosslinker (BIS), initiator (KPS) and accelerator (TEMED) were kept the same, while the volume ratios of solvents (DMF: Water) changed gradually

Figure 1. The structures of the monomers and crosslinker and synthetic procedure for P(NIPAAm-co-IA) Hydrogels.

Figure 2. Optical photos of the formed P(NIPAAm-co-IA) hydrogels (before disposal). From the left to the right: G80, G71, G62, G53, G44 and G35.

from 0:8 to 5:3. The massive weight of the resultant hydrogels showed little difference. However, the physical appearances of the formed hydrogels were somewhat different, as shown in the Figure 2. It can be found that from G80 to G53, the hydrogels in the tubes are transparent at room temperature while G44 shows somewhat phase separation. If shifting the synthetic temperature from 15 °C to 20 °C, the phase separation becomes more pronounced and the resulted gel becomes translucent (Figure 3b). More phase separation is found from G35 where even precipitation can be observed (Figure 3c), and if doubling the amount of initiator, the gel becomes opaque which can be recognized from the Figure 3d. It is because polymer chain conformations are not only dominated by the static factors, such as temperature and mixed cononsolvents ratios, but also controlled by the dynamic factors concerned with the rate of

Figure 3. Optical photos of the formed P(NIPAAm-*co*-IA) hydrogels fabricated under different conditions. a: G44 at 15 °C; b: G44 at 20 °C; c: G35 with 0.0125 g KPS; d: G35 with 0.025 g KPS.

polymer growth induced by temperature or initiator amount etc.

Usually, both DMF and water are good solvent candidates for the polymerization of NIPAAm because each of them is good solvent for PNIPAAm.⁴² However, when these two solvents mixed together in some ratios, they became co-no solvents and the re-entrant phenomenon took place which resulted in the phase separation.⁴³ Correspondingly, the physical appearances of gels changed from transparent to translucent or opaque. The exact nature of the cononsolvency behavior of linear chains and the corresponding re-entrant phenomenon observed in hydrogels is still an open question.¹⁰ It was proposed that when DMF was mixed with water, different water/DMF complexes formed, which were poor solvents for PNIPAAm and its copolymers.⁴⁴ During the growth of P(NIPAAm-*co*-IA) chains, competitive interactions existed between DMF, water and P(NIPAAm-*co*-IA) chains. First, attractive interactions between polymer chains and water molecules dominated over the attraction between the polymer chains. With the increase of DMF, attractive interactions between two solvents became predominant, such resulting in an increase in the free energy for polymer-polymer contact.⁴⁵ Finally, these increase in the affinity among polymer segments induced the collapse of the polymer network.⁴⁶

The appearances and shapes of the swollen hydrogels are shown in Figure 4 except G35 because it is too hard to pick up in a whole due to its huge amount of water adsorption. It is interesting to find that with the increase of DMF amount in the mixed solvents, the water absorption of purified gels increase in the order of G80 < G71 < G62 < G53 < G44 < G35. It is because during crosslinking in the mixed solvents, the polymer chains were often curled, intertwined each other, and itaconic acid could not be ionized fully. With the amount of DMF increased,

Figure 4. Optical photos of the swollen equilibrium P(NIPAAm-*co*-IA) hydrogels. From the left to the right: G80, G71, G62, G53 and G44.

the growing P(NIPAAm-*co*-IA) chains took somewhat coil-globule conformations transition exhibiting in the form of phase separation, and the ionization of carboxyl of itaconic acid became even harder. When the DMF was replaced by water after the purification, the itaconic acid ionized and the repulsion forces intrigued the polymer chains to relax and extend. So, it is reasonable that when DMF was used in the gelation, the swelling ratios of the hydrogels were higher than those prepared in pure water and the differences became more dramatic as the DMF content increased attributed to the expanded network structure formed after the purification as discussed above. Thus, the higher the DMF content, the greater the network expansion, the more water was contained in the hydrogels.

The percent gelation of G80, G71, G62, G53, G44 and G35 was 96.3, 95.1, 94.2, 92.9, 92.1 and 91.0, respectively, as determined by mass measurements, suggested that the polymerization and cross-linking reactions were close to complete. Furthermore, the hydrogels were subjected to acid-base titration analysis after extraction.⁴⁰ It was found the Mol percentage of PIA in hydrogels of G80, G71, G62, G53, G44 and G35 was 2.401, 2.399, 2.398, 2.401, 2.402 and 2.398, respectively. The results revealed that the percentage of PIA in gels very little changed from G80 to G35. Similar results were reported by other authors.⁴² Hence, the copolymer composition could be approximated very well to the initial feed composition.

SEM

After the purification and freeze-dried treatment, the honeycomb structures of the gels were formed by relaxation of polymer chains and kept as shown in Figure 5. All of the hydrogels exhibit micro-, even macro-porous structures except the sample prepared in pure water. The surface morphology of normal hydrogels such as G80 is dense, smooth and homogeneous. With the addition of DMF, it becomes loose and porous connecting to each other to form open capillary channels. As a result, water molecules can easily diffuse in and out. Therefore, the response rate of the swelling or deswelling could be greatly enhanced as described below.

Temperature Dependence of the Swelling Ratio

The classical temperature dependence of Equilibrium Swelling Ratios (ESRs) of the resultant P(NIPAAm-*co*-IA) hydrogels in distilled water were studied over a temperature range from 25 to 60 °C as shown in Figure 6. It can be found

Figure 5. SEM images of the hydrogels (a) G80, (b) G71, (c) G62, (d) G53, (e) G44, (f) G35.

Figure 6. The temperature dependence of Equilibrium Swelling Ratios of the resultant hydrogels in distilled water.

that at an initial temperature of 25 °C, all the hydrogels show high swelling ratios compared with traditional pure P(NIPAAm) hydrogels, due to the incorporation of hydrophilic monomer, IA. And with the increase of the DMF content, the ESR of the corresponding hydrogels increases. For example, the ESR of G80, G71, G62, G53, G44 and G35 is 65.2, 109.8, 119.2, 164.3, 337.2 and 697.1, respectively. This difference may be attributed to the stretched chain conformations and various porous structures of the network which provide more free space for accommodation of water molecules. As temper-

ature increases, the ESR of all gels decrease continuously and the temperature range of the transition broadened for all P(NIPAAm-co-IA) gels relative to the poly(NIPAAm). These results mean that the thermo-sensitivity successfully preserved within those super-absorbent gels whose networks were in highly swollen state and polymer chains were highly relaxed, hydrated. As for the phase transition temperature or Lower Critical Solution Temperature (LCST), there was a pronounced shift toward higher temperatures for all gels, estimated in the vicinity of 50 °C. Generally, for temperature-sensitive polymers, incorporation of a hydrophilic comonomer leads to an increase in LCST. As the hydrophilic moiety, itaconic acid was introduced into the network, the hydrophilic/hydrophobic balance in copolymers was shifted toward a more hydrophilic nature, and its LCST shifted to a higher temperature. The difference of LCST among gels was not apparent because the chemical compositions of each sample were nearly same. This ability to improve swelling ratios dramatically without losing thermo-sensitivities and the LCST of copolymers can be reserved to be as high as 50 °C provides excellent flexibility in tailoring transitions for specific uses by alternating the feed ratio of the hydrophobic NIPAAm monomer and hydrophilic IA monomer, *e.g.*, the LCSTs of gels could be adjusted to be about 37 °C just around the human body's temperature. From Figure 6, it may also be found that eventually at shrunken state

of 60 °C the ESRs of G35 and G44 were a little higher than that of the other gels, because their loose structures and macropores cannot be occupied entirely by the hydrophobic cross-linked polymer chain and can even hold a part of water.

The Equilibrium Swelling Ratio in pH Buffer Solutions

As the P(NIPAAm-*co*-IA) hydrogels contain functional groups, -COOH, which can be protonated or ionized at a suitable pH, then variation in the pH of the swelling medium causes an appreciable volume phase transition, which also forms the basis for the swelling dependent pH-sensitive drug delivery system. In this work, the effect of pH on the equilibrium water uptake was investigated for all hydrogel samples, in the swelling media of five pH buffer solutions at room temperature as demonstrated in Figure 7. As can be seen, the P(NIPAAm-*co*-IA) hydrogels exhibited the highest swelling ratios in basic medium and decreased with the decrease of pH from 9.18 to 1.67. For example, the swelling ratio of G35 in the media of pH 9.18, 6.86, 4.01, 3.55 and 1.67 is 62.7, 40.3, 32.5, 29.8 and 25.2, respectively. This phenomenon is related to the ionization and protonation balance of the carboxyl groups of IA. At pH 9.18, carboxyl groups were ionized in the form of COO⁻, and the resulted electrostatic repulsion pushed the network to expansion leading to higher swelling ratios. While at low pH values, such as 1.67, the carboxyl groups protonated and the hydrogen bonding between polymer chains produced which constrained the network, resulting in low swelling ratios. From the Figure 7, we can also find that at every pH condition, the swelling ratio increases with the increase of DMF. For instance, at pH 9.18, the swelling ratio of

Figure 7. The equilibrium swelling ratio in pH buffer solutions.

G80, G71, G62, G53, G44 and G35 is 32.3, 36.4, 39.2, 47.6, 56.6 and 62.7, respectively. The observed findings may be explained on the basis of the fact that gels have different loose, relaxation chains conformations and porous structures. Certainly, it is clear that these swelling ratios are much smaller than those exhibited in distilled water ascribed to the impact of ionic strength.

Measurement of Deswelling Kinetics

Although the temperature and pH dependences of the swelling ratios are important factors for hydrogels, yet in the view of practical application, the response rate upon external temperature is another concern and even more critical. For better understanding the thermo- and pH-responsive capabilities, the deswelling kinetics of the P(NIPAAm-*co*-IA) hydrogels upon temperature jumping from 25 to 60 °C were further investigated in distilled water and three pH buffer solutions. The results are shown in Figure 8.

Figure 8. Deswelling kinetics in distilled water and pH buffer solutions jumping from 25 °C to 60 °C. (a: distilled water; b: pH 1.67; c: pH 6.86; d: pH 9.18)

From Figure 8a, it can be found that in distilled water both nonporous and porous P(NIPAAm-co-IA) hydrogels exhibited fast deswelling behaviors. All samples from G80 to G35 need about 120 min to shrink to equilibrium states. These results together with the experiment fact that no small water bubbles appeared on the surfaces of P(NIPAAm-co-IA) hydrogels during the deswelling process lead to the conclusion that the introduction of itaconic acid component could inhibit the formation of the dense hydrophobic skin layer and improve the temperature sensitivity and permeability of the resultant hydrogels.⁴⁷ Generally, hydrogels with expanded network structures should behave the fast deswelling kinetics.²⁹ However, the deswelling rate of porous gel G35 was not significantly faster than nonporous gel G80. In these systems, the continuous sequence of isopropylamide groups in polymer chains was disrupted as itaconic acid was incorporated and more hydrogen bonds produced. It is known that the deswelling process required the breakage of H-bonds and the aggregation of hydrophobic polymer chains. However, both of them were greatly weakened due to the existence of the hydrated charged itaconic acid units,⁴⁷ so the acceleration effect induced by the pores of the network was shielded. But the porous hydrogel was superior to the nonporous hydrogel in the magnitude of its swelling ratios during the deswelling processes. Within 2 h, the swelling ratio of G35 changes from 697.8 to 18.2, and the water-loss is as high as 679.6, while that of G44, G53, G62, G71 and G80 is 326.6, 155.1, 111.8, 104.5 and 61.8, respectively. This feature could be particularly beneficial in controlled drug release applications because gels prepared with DMF can release much water or drugs, and the more DMF amount used in the preparation of the gels, the more water or drugs can be carried. In other words, to achieve the same amount of drug release, less gel was needed.

However, in 1.67 pH buffer solutions, as shown in Figure 8b, it is obvious that G35 exhibits the fastest shrinking rate. Its swelling ratio reduces from 695.4 to 8.6 within 60 min. G44 also shows a fast deswelling rate, and dehydrates to equilibrium states within about 100 min. The others exhibit almost same and low deswelling rates. For instance, after 2 h, the swelling ratio of G53, G62, G71 and G80 still stays in 82.4, 50.5, 50.0 and 37.5, respectively. In low pH, the carboxyl groups became protonated after transferring from distilled water and the extensive hydrogen bonding between polymer chains produced correspondingly which constrained the motion of the networks. Moreover, the thick, dense layer formed on its surface, which restricted water molecules from being squeezed out and resulted in such a slow response rate.²³ However, G35 and G44 can dehydrates quickly due to its macro-pores structures that can be served as the water release channels.

Figure 8c shows the deswelling profiles of the hydrogels at pH 6.86, where the fastest deswelling behaviors were observed. It is surprising to find that G35 dropped from a huge water content (701.5) to equilibrium (4.0) only within 20 min, and the other gels shrank and lost water rapidly, too. They lost over 95% of water and reached constant water retention within

the same time period. It is because, at pH 6.86, the carboxyl groups were in ionized state and effective in facilitating deswelling, and the hydrophilicity of the gel matrix makes it difficult to form a skin layer. Otherwise, the charge-screening effect of excess ions in the swelling media shielded the anion–anion repulsion between polymer chains. So water could be diffused out quickly.

At last, the deswelling in basic conditions was examined at pH 9.18, (Figure 8d), all the hydrogels dehydrates to equilibrium within 80 min, but the remained water content is higher than one of above the three conditions and increases in the order of G35>G44>G53>G62>G71>G80. In details, after 2 h, the water conservation is 21.2, 14.7, 9.1, 8.6, 8.0 and 6.9, respectively. In the basic conditions the carboxyl groups become almost completely ionized, the resulted electrostatic repulsion pushes the network to expansion and finally leads to the higher water retention.

Therefore, we may draw a conclusion that the modulated release can be achieved not only by adjusting temperatures but also by pHs and ionic strengths.

Reswelling Kinetics

The dynamic swelling ratios of the freeze-dried P(NIPAAm-co-IA) copolymers hydrogels in distilled water are given in Figure 9. It can be found that the reswelling rate of hydrogels got improved with the increasing amount of DMF. The swelling ratio of G35, G44 reached 603.5 and 249.3 within 30 min, respectively while G71 and G80 just reached 55.5 and 35.4. The reswelling rate is in the order: G35>G44>G53>G62>G71>G80. This tendency is easily understood as the macroporous structures are taken into account. Generally speaking, the swelling process involved three successive steps: (1) the diffusion of water molecules into the matrices, (2) the hydrated polymer chains gets relaxation, and (3) the expansion of the polymer network.^{48,49} Increasing DMF content in polymerization made the network much looser. Even after the treatment of freeze-dried, the polymer chains remained relaxation and networks kept their expanded conformations in some extent. Water may be easier to penetrate into the polymer matrix to initiate the swelling process. All these factors lead to fast reswelling kinetics, as identified by rapid water uptake.

Figure 9. The reswelling kinetics of P(NIPAAm-co-IA) hydrogels.

Figure 10. Oscillating swelling-deswelling behavior of hydrogels in response to temperature cycles between 25 °C (distilled water) and 60 °C (pH: 6.86).

Deswelling-Reswelling Cycles

To investigate whether the responses to the environmental pH and temperature change were reversible and to examine how fast the hydrogels could respond to the external stimuli, the pulsatile stimuli-responsive swelling were performed in water and pH 6.86 buffer solutions with the temperature alternating between 25 and 60 °C. The swelling ratio of the hydrogels was measured every ten minutes and the results were shown in Figure 10. It can be seen that all hydrogels are thermo-reversible except for G35, which is too fragile. After every deswelling-reswelling cycle, each regains its original volume, but the time for achieving equilibrium is different and independent on the pore structure. The higher water content at swollen state, the longer time for recovery. The slow reswelling can be attributed to the fact that before reswelling, gels had suffered completely deswollen, making networks collapse and some pores shut down. So it needs more time to relax after water diffused into the gels.

CONCLUSIONS

In this paper, a series of pH and temperature dual sensitive P (NIPAAm-*co*-IA) hydrogels have been fabricated using DMF and water as mixed solvents. As the increases of DMF in polymerization, the polymer chains become more relaxed and networks become more expanded. These expanded macroporous hydrogels exhibit remarkably high swelling ratios without losing thermo-sensitivities, and the response kinetics can be improved and modulated by controlling polymerization condition, mixed solvent ratio, medium pH etc. After several swelling-deswelling cycles, thermo and pH responsibilities of these gels still remain and keep robust. These P (NIPAAm-*co*-IA) hydrogels may have potential in the drug delivery systems.

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