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Thermo- and pH- responsive copolymers: Poly(*N*-isopropylacrylamide-*co*-IAM) copolymers

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ABSTRACT: Poly(*N*-isopropylacrylamide) (NIPAAm) is well known as a smart material with good thermal sensitivity and favorable biocompatibility. A series of new smart hydrogels, NIPAAm copolymerized with IAM (itaconamic acid; 4-amino-2-methylene-4-oxobutanoic acid), were synthesized through radical solution polymerization in this work. Poly(NIPAAm-*co*-IAM) can respond to the changes of temperature as well as pH value. Such a characteristic is due to the fact that IAM contains not only a hydrophilic acrylic acid moiety but also an acrylamide moiety to be thermal and pH sensitive. The experimental results show that the lower critical solution temperature (LCST) of the copolymer increases as the molar fraction of IAM increases. Moreover, based on the current experimental data, 3 wt % of Poly(NIPAAm-*co*-IAM) aqueous solution in this study exhibits a phase transition temperature (37.8°C) close to the human body temperature in the buffer solution of pH 7 possibly to be useful in drug delivery. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42367.

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INTRODUCTION

A smart polymer or hydrogel is responsive to an external stimulus or stimuli such as changes in temperature, pH values, ionic strengths, light intensity, electric fields.[1,2] Recently, it shows the potential in biomedical applications such as controlled drug release.[3–9] The most representative temperature responsive polymer, poly(NIPAAm),[10–18] has a lower critical solution temperature (LCST) of 32°C which is close to the body temperature. Since poly(NIPAAm) has both hydrophilic (amide) groups and hydrophobic (isopropyl) groups, hydrogen bonds between poly(NIPAAm) and water are strong to show hydrophilicity and a mixture of poly(NIPAAm) and water is a homogeneous solution as the temperature is below its LCST. On the contrary, as the temperature is beyond its LCST, the interaction within poly(NIPAAm) is stronger than the hydrogen bonds between poly(NIPAAm) and water to show hydrophobicity and the mixture appears to be a heterogeneous solution. Therefore, poly(NIPAAm) is widely used as a thermo-sensitive carrier to control drug activity and NIPAAm is often used as a monomer to contribute the thermo-sensitive or thermo-responsive segments to a multiple responsive copolymer.

A pH-responsive polymer responds to changes in the pH of the surrounding medium by varying its dimension. Various acids such as acrylic acid, itaconic acid, vinylphosphonic acid, etc. were reported as a monomer to contribute the pH-sensitive segments to a multiple stimuli-responsive copolymer.[11,18–21] For example, itaconic acid and NIPAAm were copolymerized in aqueous sodium chloride solutions to give a thermo and pH dual responsive copolymer (P(NIPAAm-co-IA)).[11] A multiple stimuli-responsive polymer, such as a thermo- and pH- dual stimuli-responsive polymer, is more flexible in controlling drug release than a single stimuli-responsive polymer. For example, a thermo- and pH- dual stimuli-responsive polymer can respond to not only the temperature change but also the pH change of the environment by varying its solubility, dimension, etc. to carry or release drugs. By copolymerization of two or more monomers containing two or more than two different functional groups, the resulting copolymer can be expected to have more functionalities as a smart polymer or environmental responsive polymer. However, the synergistic effect of containing various functional groups in a molecule does not necessarily occur due to complexity of interaction between the functional groups. For example, vinylphosphonic acid was copolymerized with NIPAAm to biomineralization but not pH sensitivities.[18] In addition, the introduction of pH sensitivities to temperature responsive hydrogels may result in fading or eliminating thermal sensitivities.[11,22] For example, temperature/pH sensitive poly(NIPAAm-*co*-acrylic acid) hydrogels were prepared and found that the LCST of poly(NIPAAm-co-acrylic acid) increased with pH value and disappeared above the pKa value of poly(acrylic acid).[22]

The copolymers in the current work were synthesized using NIPAAm as a monomer to give the thermo-sensitive or thermo-responsive segments and using IAM (itaconamic acid; 4-amino-2-methylene-4-oxobutanoic acid)[23] as a monomer to give the pH-sensitive segments. The properties of poly(NIPAAm-*co*-IAM) were studied and the results show the possibility of biomedical applications.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAAm; $C_6H_{11}NO$) obtained from Aldrich Chemical Corp. was purified through recrystallization from n-hexane twice. Itaconamic acid (IAM; also called "4-amino-2-methylene-4-oxobutanoic acid") was prepared according to the method disclosed in US patent publication No. 2013/0172490. 2,2′-Azobis(isobutyronitrile) (AIBN) (purity 98%), diethyl ether (purity 99.7%), *N*,*N*-dimethylformamide (DMF) (purity 99.8%), H_3PO_4 (purity 85%) and NaOH (purity 98%) were obtained from Aldrich Chemical Corp. without further purification. The buffer solution of pH = 4, obtained from Aldrich, was prepared from potassium hydrogen phthalate; the buffer solution of pH = 7, obtained from Aldrich, was prepared from potassium dihydrogen phosphate and disodium hydrogen phosphate; and the buffer solution of pH = 12, obtained from Aldrich, was prepared from di-sodium hydrogen phosphate and sodium hydroxide solution.

Synthesis of Poly(NIPAAm-*co*-IAM) Copolymers (R-10, R-8, and R-3)

Poly(NIPAAm-*co*-IAM) copolymers were synthesized by radical polymerization shown in Scheme 1. NIPAAm (20 mole) and itaconamic acid (IAM) (with a molar ratio of NIPAAm/IAM = 10/1, 8/1 or 3/1; that is, 2, 2.5, or 6.7 mole) were dissolved in DMF (20 mL) in a flask and 2,2′-Azobis(isobutyronitrile) (AIBN; 0.24 mmole) as the initiator was added to the flask. Before polymerization, the flask was vacuumed for 20 min and nitrogen-purged for 10 min. Then, the flask was kept at about 78°C in the nitrogen environment for polymerization for 24 h. After the reaction was complete, the reaction mixture was added dropwise to diethyl ether for purification through precipitation. After filtration, white solids were obtained and vacuum-dried as samples R-10, R-8, and R-3 for NIPAAm/IAM = 10/1, 8/1, and 3/1, respectively.

Synthesis of Poly(NIPAAm) Homopolymer (H-1)

Poly(NIPAAm) homopolymer was also synthesized by radical polymerization as a comparison to poly(NIPAAm-*co*-IAM) copolymers in this study. NIPAAm (20 mole) was dissolved in DMF (20 mL) in a flask and 2,2′-Azobis(isobutyronitrile) (AIBN; 0.24 mmole) as the initiator was added to the flask. Before polymerization, the flask was vacuumed for 20 min and nitrogen-purged for 10 min. Then, the flask was kept at about 75°C in the nitrogen environment for polymerization for 24 h. After the reaction was complete, the reaction mixture was added dropwise to diethyl ether for purification through precipitation. After filtration, white solids were obtained and vacuum-dried as sample H-1.

Identification and Characterization

NMR spectra were measured using a Bruker Advance 300 MHz NMR spectrometer by weighing 10 mg of a test sample and dissolving in 1 mL of DMSO-d_6 placed in a standard 507-HP NMR test tube. FTIR spectra were measured by Perkin Elmer Spectrum RXI FTIR within 4000−400 cm^{-1} having resolution of 4.00 cm^{-1}.

A test sample 0.1g was added to deionized water 100 mL to obtain a diluted solution for the dynamic light scattering (DLS) measurement. The weight average molecular weight (M_w), number average molecular weight (M_n) and PDI (M_w/M_n) of the polymers were determined by a Viscotek GPC (Gel permeation chromatography) system from Malvern Ltd. The test sample was prepared by weighing 3 mg of a test material and dissolving in 10 mL of THF under the conditions that a column 300 × 810 mm^2 and a flow rate of 1 mL/min were used, the temperature of the column was set to 50°C, the temperature of the detector was set to 50°C, and the injection quantity of the test sample and the standard, separately, was 50 μL.

Each of the LCSTs was determined from the transmittance of the sample containing poly(NIPAAm) homopolymer or poly(NIPAAm-*co*-IAM) copolymers as a function of temperature using a laser transmittance meter (LASOS LGK 7628), that is, the LCST is the temperature when the transmittance of the solution is 50%. The test samples containing poly(NIPAAm) homopolymer and poly(NIPAAm-*co*-IAM) copolymers were prepared by adding poly(NIPAAm) homopolymer or poly(NIPAAm-*co*-IAM) copolymers (H-1, R-10, R-8, R-3) to water in a 1 mL vial to obtain the samples with different concentration (1, 3, 5, 7, 10, 13, 15, or 20 wt %). Besides, the samples containing poly(NIPAAm) homopolymer or poly(NIPAAm-*co*-IAM) copolymers (H-1, R-10, R-8, R-3) in the solutions having different pH values (2, 4, 8, and 12) were prepared by adding 1.5 mL of 1, 3, 5, or 10 wt % polymer solution to the H_3PO_4 (0.04*M*) solution or the NaOH (0.1*M*) solution to adjust the pH values (2, 4, 8, and 12) for the study of the LCSTs at the environmental pH values. The samples containing poly(NIPAAm) homopolymer or poly(NIPAAm-*co*-IAM) copolymers (H-1, R-10, R-8, R-3) in the buffer solutions (pH4, 7, or 12) were prepared adding 10 mL of the aqueous solutions containing 3 wt % polymers to the buffer solutions (pH4, 7, or 12) for the study of the LCSTs in the buffer solutions.

The content of the carboxyl groups derived from IAM in the copolymers was determined by acid-base titration using the NaOH solution to neutralize the carboxyl groups in 10 mL of the 3 wt % solution with the phenolphthalein indicator.

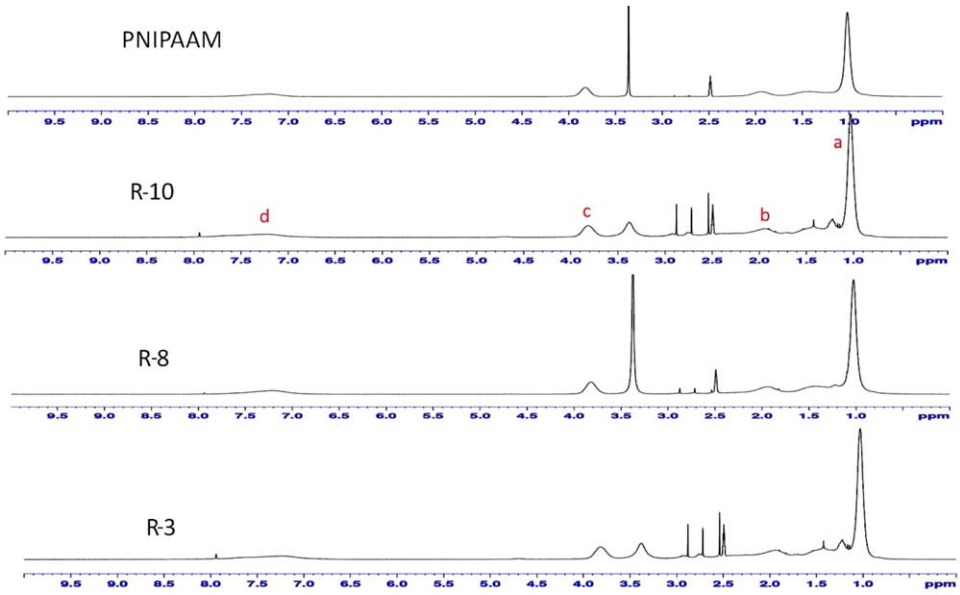

Figure 1. ^{1}H-NMRspectra of Poly(NIPAAm) and Poly(NIPAAm-*co*-IAM). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

RESULTS AND DISCUSSION

NMR Results

Poly(NIPAAm-*co*-IAM) Copolymers (R-10, R-8, R-3). In ^{1}H-NMR, the characteristic peaks from IAM are at $\delta = 1.2-2.2$ ppm (^{3}H, –C–C$\underline{H}_2$– on the polymer chain), $\delta = 6.5$–7.5 ppm (^{2}H, –CH$_2$–CO–N$\underline{H}_2$) and $\delta = 12-13$ ppm (^{1}H, OH) and the characteristic peaks from NIPAAm are at $\delta = 0.8-1.2$ ppm (^{6}H, CH$_3$, isopropyl), $\delta = 3.7-4.0$ ppm (^{1}H, CH, isopropyl), $\delta = 5.0-6.0$ ppm (CH$_2$ = CH-) and $\delta = 7.0-7.8$ ppm (^{1}H, NH, amide). From ^{1}H-NMR spectra of poly(NIPAAm-*co*-IAM) copolymers and Poly(NIPAAm) in Figure 1, the band "*a*" ($\delta = 0.8-1.5$ ppm) is attributed to two CH$_3$ from the isopropyl group and CH$_2$ from the polymer chain (two H from NIPAAm and two H from IAM), the band "*b*" is attributed to CH$_2$ from IAM and CH from NIPAAm, the band "*c*" is attributed to the –C$\underline{H}$–NH– group of NIPAAm and the band "*d*" is attributed to the NH$_2$ group from IAM and NH group from NIPAAm.

The ratio of the composition units from NIPAAm to the composition units from IAM in R-10, R-8, or R-3 was determined by ^{1}H-NMR where the area of the peak at $\delta = 3.7-4.0$ ppm (–C$\underline{H}$–NH–) is defined as 1 and the peaks at $\delta = 0.8-1.5$ ppm (6H+2H from NIPAAm and 2H from IAM) and $\delta = 1.5-2.4$ ppm (1H from NIPAAm and 2H from IAM) are used to quantize the composition units from NIPAAm and the composition units from IAM. That is, if Hx represents H from NIPAAm and Hy represents H from IAM, the following two equations will be obtained: 6Hx+2Hx+2Hy = ING1 and Hx+2Hy = ING2 where ING1 and ING2 are the value from integrating the area of the peak at $\delta = 0.8-1.5$ ppm and $\delta = 1.5-2.4$ ppm, respectively. Table I shows the feeding ratios of NIPAAm to IAM monomers compared with the polymerized ratios (NIPAAm/IAM) in copolymers, together with the result from the acid-base titration. The IAM content from the acid-base titration is also shown in Table I and the comparison of the two results will be discussed later. For the purpose of comparison, the molar fraction of IAM from NMR for R-3 are assumed to be the same as that from the titration. In the "[%]", the calculated molar fraction of IAM based on the titration is shown. From Table I, it is found that the polymerized molar fractions of the composition units from IAM in the copolymers are consistently higher than the feeding molar fractions probably because diethyl ether with low polarity was used as the precipitator to cause the copolymers having more functional groups with high polarity such as amino, carbonyl, and carboxyl groups to precipitate or because IAM has two electron-withdrawing groups to have better reactivity than NIPAAm.

Table I. Composition Ratios of NIPAAm/IAM for Poly(NIPAAm-*co*-IAM)

Sample	Feeding raio (mol/mol) NIPAAM : IAM	Polymerized ratio (mol/mol) NIPAAM : IAM	IAM content from NMR	IAM content (%) from titration
R-3	3 : 1	3 : 2	40%	18.4% [40%][a]
R-8	8 : 1	5 : 1	17%	10.3% [23%]
R-10	10 : 1	6 : 1	14%	8.1% [18%]

[a] It is assumed that the ratio of IAM from NMR is the same as that from titration for R-3 and thereby the numbers in [] in the same column for R-8 and R-10 are calculated.

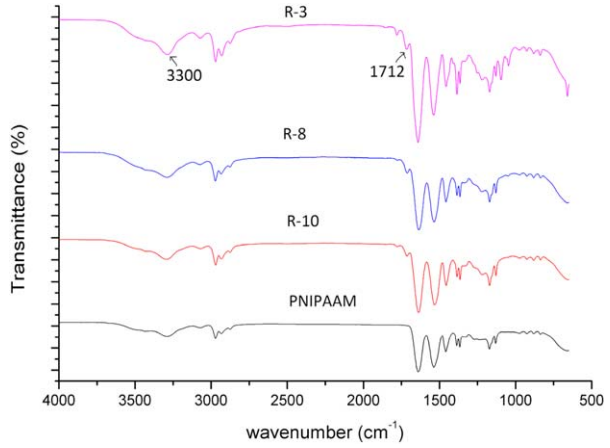

Figure 2. FTIR spectra of poly(NIPAAm-*co*-IAM) and poly(NIPAAm). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FTIR RESULTS

The FTIR spectra of poly(NIPAAm) and poly(NIPAAm-*co*-IAM) copolymers are shown in Figure 2. In the spectrum of NIPAAm, the amide C═O stretching peak is shown at 1655 cm^{-1}; the amine N—H bending peak is shown at 1549 cm^{-1}; the amine N—H stretching peak is shown at 3500−3300 cm^{-1}; and the mono-substituted C═C (vinyl) peak is shown at 900 cm^{-1}. After polymerization, the spectrum of poly(NIPAAm) labeled as PNIPAAM shows an absence of the 990 cm^{-1} peak indicating C═C is formed into C—C in poly(NIPAAm).

As show in Figure 2, the spectra of the copolymers show the intensity of the 1712 cm^{-1} peak (due to C═O stretch of carboxylic group of IAM) increases with the molar fraction of IAM and the intensity of the 3300 cm^{-1} peak (due to O—H of the carboxylic group of IAM) increases with the molar fraction of IAM. Thus, the FTIR spectra also confirm successful synthesis of poly(NIPAAm-*co*-IAM) copolymers.

GPC Analysis

The GPC curves of poly(NIPAAm) and poly(NIPAAm-*co*-IAM) labeled as H-1, R-10, R-8, and R-3 are shown in Figure 3 and the weight average molecular weight (M_w), the number average molecular weight (M_n), and PDI (M_w/M_n) calculated from GPC are shown in Table II. As the molar fraction of IAM increases, the molecular weight of the copolymer is higher which may be because of hydrogen bond formation between the solvent (THF) and the copolymer which has more hydrophilic groups derived from IAM or more proton-donor groups (NH_2 and COOH) but PDI is about 1.8 which is almost the same regardless of the molar fraction of IAM.

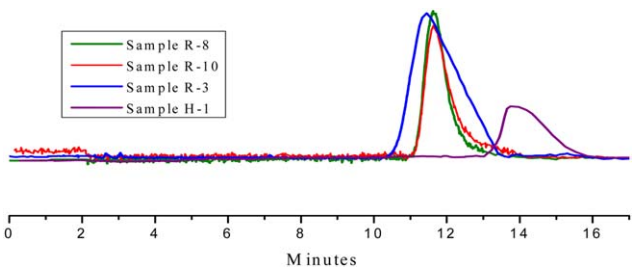

Figure 3. Molecularweight determination by GPC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Acid−Base Neutralization Titration

The acid-base neutralization titration was used to quantize the content of the carboxyl groups in the copolymers. When the equivalence point of the titration using NaOH with the phenolphthalein indicator is reached, the solution will turn light purple. The amont of NaOH used in the titration is converted to the molarity of the carboxyl groups in the copolymers. The molarity of carboxyl groups in the copolymers was used to determine the content of IAM. The titration result in Table I shows consistently lower IAM content than the NMR result but the trend is in agreement with the the molar ratio of NIPAAM/IAM from NMR. It may be because the copolymer has NH_2 groups to interfere the determination of the titration end point. In view of the presence of the amino group, for example, an amino acid cannot be correctly titrated for its acidity because the H ion formed by the ionization of COOH will be taken by NH_2 and be present as NH_3^+. The total acidity based on the titration end point will be less than the actural. However, the titration result was only intended to show the trend of the molar ration of IAM (R-3, R-8, R-10). Since Table I was targeted to show the molar fraction of IAM for R-3, R-8, R-10, the NMR result is considered more suitable than the titration.

LCST Analysis

The dependence of the LCST on the concentration (1, 3, 5, 7, 10, 13, 15, or 20 wt %) for samples H-1, R-10, R-8, and R-3 is shown in Figure 4(a). The LCST of the copolymer increases as the IAM molar fraction increases and the LCST of poly(NIPAAm) homopolymer does not have IAM units and has the lowest LCST. Such a phenomenon may be because the hydrophilic groups such as carboxyl and amino groups in the copolymers originated from IAM form hydrogen bonds with water so as to increase the LCST. That is, there are more hydrophilic groups in the copolymer than poly(NIPAAm) and the addition of IAM in the copolymer will effectively increase the LCST of the copolymer. In addition, the LCST of the copolymer decreases as the concentration increases while the LCST of poly(NIPAAm) homopolymer does not show a significant concentration effect. The low LCST at the high concentration indicates molecular chains are close to each other and apt to get entangled and gather together and thus the interaction force between the molecules is larger than the strength of the hydrogen bonds with water so as to expell water molecules from the copolymer. On the contrary, at the low concentration molecular

Table II. Molecular Weight Determination

Sample	$M_w/10^5$	$M_n/10^5$	PDI
H-1	2.15	1.58	1.36
R-10	3.40	1.83	1.86
R-8	3.53	1.90	1.82
R-3	5.15	2.76	1.87

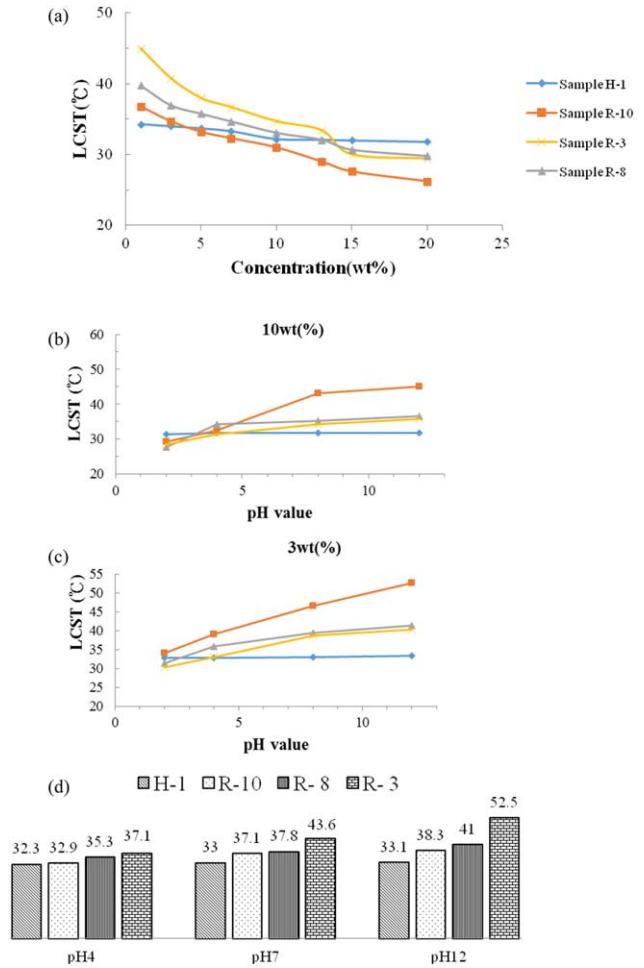

Figure 4. (a)dependence of LCST on concentration for samples H-1, R-10, R-8, and R-3; (b): dependence of LCST on pH values for samples H-1, R-10, R-8, and R-3 in a 10 wt % aqueous solution; (c) dependence of LCST on pH values for samples H-1, R-10, R-8, and R-3 in a 3 wt % aqueous solution; and (d): Dependence of LCST (°C) on pH values for samples H-1, R-10, R-8, and R-3 in buffer solutions of pH = 4, 7, and 12 with 3 wt % concentration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

chains are far away from each other and thus the interaction force between the molecules is weaker than the strength of the hydrogen bonds with water.

Figure 4(b) shows the dependence of LCST on pH values for samples H-1, R-10, R-8, and R-3 in a 10 wt % aqueous solution and Figure 4(c) shows the samples in a 3 wt % aqueous solution. The 10 wt % aqueous solution represents the case of a solution containing high concentration of the copolymer while the 3 wt % aqueous solution represents the case of a solution containing low concentration of the copolymer. At first, the LCST of poly(NIPAAm) homopolymer is expected to have no significant dependence on pH values shown in Figure 4(b,c). Second, the copolymers are pH-responsive because IAM is introduced. At a low pH value, the low LCST of the copolymer indicates low water solubility of the copolymer in the acidic environment. Besides, at a low pH value, less carboxyl groups from IAM units in the copolymer are charged and lead to enhance the formation of hydrogen bonds between COOH moiety from IAM and NHCO moiety from NIPAAm. It would make the copolymer have lower water solubility so that the LCST is lowered. In the low pH environment, the copolymer has more carboxyl groups from IAM units being charged to become swelling and lead to enhance the formation of hydrogen bonds between polymer chain-segments and water. Thus, the LCST is higher at a high pH value and the trend is more significant for the copolymer having a higher molar ratio of IAM/NIPAAm. Third, molecular chains are closer to each other at the high concentration than at low concentration to drive the hydrophobic moieties ($-CH(CH_3)_2$) to get entangled and gather together so that the cohesive force between the molecular chains increases to show more hydrophobicity. Thus, the range of the LCSTs is narrower at the high concentration than at the low concentration. At the low concentration, the molecular chains are far away from each other to become swelling and have weaker interaction but the strength of hydrogen bonds between the molecular chains and water is stronger and the hydrogen bonds are required more energy to break. Thus, the LCST is higher at the low concentration than at the high concentration.

Furthermore, Figure 4(d) shows the dependence of LCST (°C) on pH values for samples H-1, R-10, R-8, and R-3 in the buffer solutions of pH = 4, 7, and 12 with 3 wt % concentration. The difference between Figure 4(c) and Figure 4(d) is that the solutions for various pH values in Figure 4(c) were prepared using H_3PO_4 or NaOH and the buffer solutions in Figure 4(d) were prepared using the commercially available buffer solutions which contains salts. In the current work, the two different pH conditions were studied. The difference between the two conditions is not very significant and the LCST in buffer solutions is slightly lower. At the high concentration, the salts in the buffer solution may cause the shielding of the electrostatic repulsions between the COO^- groups, and the copolymers were not in such an extended conformation like in the absence of salt which leads to lower the LCST. The salts in the buffer solution form hydrogen bonds with water instead of the molecular chains of the copolymer, which leads to lower the hydrophilicity of the copolymer so as to lower the LCST.

As shown in Figure 4(d), at pH = 7, the LCSTs of samples R-8 and R-10 are 37.1°C and 37.8°C, respectively, which are close to the body temperature, 37°C. It indicates the possibility of applying these copolymers to drug release.

Morphological and Dimensional Analysis

The dynamic light scattering (DLS) measurement was used to determine the particle diameters of samples H-1, R-10, R-8, and R-3. The particle diameters of samples H-1, R-10, R-8, and R-3 at 25°C are 150.6, 223.6, 234.5, and 414.3 nm, respectively.

Figure 5(a) shows the dependence of effective diameters on pH values for samples H-1, R-10, R-8, and R-3 in a 3 wt % aqueous solution and Figure 5(b) shows the dependence of effective diameters on pH values for samples H-1, R-10, R-8, and R-3 in the buffer solutions of pH = 4, 7, and 12 with polymer concentration of 3 wt %. The results from Figure 5(a,b) both indicate the particle diameters of the copolymers vary with the pH value in the environment and the particle diameter of poly(NIPAAm)

homopolymer does not vary with the pH value. The difference between Figure 5(a,b) is that the salts in the buffer solution has influence on the particle size for the copolymers where the effective diameter in the buffer solution is smaller.

Figure 6 shows the proposed conformation of poly(NIPAAm-*co*-IAM) at different pH values. In an acidic environment, at the LCST, most of the carboxyl groups from IAM units are not ionized and have the COOH form and the COOH goups from IAM units and the NHCO groups from NIPAAm units form hydrogen bonds, which leads to chain entaglement to deswell the particle (reducing the particle diameter). On the contrary, in an alkaline environment, at the LCST, most of the carboxyl groups from IAM units are ionized and have the COO?-?− form and the polymer chains are hydrated, which leads to swell the particle because of repulsion force (increasing the particle diameter). Similarly, at different pH values, the swelling−deswelling mechanism causes the difference in LCSTs. However, the salts in the buffer solution compete with the copolymer to form hydrogen bonds with water. The factors of the hydrogen bond formation with water and the hydrogen bond formation within the copolymer cause the difference of the particle diameters between Figure 5(a,b).

CONCLUSIONS

In the current work, the thermo- and pH- responsive copolymers poly(NIPAAm-co-IAM) were prepared as new materials by radical polymerization. The segments originated from IAM were introduced to make the copolymer be pH-sensitive. The molar ratio of IAM to NIPAAm can be adjusted to control the resulting copolymer to have the desired LCST. The LCST of the copolymer

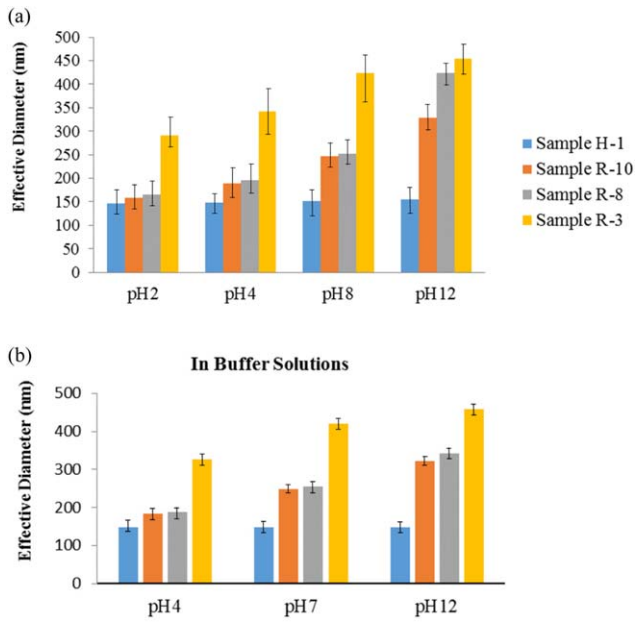

Figure 5. (a)Dependence of effective diameters on pH values for samples H-1, R-10, R-8, and R-3 in a 3 wt % aqueous solution; and (b) dependence of effective diameters on pH values for samples H-1, R-10, R-8, and R-3 in buffer solutions of pH = 4, 7, and 12 with polymer concentration of 3 wt %. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

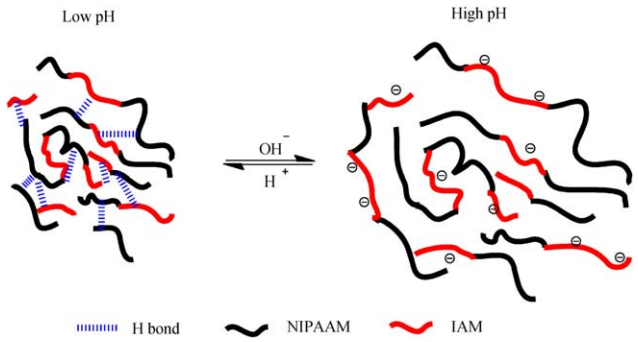

Figure 6. Conformation of poly(NIPAAm-*co*-IAM) at different pH values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

increases as the molar fraction of IAM increases which indicates IAM can effectively increase the LCST of the copolymer. The data show that the LCST of the poly(NIPAAm-*co*-IAM) copolymer changes with the pH value. In an acidic environment, the copolymer shows hydrophobic to have a low LCST while in an alkaline environment, the copolymer shows hydrophilic to have a high LCST. Besides, the 3 wt % aqueous solution of poly(NIPAAm-*co*-IAM) (sample R-8) based on this study shows the applicability to drug release because it has the LCST, 37.8°C, close to the body temperature, in the buffer solution of pH = 7. The results in the current work encourage the further study in utilizing poly(NIPAAm-*co*-IAM) to drug release application by varying the molar ratio of IAM to NIPAAm or adding additional monomers to adjust the conformation of the copolymer.

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REFERENCES

1. Aguilar, M. R.; Elvira, C.; Gallardo, A.; Vázquez, B.; Román, J. S. Topics in Tissue Engineering, **2007**, Vol. *3*, Chap 6, p. 1.
2. Kumar, A.; Srivastava, A.; Galaev, I. Y.; Mattiasson, B. *Prog. Polym. Sci.* **2007**, *32*, 1205.
3. Fang, S.; Kawaguchi, H. *Colloid. Polym. Sci.* **2002**, *280*, 984.
4. Cirillo, G.; Iemma, F.; Spizzirri, U.; Puoci, F.; Curcio, M.; Parisi, O.; Picci, N. *J. Biomater. Sci.* **2011**, *22*, 823.
5. Ho, K. M.; Li, W. Y.; Wong, C. H.; Li, P. *Colloid. Polym. Sci.* **2010**, *288*, 1503.
6. Cai, J.; Guo, J.; Ji, M.; Yang, W.; Wang, C.; Fu, S. *Colloid. Polym. Sci.* **2007**, *285*, 1607.
7. Ramkissoon-Ganorkar, C.; Vaudyš, M.; Kim, S. W. *J. Biomater. Sci. Polym. Ed.* **2000**, *11*, 45.
8. Zhao, S.-P.; Zhou, F.; Li, L.-Y. *J. Polym. Res.* **2012**, *19*, 9944.
9. Gupta, B.; Kumari, M.; Ikram, S. *J. Polym. Res.* **2013**, *20*, 95.
10. Liu, R.; Fraylich, M.; Saunders, B. R. *Colloid. Polym. Sci.* **2009**, *287*, 627.
11. Ling, Y.; Lu, M. *J. Polym. Res.* **2009**, *16*, 29.

12. Ivan Meléndez-Ortiz, H.; Bucio, E. *Des. Monomers Polym.* **2009**, *12*, 99.

13. Zhao, C.; Gao, X.; He, P.; Xiao, C.; Zhuang, X.; Chen, X. *Colloid. Polym. Sci.* **2011**, *289*, 447.

14. Bai, Y.; Wei, J.; Yang, L.; He, C.; Lu, X. *Colloid. Polym. Sci.* **2012**, *290*, 507.

15. Li, P.; Xu, R.; Wang, W.; Li, X.; Xu, Z.; Yeung, K.; Chu, P. *Colloid. Surf. B: Biointerfaces* **2013**, *101*, 251.

16. Pei, Y.; Chen, J.; Yang, L.; Shi, L.; Tao, Q.; Hui, B.; Li, J. *J. Biomater. Sci. Polym. Ed.* **2004**, *15*, 585.

17. Stile, R. A.; Chung, E.; Burghardt, W. R.; Healy, K. E. *J. Biomater. Sci. Polym. Ed.* **2004**, *15*, 865.

18. Kim, S. Y.; Lee, S. C. *J. Appl. Polym. Sci.* **2009**, *113*, 3460.

19. Abdullah-Al-Nahain, K.; Lee, S.; Mosaiab, T.; Park, S. Y. *J. Appl. Polym. Sci.* **2013**, *130*, 168.

20. Lee, W.-F.; Cheng, T.-S. *J. Appl. Polym. Sci.* **2013**, *128*, 230.

21. Erbill, C.; Yildiz, Y.; Uyanik, N. *Polym. Adv. Technol.* **2009**, *20*, 926.

22. Yoo, M. K.; Sung, Y. K.; Lee, Y. M. *Polymer* **2000**, *41*, 5713.

23. Way, T.-F.; Chen, Y.-T.; Chen, J.-J.; Teng, K. US patent application No. **2013**/0172490 A1.