

Synthesis, Characteristics, and Phase Behavior of a Thermosensitive and pH-Sensitive Polyelectrolyte

Wenting Zhou, Xueqin An, Jun Gong, Weiguo Shen, Zhiyun Chen, Xiaoyong Wang

School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China

Received 13 September 2010; accepted 25 November 2010

DOI 10.1002/app.33833

Published online 14 March 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: A series of poly(*N*-isopropylacrylamide-*co*-methacrylic acid-*co*-octadecyl acrylate) (poly(NIPAM-*co*-MAA-*co*-ODA)) with different monomer molar ratios was synthesized. Critical micelle concentration (CMC) of the polyelectrolyte solution was determined and the CMC increase with methacrylic acid content in the polyelectrolyte. The phase behaviors of the polyelectrolyte solution were studied, and the effects of various factors on the phase transition were discussed. The experimental results indicate that the lower critical solution tem-

perature and the phase transition pH depend on the monomer molar ratio in the polyelectrolyte. Effect of polyelectrolyte concentration on phase transition pH was studied, and results shown that the phase-transition pH is independent of the polyelectrolyte concentration. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 121: 2089–2097, 2011

Key words: poly(NIPAM-*co*-MAA-*co*-ODA); thermo-sensitive; pH-sensitive; phase behavior; micelles

INTRODUCTION

Polyelectrolytes are an intriguing class of the polymers with ionized groups. Stimuli-sensitive polyelectrolytes that contains hydrophobic and hydrophilic segments in the same molecule is highly attracting researchers' attentions. Such a composition tends to lead to an interesting behavior in water. The solution properties of polyelectrolytes differ considerably from that of polymer without ionized groups.¹ As a consequence, they were found to apply in a variety of drug delivery systems,² enzyme and protein immobilization and adsorption,³ and responsive colloidal arrays.⁴ Stimuli-sensitive polyelectrolyte shows a sharp change in properties upon a small or modest change in environmental condition. The most important stimuli are temperature,^{5–7} pH,^{8–11} light,¹² and ionic strength.¹³ Among several stimuli, temperature and pH are commonly used because

they are easy to control and have practical advantages *in vitro* and *in vivo*.^{14,15}

The behavior of thermosensitive polyelectrolyte is based on their amphiphilic character,¹⁶ which includes change in the efficiency of hydrogen bonding. Most of the thermosensitive polyelectrolyte has a lower critical solution temperature (LCST). Below the LCST, the polymer chains are highly solvent swollen. Above the LCST, the polymer chains undergo a coil-to-globule transition, in which water dissociates from the polymer allowing for polymer self-association resulting in deswollen microgels.¹⁷ Many studies have been focused on poly(*N*-isopropylacrylamide) (PNIPAM) and its copolymers.^{17–25} PNIPAM exhibits a LCST in water at around 32°C.^{20,26,27} The LCST can be changed by copolymerizing a suitable hydrophilic or hydrophobic monomer with the NIPAM.²⁸ Based on the LCST behavior, several PNIPAM-containing copolymers have been reported to prepare thermosensitive micelles for drug delivery system.²⁹ Besides the thermosensitive polyelectrolyte, pH-sensitive polyelectrolyte also has been studied, whose phase behaviors in aqueous solution are usually based on the presence of ionized groups in the polymer chains. It is well known that poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA) in aqueous solutions exhibit pH sensitivity.^{30–33} The phase transition pH value could be varied by modulating the AA contents in poly(acrylamide-*co*-acrylic acid),³⁴ or by adding polyethylene glycol (PEG) and salts.³⁵ Combined with the thermo- and pH-sensitivity, a

Correspondence to: X. An (anxueqin@ecust.edu.cn).

Contract grant sponsor: National Natural Science Foundations of China; contract grant numbers: 20673059, 21073063.

Contract grant sponsor: Committee of Science and Technology of Shanghai; contract grant number: 08jc1408.

Contract grant sponsor: Fundamental Research Funds for the Central Universities; contract grant number: WK0913002.

new polyelectrolyte that can respond to either temperature or pH stimuli was born. The ability of the polyelectrolyte responding to both temperature and pH offers an additional control over its phase behavior. Poly(amino urethane) with both temperature sensitivity and pH sensitivity have been synthesized and the aqueous solution showed a sol-gel-aggregation transition with increasing temperature at a relatively higher pH (7.0 or above).^{36,37} One poly(*N*-isopropylacrylamide-*co*-methacrylic acid-*co*-octadecyl acrylate) with the fixed monomer molar ratio (93.7 : 4.9 : 1.4) was synthesized, and the transition pH was found to be 5.6.^{14,38}

In this study, to better understanding of the LCST and pH phase transition in the stimuli-sensitive polyelectrolyte solution, a series of polyelectrolyte (NIPAM-*co*-MAA-*co*-ODA) with both thermo- and pH-sensitivity was synthesized. The NIPAM and the MAA in the polyelectrolyte acted as the thermo- and pH-sensitive parts, respectively, and the ODA was used as the anchor to join into the bilayer of the liposome that is used as drug carriers. The LCST and phase transition pH in various polyelectrolyte aqueous solutions were determined. The polyelectrolyte characterizations and various effects on the phase transition of polyelectrolyte solutions were discussed. By understanding the phase behavior of the polyelectrolyte, we might choose a suitable polyelectrolyte and establish a better way to using them as stimuli-sensitive drug carriers.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAM) (Shanghai Wujing Chemical Science and Technology) was dispersed in heptane, solubilized by acetone addition, and then allowed to recrystallized at -20°C prior to use.¹⁴ Methacrylic acid (MAA) (Shanghai Lingfeng Chemical Reagent) was distilled under reduced pressure to remove inhibitors at 55°C before used. Azobisisobutyronitrile (AIBN) (Shanghai Lingfeng Chemical Reagent) was recrystallized in ethanol and dried under vacuum. Octadecyl acrylate (ODA) (Beijing East Yakeli Chemical Science and Technology), 1,4-dioxane, diethyl ether, and tetrahydrofuran (Shanghai Lingfeng Chemical Reagent) were analytical reagent grades and used as received.

Methods

Synthesis and characterization of polyelectrolyte

Poly(NIPAM-*co*-MAA-*co*-ODA) was synthesized by radical polymerization.³⁹ Poly(NIPAM₉₅-*co*-MAA₄-*co*-ODA) was synthesized as following steps. Monomers (NIPAM: 3.1788 g, MAA: 0.1045 g, and ODA:

0.0965 g) of the molar ratio 95 : 4 : 1 and the initiator (AIBN: 0.0048 g) were dissolved in an appropriate amount of distilled 1,4-dioxane. The mixture was degassed by bubbling N_2 for 15 min, and then was refluxed at 69°C for 15 h under N_2 atmosphere. The polyelectrolyte was recovered by precipitation in diethyl ether, resolubilized in tetrahydrofuran, reprecipitated, and washed extensively with diethyl ether. After repeated above operations three times, the product was dried under vacuum for 5 days. The other polyelectrolytes with different content were synthesized using aforementioned method.

The polyelectrolyte was characterized by $^1\text{H-NMR}$ spectrometry. $^1\text{H-NMR}$ spectra was recorded on the BRUKER AVANCE 500 spectrometer in deuterated chloroform solution.⁴⁰ The content of MAA was estimated by an acidimetric titration method.²⁰ The copolymer samples (100 mg) were dissolved in 15 mL of 0.15M NaCl aqueous solution. All MAA groups were ionized by adding 3 mL of 0.015M NaOH and titrated with 0.015M HCl using a phenolphthalate solution as an indicator. The temperature was kept constant at 20°C during the titration process. Average molecular weight of the polyelectrolyte was determined by gel permeation chromatography (GPC, DAWN HELEOS, Optilab rEX; Wyatt Technology Corp.).

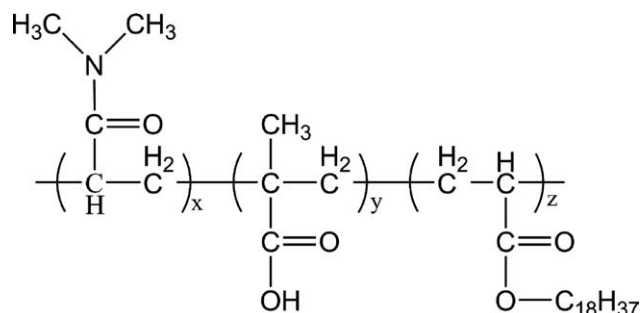
Determination of the critical micelle concentration of polyelectrolyte

The critical micelle concentration (CMC) of polyelectrolyte water solution (pH = 7.0) was determined by surface tension method. The surface tensions of the polyelectrolyte water solution with different concentrations at temperature 18°C were determined by Hanging plate method (DAC001, Thermo Cahn, Chance International Group).

Determination of LCST and phase transition pH of polyelectrolyte

The LCST and phase transition pH were determined by turbidity method. The polyelectrolyte was dissolved in PBS buffers of different pH values. Turbidities of the polyelectrolyte solutions with the percent transmittance were determined at a wavelength of 500 nm and various temperatures by ultraviolet-visible spectrophotometer (UV 2450, SHIMADZU).

The LCST of the polyelectrolyte solutions with different pH was also determined by phase transition calorimetric method. Thermograms of the polyelectrolyte solutions were recorded by the microcalorimeter (DSC, SETARAM, Micro DSC III) from 10 to 70°C at heating rate of $1.2^{\circ}\text{C}/\text{min}$ in all cases. The temperature at the maximum of the endothermic peak in DSC measurement was taken as the LCST of the copolymer.



Scheme 1 The structural formula of the polyelectrolyte (x : the molar ratio of NIPAM, y : the molar ratio of MAA, z : the molar ratio of ODA).

Determination of micelle size

The polyelectrolyte solution was filtered by 220 nm filter membranes and was kept at a certain temperature for 10 min before tested. Mean diameters of the polyelectrolyte micelles at various temperatures in different PBS buffer solutions were determined by dynamic light scattering (Nano-ZS, Malvern).⁴¹ Nano-ZS with backscatter detection was used for light scattering measurements with a detecting angle of 173°. The particles size and the polydispersity were analyzed with the software supplied for the instrument.

RESULTS AND DISCUSSION

Synthesis of poly(NIPAM-*co*-MAA-*co*-ODA)

A series of poly(NIPAM-*co*-MAA-*co*-ODA) with different monomer molar ratios was synthesized by radical polymerization. The structural formula of the polyelectrolyte was shown in Scheme 1. The corresponding signals of NIPAM and ODA monomer in the polyelectrolyte were retrieved in the ¹H-NMR spectra, shown in Figure 1. The proton H_a (NIPAM) was at the signal 4.03 ppm and the proton H_b (ODA) was at the signal 0.89 ppm. The content of MAA was estimated by an acidimetric titration method. The results show that the compositions of polyelectrolyte correspond to the monomer feed ratios within the experimental errors of the ¹H-NMR and titration (Table I). Average molecular weight of the polyelectrolyte obtained by GPC was approximately $M_w = 120,000$ g/mol with a polydispersity index (M_w/M_n) of 1.6, using dimethylformamide (DMF) as the eluant solvent. Recent research shown that the LCST of the copolymers was not affected by the molecular weight.⁴²

Effect of MAA content on the critical micelle concentration of the polyelectrolyte

The CMC values of different polyelectrolytes aqueous solution (pH = 7.0) were determined by the sur-

face tension at 18°C. The results were listed in Table II, and the relationship between CMC and the molar ratios of MAA to NIPAM was shown in Figure 2. The CMC of the polyelectrolyte solution increases with MAA content when ODA content in the polyelectrolyte was fixed. As the hydrophilic group increases in the polyelectrolyte, the CMC increases slowly, showing that the ability and the efficiency of the copolymers on decreasing surface tension tend to be weaker. It is mainly attributed to the MAA segments that make more contributions to the hydrophilic of the polyelectrolyte, resulting in higher CMC values of the polyelectrolyte.⁴³

Effect of polyelectrolyte concentration on the LCST

The temperature response of the polyelectrolyte is characterized by a LCST behavior; i.e., the polyelectrolyte is water-soluble below its LCST phase transition temperature, while above LCST the polyelectrolyte solution becomes cloudy as the polymer collapses and aggregates. The LCST of the copolymers in various PBS buffer solutions was determined by calorimetric method and turbidity method. The temperature at the maximum of the endothermic peak in DSC measurement and the temperature at the break point in the curve of the transmittance versus temperature in turbidity measurement were taken as the LCST of the copolymer.⁴⁴ The LCST values of the copolymer in different pH PBS solutions determined by two methods were listed in Table III. The results show good agreement with each other within the measurement errors of turbidity and calorimetry.

To understand the effect of polyelectrolyte solution concentration on the LCST, the turbidity of different concentration solutions was measured and the LCST of polyelectrolyte solution with various concentrations was obtained. The results were shown in Figure 3. The temperature at the break point in the

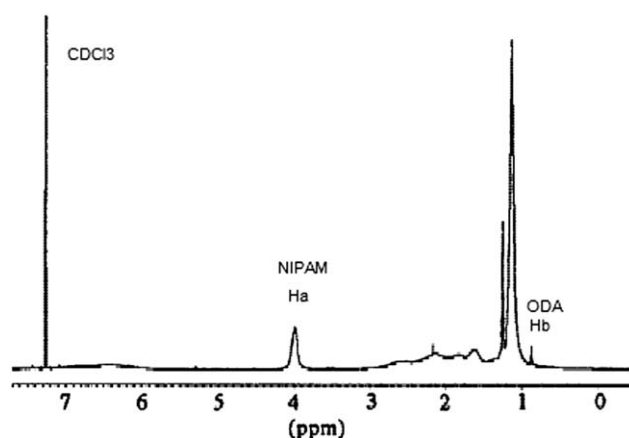


Figure 1 ¹H-NMR spectrum of poly (NIPAM-*co*-MAA-*co*-ODA) in CDCl₃.

TABLE I
The Polyelectrolytes with Various Monomer Molar Ratios Synthesized by Radical Polymerization

Sample	NIPAM/MAA/ODA molar ratio in feed	NIPAM/MAA/ODA molar ratio in copolymer
P(NIPAM _{95-co} -MAA _{4-co} -ODA)	95/4/1	95.8/4.1/1.1
P(NIPAM _{93-co} -MAA _{6-co} -ODA)	93/6/1	93.2/5.8/1.0
P(NIPAM _{89-co} -MAA _{10-co} -ODA)	89/10/1	89.4/9.8/0.8
P(NIPAM _{82-co} -MAA _{17-co} -ODA)	82/17/1	81.7/17.1/1.2
P(NIPAM _{92-co} -MAA _{6-co} -ODA ₂)	92/6/2	91.8/5.8/2.3

curve of the transmittance to temperature was the LCST of the copolymer solution.⁴⁵ From the Figure 3, we can see the thermosensitivity of the copolymer was increased as the increasing of the concentration. This is maybe due to the increasing the intermolecular interaction between copolymers in the same volume. Moreover, high concentration polyelectrolyte solution results in the enthalpy contribution of the water hydrogen bonds to the polymer chain become less than the entropic gain of the system as a whole.⁴⁶ So the LCST of the polyelectrolyte solution was decreased as the increase of the concentration, it was shown in Figure 4. This relationship between the concentration and the LCST of the copolymer is similar to the homopolymer PNIPAM⁴⁷ and poly(*N,N*-diethylacrylamid-*co*-acrylic acid).⁴⁴

Effect of polyelectrolyte concentration on phase transition pH

pH-sensitive properties of polyelectrolyte are usually based on the presence of ionized units. Phase transition pH values were obtained by turbidity measurement. Effect of the solution concentration on the pH phase-transition was studied by comparison of cloud point for various concentration polyelectrolyte (NIPAM_{92-co}-MAA_{6-co}-ODA₂) solutions, and the results were shown in Figure 5. Below the LCST, the phase-transition pH was not observed at 19°C, but above the LCST, the phase-transition pH is approximately 6.0 for both polyelectrolyte concentrations of 0.6 and 0.9 mg/mL, respectively. This means that the phase-transition pH is independent of the polyelectrolyte concentration because intermolecular interactions between water and polyelectrolyte in the dilute solution were too weak to affect the phase-transition.

TABLE II
The CMC of the Polyelectrolyte Water Solution at 18°C

Sample	CMC (mg/mL)
P(NIPAM _{95-co} -MAA _{4-co} -ODA)	0.042
P(NIPAM _{93-co} -MAA _{6-co} -ODA)	0.094
P(NIPAM _{89-co} -MAA _{10-co} -ODA)	0.126
P(NIPAM _{82-co} -MAA _{17-co} -ODA)	0.129

Effect of NIPAM content in the polyelectrolyte on LCST of the polyelectrolyte solution

As well know that the LCST is a great important parameter for temperature-sensitive polyelectrolyte. Aqueous solutions of the polyelectrolyte undergo a thermally induced, reversible phase separation above phase separation temperatures (LCST), which depend on their structures. To understand the effect of NIPAM content on LCST, LCST values of polyelectrolyte with various NIPAN contents were determined and relationship between LCST and NIPAM content in polyelectrolyte in pH 5.0 PBS buffer solutions was shown in Figure 6. The LCST of the polyelectrolyte depends on monomer NIPAM content in the polyelectrolyte and it decreased with the increase of NIPAM content in the polyelectrolyte solution. It has been suggested that LCST behavior is caused by a critical hydrophilic/hydrophobic balance of polymer side groups.⁴⁸ The amide groups in the polyelectrolyte can form hydrogen bonds with the carboxylic acid groups and hydration layers surrounding the polyelectrolyte. As the NIPAM content was increased, the interaction between the hydrophilic groups became dominant and the polymer-polymer interactions were enhanced. Therefore, the behaviors induce the form of the hydration layer

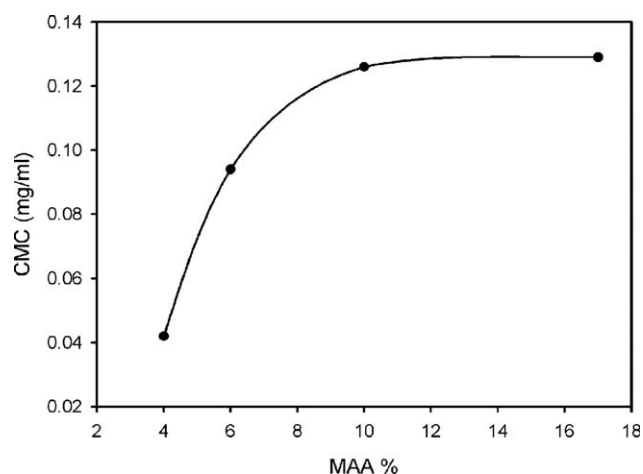


Figure 2 The CMC of the polyelectrolyte water solutions of different molar ratio of MAA to NIPAM at 18°C.

TABLE III
The LCST in Various PBS Buffer pH Solutions
(P(NIPAM₈₉-*co*-MAA₁₀-*co*-ODA)) Determined from the
Turbidity Method and Calorimetric Method

pH value of buffer solution	LCST (°C)	
	Turbidity method	Calorimetric method
4.6	25.3 ± 0.3	25.9 ± 0.4
5.0	29.9 ± 0.4	29.6 ± 0.3
5.5	37.8 ± 0.4	38.0 ± 0.6

surrounding the polyelectrolyte and shift the LCST to a lower temperature. The phase transition temperature of the polyelectrolyte can be tailored in the range of 22–32°C by controlling the NIPAM/MAA ratio of the copolymer.

Effect of MAA content in the polyelectrolyte on phase transition pH

It is known that acidic monomer MAA in the polyelectrolyte makes the polyelectrolyte pH sensitive. Above the phase transition pH, the MAA is ionized and thus the polyelectrolyte becomes soluble. Below the phase transition pH, the deionization and the removal of charge of MAA bring polyelectrolyte to precipitation. To investigate the relationship between monomer MAA content and phase-transition pH values in the polyelectrolyte, the turbidities of a series of polyelectrolyte solutions in different pH PBS buffer solutions were measured. The relationships between transmittance and pH were shown in Figure 7. The inflection point on each curve in Figure 7 was considered as the phase transition point.³⁶ The phase transition pH values of P(NIPAM₉₅-*co*-MAA₄-*co*-ODA), P(NIPAM₉₃-*co*-MAA₆-

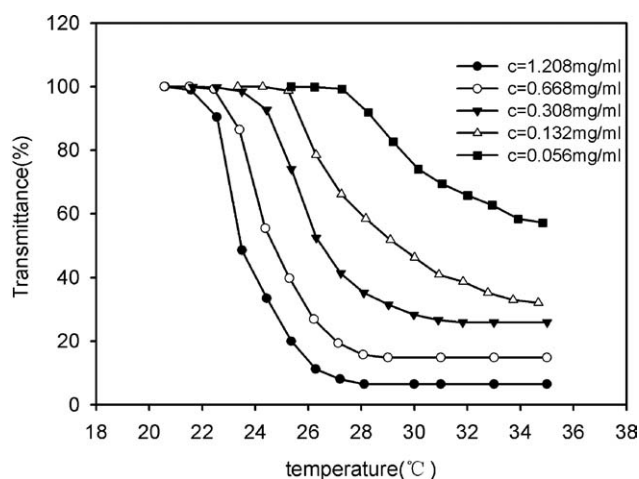


Figure 3 The turbidities of polyelectrolyte solutions at various concentrations and different temperatures (copolymer was NIPAM₉₂-*co*-MAA₆-*co*-ODA₂, pH = 5.0).

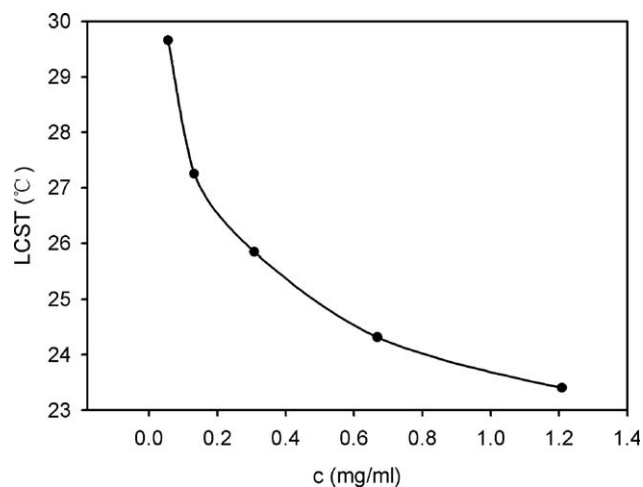


Figure 4 The LCST of polyelectrolyte solutions (copolymer was NIPAM₉₂-*co*-MAA₆-*co*-ODA₂, pH = 5.0) of different concentrations.

co-ODA), P(NIPAM₈₉-*co*-MAA₁₀-*co*-ODA), and P(NIPAM₈₂-*co*-MAA₁₇-*co*-ODA) were about 6.5, 6.1, 5.0, and 4.6, respectively. The phase transition pH value (6.5) for the system of P(NIPAM₉₅-*co*-MAA₄-*co*-ODA) is little different of the phase transition pH value (5.6) in previous work.³⁸ The relationship between the phase transition pH and the MAA molar fraction was shown in Figure 8. The phase transition pH value was decreased as the increase of the MAA molar ratio in the copolymer. This phenomenon could be attributed to the ionization behavior of —COOH groups along the network chains in response to external pH changes. The increase of the MAA content in the polyelectrolyte restrains ionization of hydrogen ions, most —COOH groups were kept in the form of —COOH, which might induce the formation of

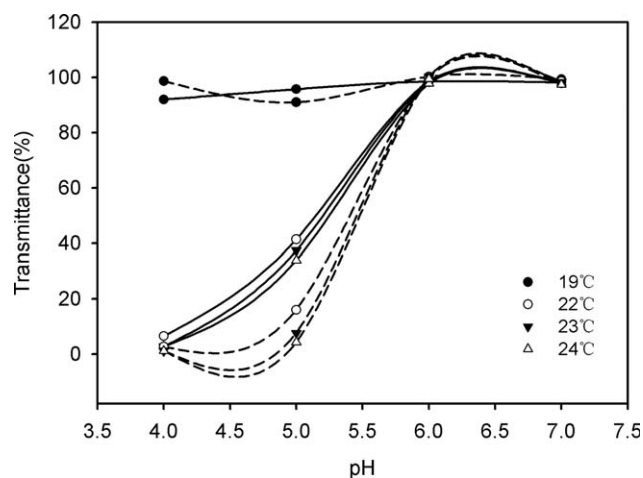


Figure 5 The turbidities of polyelectrolyte solutions (NIPAM₉₂-*co*-MAA₆-*co*-ODA₂) at various concentrations and different pH values (solid line $c = 0.6$ mg/mL; broken line $c = 0.9$ mg/mL).

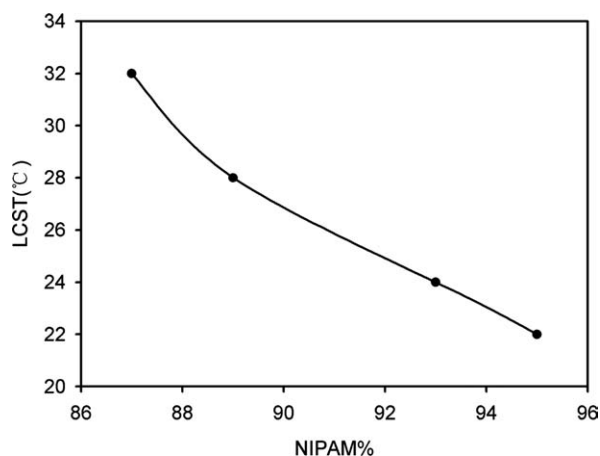


Figure 6 LCST at different NIPAM content in polyelectrolyte PBS buffer solution (pH 5.0).

hydrogen bonds of $-\text{COOH}$ groups with MAA and NIPAM units, shifting the phase transition to a lower pH. Hereby, the phase transition of the polyelectrolyte

solutions depends upon both pH values of buffer solution and monomer molar ratios of MAA to NIPAM in the polyelectrolyte.

Figure 7 indicated that the pH-sensitivity increased with the molar ratio of MAA to NIPAM in the polyelectrolyte solutions. The phenomena may be due to MAA enhance the hydrophilicity of the polyelectrolyte as the increase of the molar ratio of MAA to NIPAM. This pH-sensitive behavior of polyelectrolyte may be attributed to their hydrophilicity and molecular interaction.⁴⁴

Moreover, the relationships between transmittance and temperature were shown in Figure 9 for polyelectrolyte solutions with various monomer molar ratios. The inflection point on each curve in Figure 9 was considered the phase transition temperature (lower critical solution temperature, LCST).³⁶ The results indicated that the polyelectrolyte became more thermosensitive as the molar ratio of MAA to NIPAM increased. This phenomena could be due to the interactions of the hydrogen bonding between

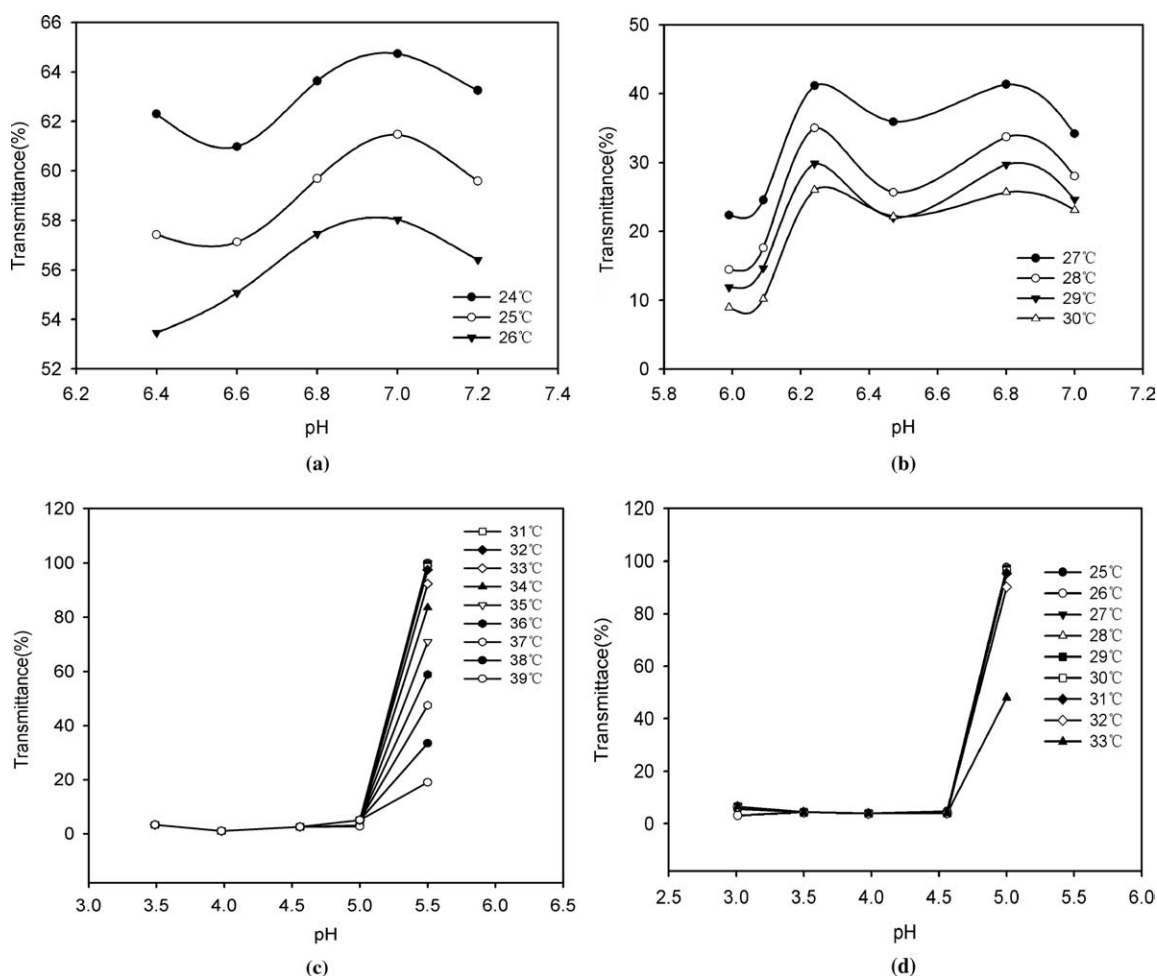


Figure 7 The transmittance versus pH value curves for polyelectrolyte systems with various monomer molar ratios at different temperatures (a, b, c, and d show $\text{P}(\text{NIPAM}_{95}\text{-co-MAA}_4\text{-co-ODA})$, $\text{P}(\text{NIPAM}_{93}\text{-co-MAA}_6\text{-co-ODA})$, $\text{P}(\text{NIPAM}_{89}\text{-co-MAA}_{10}\text{-co-ODA})$, and $\text{P}(\text{NIPAM}_{82}\text{-co-MAA}_{17}\text{-co-ODA})$ respectively, concentrations of copolymer solutions were 0.3 mg/mL).

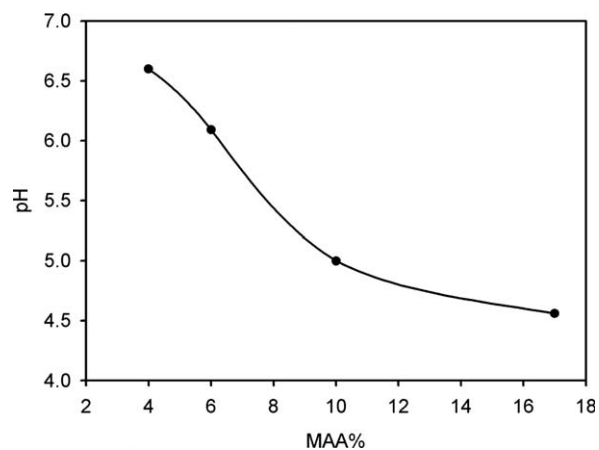


Figure 8 The phase-transition pH values of the polyelectrolyte solutions with different molar ratios of MAA to NIPAM.

two carboxylic acid groups, and between carboxylic acid and amide groups (intramolecular and intermolecular) also were increased, and the interactions bring on enhancement of thermosensitive property.⁴⁴

Effect of temperature and pH on the mean diameters of the polyelectrolyte micelles

The size and size distributions of the micelles in different pH polyelectrolyte solutions at various temperatures were determined by dynamic light scattering (DLS) and was shown in Figure 10. From Figure 10, we can see that size changes of the micelles in different pH polyelectrolyte solutions (P(NIPAM₉₅-co-MAA₄-co-ODA)) was similar at various temperatures. The micelle mean diameter in various pH buffer solutions was changed with temperature as shown in Figure 11. A special temperature (22°C) of break point in the curve in Figure 11 was taken for LCST, which was consistent with that obtained from turbidity method [Fig. 9(a)]. Below the LCST, the copolymer was soluble and the mean diameter of the micelles in the solution was about 20 ± 2 nm with a rather narrow distribution. The phase transition was taken above the LCST, and the micelles began to gather and the mean diameter increased with the temperature.

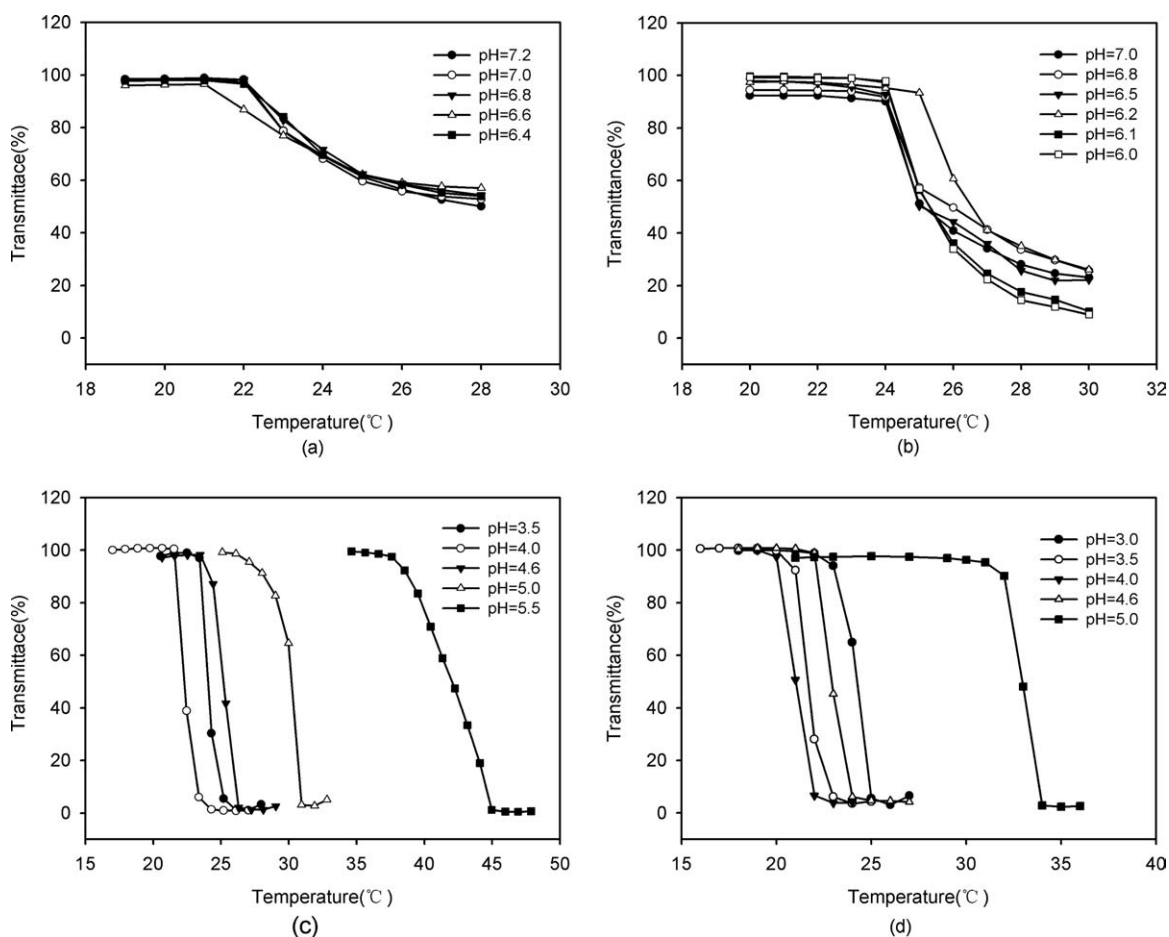


Figure 9 The transmittance versus temperature curves for polyelectrolyte solutions with various monomer molar ratios at different pH PBS buffer solutions (a, b, c and d show P(NIPAM₉₅-co-MAA₄-co-ODA), P(NIPAM₉₃-co-MAA₆-co-ODA), P(NIPAM₈₉-co-MAA₁₀-co-ODA), and P(NIPAM₈₂-co-MAA₁₇-co-ODA), respectively, concentrations of polyelectrolyte solutions were 0.3 mg/mL).

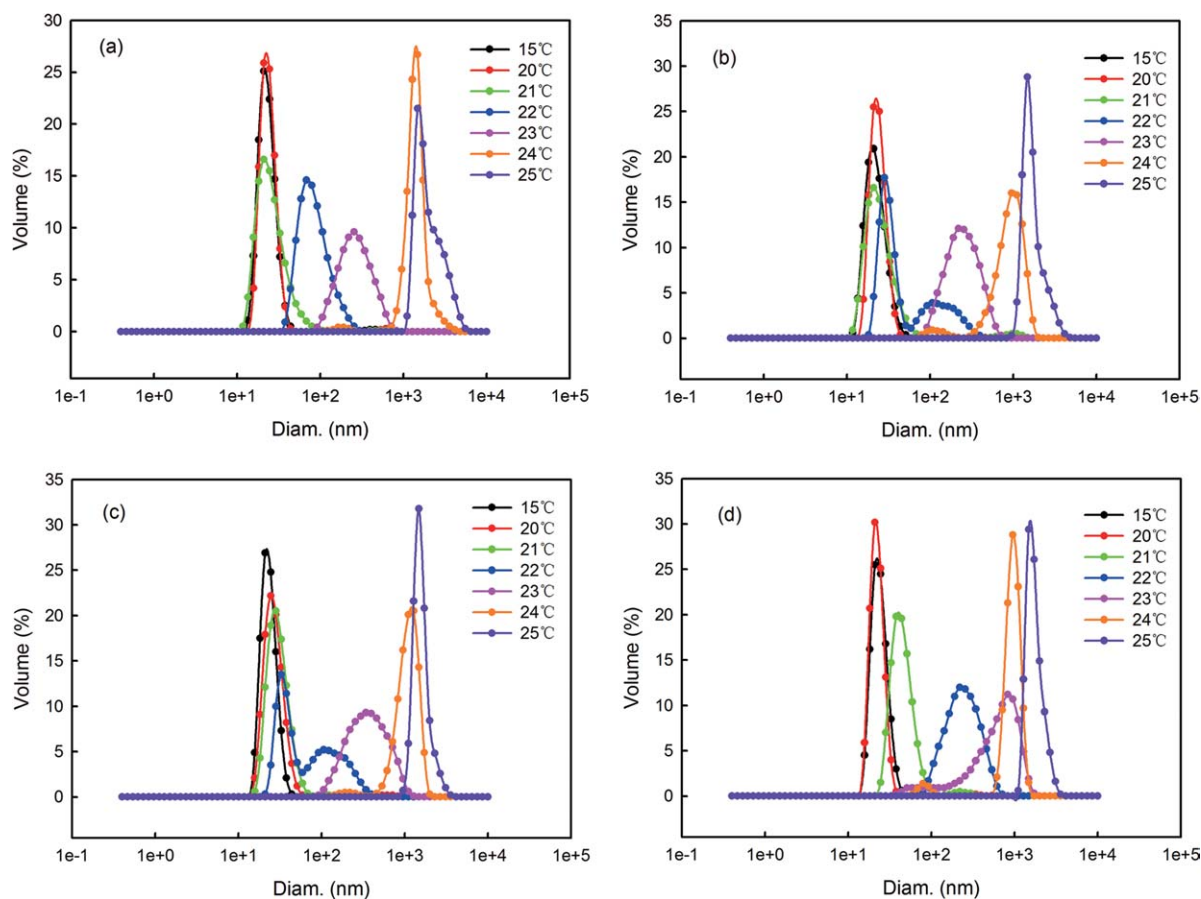


Figure 10 The size distributions of the micelles in the different pH polyelectrolyte solutions at various temperatures (P(NIPAM₉₅-co-MAA₄-co-ODA), the concentrations of the polyelectrolyte solutions were 0.3 mg/mL, (a) pH = 5.5; (b) pH = 6.0; (c) pH = 6.4; (d) pH = 6.5). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The relationship between the pH and the mean diameter of the polyelectrolyte micelles was shown in Figure 12. The pH value (6.4) at the break point

of the curve in Figure 12 was taken as the phase transition pH of the polyelectrolyte, which phase transition pH value consistent with that obtained

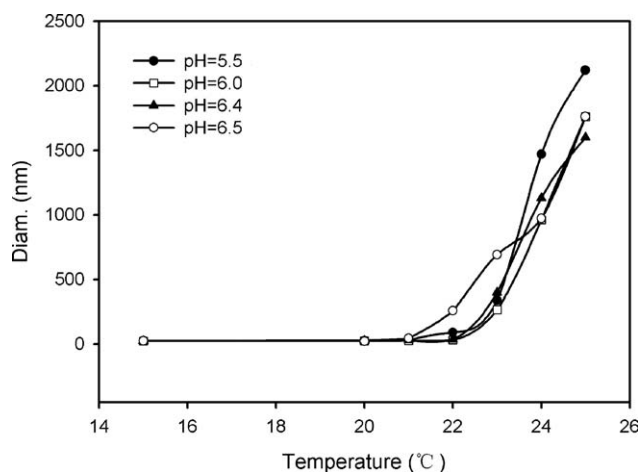


Figure 11 The mean diameters of polyelectrolyte micelles in the different pH PBS buffer solutions at various temperatures (P(NIPAM₉₅-co-MAA₄-co-ODA), the concentrations of the polyelectrolyte solutions were 0.3 mg/mL).

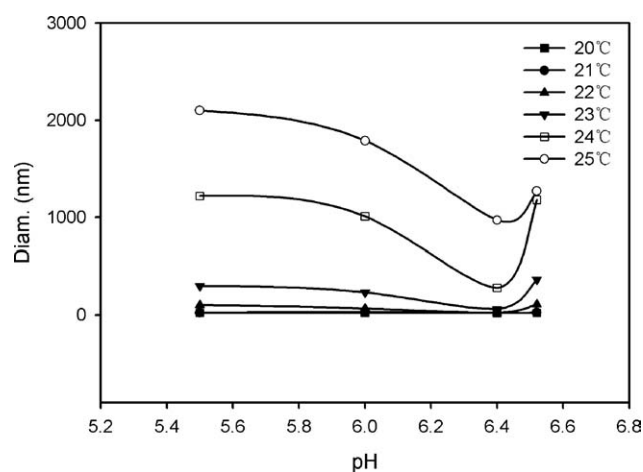


Figure 12 The relationships between the pH and the mean diameters of the polyelectrolyte micelles (P(NIPAM₉₅-co-MAA₄-co-ODA), the concentrations of the polyelectrolyte solutions were 0.3 mg/mL).

from turbidity method [Fig. 7(a)] within the measurement errors. Above the phase transition pH 6.4, the overall surface of the particles should be covered exclusively by the hydrophilic and charged MAA segments. The charged hydration layer surrounding the particles was formed and the hydration and particularly the charge repulsion may avoid agglomeration of the particles.¹ Below the phase transition pH, the small segments gathered again due to the interactions between the polyelectrolyte and polyelectrolyte.⁴⁹

CONCLUSIONS

In this study, a series of poly(NIPAM-*co*-MAA-*co*-ODA) was synthesized and phase behavior of thermosensitive and pH-sensitive polyelectrolyte solution were studied. The results reveal that the phase transition pH and LCST can be controlled by adjusting monomer molar ratio of NIPAM to MAA. An important feature is that LCST of the polyelectrolyte solution was affected evidently by the polyelectrolyte concentration, but the phase transition pH does not depend on the concentration. By understanding the phase behavior of the polyelectrolyte, we might choose a suitable polyelectrolyte and establish a better way to using them as stimuli-sensitive drug carriers.

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