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Dual thermo-responsive and ion-recognizable monodisperse microspheres

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ABSTRACT

A novel type of dual stimuli-responsive microspheres that simultaneously exhibit ion-recognition property based on the supramolecular host–guest complexation of crown ether receptors (benzo-18-crown-6-acrylamide) (BCAm) with specific ions and thermo-sensitivity based on the phase transition of poly(*N*-isopropylacrylamide) (PNIPAM) is fabricated in this study. The prepared poly(*N*-isopropylacrylamide-*co*-benzo-18-crown-6-acrylamide) (P(NIPAM-*co*-BCAm)) microspheres are characterized by FT-IR spectroscopy, UV–vis absorption spectroscopy, scanning electron microscopy (SEM), and dynamic light scattering (DLS). SEM images and DLS data show that the synthesized microspheres exhibit nearly perfect spherical shape and high monodispersity. Moreover, according to the DLS results, P(NIPAM-*co*-BCAm) microspheres exhibit satisfactory thermo-responsive behavior and ion-recognition property. In K^+ solutions, due to the formation of crown ether/K^+ complexes, the LCST of P(NIPAM-*co*-BCAm) microspheres shifts to a higher temperature and the colloidal stability is increased. The P(NIPAM-*co*-BCAm) microspheres undergo a volume change from shrunken state to swollen network isothermally at a certain temperature by the addition of metal ions. Due to dual thermo-responsive and ion-recognition behaviors, this kind of microspheres would serve as promising candidates for sensors, controlled drug delivery systems and possibly new biomaterials.

1. Introduction

Stimuli-responsive "smart" microspheres are attracting increasing research interests due to their potential applications in biomedical and biotechnological fields [1–3]. Various external stimuli such as temperature [4–13], pH [14–17], electric field [18], magnetic field [19–21], ionic strength [22], and light [23] may be used to induce drastic changes in physical–chemical properties and colloidal properties of these microspheres.

Poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most widely studied temperature-responsive polymers, which exhibits a temperature-dependent phase transition in aqueous solution at a lower critical solution temperature (LCST) around 32 °C [24]. Since being reported by Pelton and Chibante for the first time in 1986 [25], thermo-sensitive PNIPAM microspheres have attracted extensive attention due to their theoretical importance and potential applications in many fields, such as controlled drug delivery systems [26,27], biosensors [28,29], enzyme and cell immobilizations [30], and microreactors [31]. As environmental temperature increases across the LCST, PNIPAM microspheres undergo a reversible volume change from swollen network to shrunken state and dramatically release free water at the same time.

Uniform particle size and shape are very important for stimuli-responsive microspheres to improve their performance in versatile applications, especially for drug delivery systems [32]. To that end, precipitation polymerization is an excellent technique which is able to prepare monodisperse microspheres without addition of any surfactant or stabilizer [33–36]. PNIPAM-based microspheres with remarkably uniform size and shape can be readily prepared by precipitation polymerization in water at a temperature above the LCST of PNIPAM [37,38].

The application of pure homopolymeric PNIPAM microspheres, however, is limited by their relatively fixed volume phase transition temperature and single thermo-sensitivity. For more favorable applications, such as drug delivery systems and chemical sensors, further functionalization of PNIPAM microspheres is needed. It is possible to increase the functionality of PNIPAM microspheres by copolymerizing with monomers that are sensitive to other stimuli [6,39,40]. Most reported multi-stimuli-responsive microspheres are dual thermo- and pH-responsive microspheres that are prepared by copolymerizing NIPAM with an ionizable monomer

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[27,41–43]. Recently, dual photo- and thermo-responsive microgels were synthesized by incorporating functional dye or gold nanoparticles to convert light energy into heat [23,44].

Sodium–potassium pump is a particularly important active transport system in biomembranes that maintains the homeostasis of life and normal metabolism [45,46]. Normally, the concentration of potassium ions in the intracellular fluid is 140 mM, while extracellularly it is 5 mM. When the ATP–ADP energy transformation cycle is broken down, this high internal K^+ concentration cannot be maintained through active transport and potassium ions release out from the cell, which results in the increase of local extracellular K^+ concentration [47]. Thus, if the controlled-release kinetics of PNIPAM-based microspheres could respond to a specific ion signal (such as K^+), such a smart system would serve as promising candidate for designing new drug delivery systems that release the drug in a controlled way to deliver the drug in the right place and at an adequate dosage guided by external ionic stimuli.

Crown ethers have remarkable properties of selectively recognizing specific ions and forming stable "host–guest" complexes. It has been reported that the copolymers of PNIPAM with pendant crown ether groups, poly(*N*-isopropylacrylamide-*co*-benzo-18-crown-6-acrylamide) (P(NIPAM-*co*-BCAm)), have both thermo-sensitive and ion-recognition properties [48–55]. When the BCAm receptors capture specific metal ions, the LCST of the copolymer shifts to a higher value. However, most of the investigated copolymers based on P(NIPAM-*co*-BCAm) were linear or linear-grafted types except our recently reported crosslinked P(NIPAM-*co*-BCAm) bulk hydrogel [56]. Monodisperse PNIPAM-based microspheres with crown ether receptors, which might be able to provide some unique functions for practical applications, have not been reported yet up to now.

In this study, we report on a novel kind of thermo-responsive microspheres possessing unique ion-recognition ability, which are monodisperse P(NIPAM-*co*-BCAm) microspheres prepared via precipitation copolymerization of NIPAM with BCAm. The chemical composition and microstructure of the prepared microspheres are characterized by FT-IR spectroscopy, UV–vis absorption spectroscopy and scanning electron microscopy (SEM), and the thermo-responsive behaviors and the isothermal swelling/deswelling behaviors triggered by ion-recognition are investigated by dynamic light scattering (DLS) technique.

2. Experimental

2.1. Materials

N-Isopropylacrylamide (NIPAM, kindly provided by Kohjin Co., Ltd., Japan) is purified by recrystallization with a hexane/acetone mixture (50/50, v/v). Benzo-18-crown-6-acrylamide (BCAm) is synthesized according to reported procedures [57,58]. *N*,*N*′-Methylenebisacrylamide (MBA, Chengdu Kelong Chemical Reagent Co.) is used as a crosslinker. 2,2′-Azobisisobutyronitrile (AIBN, Shanghai Reagent Fourth Factory) is recrystallized with ethanol and used as initiator. Tetrahydrofuran (THF) is freshly distilled over sodium metal prior to use. Other solvents and chemicals are of analytical grade and used as-received. Deionized water (18.2 MΩ, 25 °C) from a Milli-Q Plus water purification system (Millipore) is used throughout this work.

2.2. Microsphere preparation

Monodisperse P(NIPAM-*co*-BCAm) microspheres are prepared in a single step by precipitation copolymerization using MBA as crosslinker. The NIPAM (0.2 g) and BCAm (0.05 g) monomers, MBA (0.0185 g) crosslinker, and AIBN (0.0042 g) initiator are dissolved in 20 mL of mixed solvent of H_2O/THF (99/1, v/v). The solution is bubbled with nitrogen gas for 30 min to remove dissolved oxygen in the system and heated to 70 °C to start the polymerization. The reaction is maintained at 70 °C for 4 h, under a nitrogen atmosphere. After being cooled to room temperature, the resultant microspheres are purified by repeating centrifugation and redispersion using deionized water to remove the residual unreacted components. P(NIPAM-*co*-BCAm) microspheres with different particle sizes are also prepared with different recipes.

The homopolymeric PNIPAM microspheres, which served as the reference, are also prepared and purified using the protocol described above, without any addition of BCAm.

2.3. Microsphere characterization

The structure characterizations of both P(NIPAM-*co*-BCAm) and PNIPAM microspheres are determined by Fourier transform infrared spectroscopy (FT-IR, Nicolet 560, America) and UV spectroscopy (Shimadzu UV-1700, Japan). The FT-IR specimens are prepared by a freeze-drying method and using KBr disc technique. UV analyses are performed with highly diluted microsphere dispersions in deionized water at 25 °C. Microsphere concentrations of the dispersions are fixed as 0.03 g/L.

The morphology and size of microspheres in dried state are observed by scanning electron microscope (SEM, JSM-5900LV, JEOL, Japan). All specimens for SEM measurements are sputter-coated with gold for 40 s before observation.

The hydrodynamic diameters D_H of P(NIPAM-*co*-BCAm) and PNIPAM microspheres are determined by dynamic light scattering (DLS, Zetasizer Nano-ZS, Malvern Instruments, UK) equipped with a He–Ne light source ($\lambda = 633$ nm, 4.0 mW). The measurements are made at the scattering angle of $\theta = 173°$ (backscattering detection). Both thermo-sensitivity and swelling behavior upon ion-recognition are investigated by this technique with highly diluted microsphere dispersions in deionized water and metal cationic solutions at designed temperatures. The concentrations of microsphere dispersions are all 0.03 g/L. Before each data collection, the samples are allowed to equilibrate for 30 min at each designed temperature. The values presented in this paper are the average of at least three measurements.

3. Results and discussion

3.1. Strategies for fabrication and ion-recognition function of the microspheres

The chemical structure and response mechanism of the proposed thermo-responsive and ion-recognition microspheres are schematically illustrated in Fig. 1. The thermo-responsive and ion-recognition microspheres are constructed from crosslinked P(NIPAM-*co*-BCAm) copolymers, in which PNIPAM acts as an actuator and the crown ether BCAm receptor acts as an ion-signal sensor. Crown ethers have remarkable properties of selectively recognizing specific ions and forming stable "host–guest" complexes. It has been reported that, when the BCAm receptors in linear P(NIPAM-*co*-BCAm) copolymers capture specific metal ions, the LCST of the copolymer shifts to a higher value [48–55]. Therefore, the phase transition of the P(NIPAM-*co*-BCAm) microspheres can occur isothermally as a result of a specific metal ion signal at a temperature between the two LCSTs. When the recognizable specific ions do not exist in the environmental solution or the metal ions are removed from the crown ether receptors, the P(NIPAM-*co*-BCAm) microspheres are in the shrunken state; on the other hand, when there exist specific metal ions (M^{n+}) in the environmental solution, the P(NIPAM-*co*-BCAm)

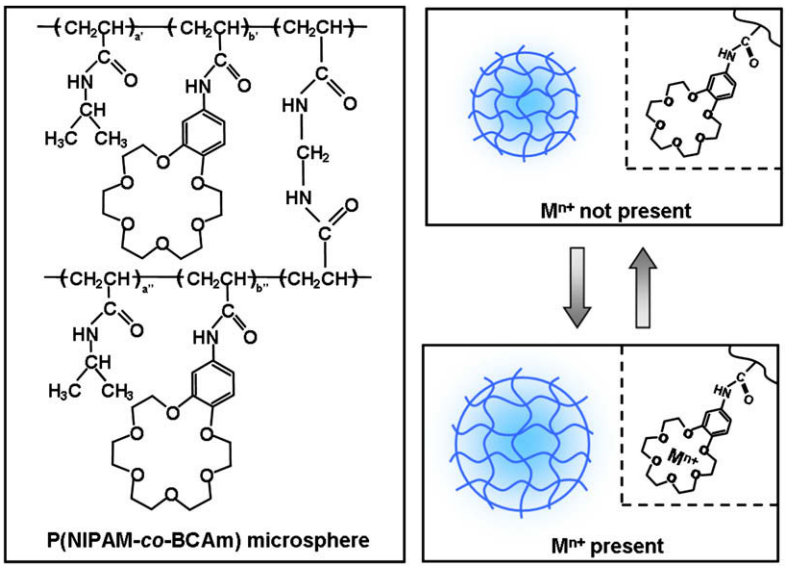

Fig. 1. Schematic illustration of the chemical structure of crosslinked P(NIPAM-*co*-BCAm) microspheres and their ion-recognition properties. When the crown ether hosts capture specific metal ions, M^{n+}, the microspheres swell; on the contrary, when the metal ions are removed from the crown ether hosts, the microspheres shrink.

microspheres can isothermally swell due to the capturing of specific metal ions by the crown ether receptors. That is, the proposed microspheres can achieve isothermal swelling/shrinking functions triggered by the presence/absence of specific metal ion signals in the surrounding solution.

3.2. Characterization of microspheres

FT-IR spectra of P(NIPAM-*co*-BCAm) and PNIPAM microspheres as well as BCAm monomer are shown in Fig. 2. According to the spectrum of BCAm monomer (Fig. 2a), the appearance of the following characteristic bands in FT-IR spectrum of P(NIPAM-*co*-BCAm) microspheres (Fig. 2c) suggests a successful polymerization of BCAm: (1) a strong 1516 cm^{-1} band for C=C skeletal stretching vibration of phenyl ring, (2) a 1230 cm^{-1} band for C–O asymmetric stretching vibration in Ar–O–R, (3) a 1130 cm^{-1} band for C–O asymmetric stretching vibration in R–O–R′, and (4) a 1057 cm^{-1} band for C–O symmetric stretching vibration in Ar–O–R. Furthermore, the characteristic double peaks at 1388 and 1366 cm^{-1} standing for isopropyl group of NIPAM appear in both FT-IR spectra of PNIPAM and P(NIPAM-*co*-BCAm) microspheres (Fig. 2b and c), which verifies the copolymerization of PNIPAM. All these feature

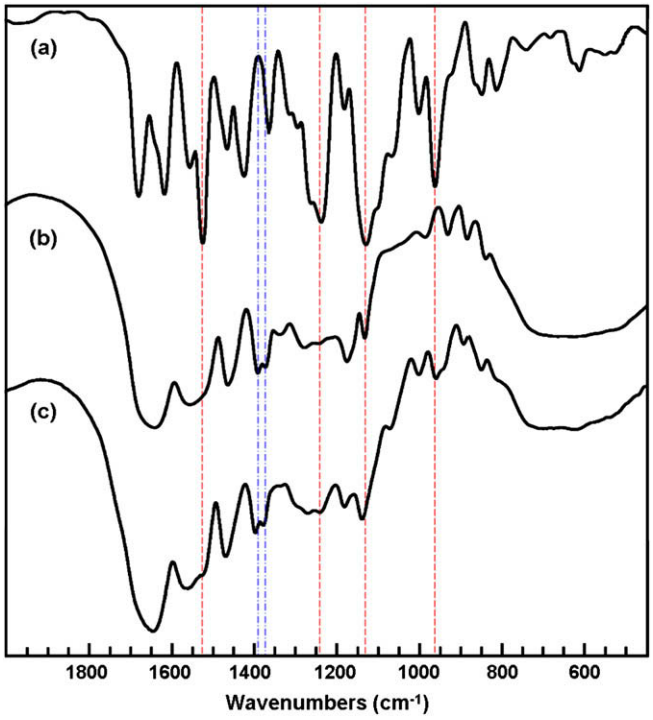

Fig. 2. FT-IR spectra of BCAm monomer (a), PNIPAM microspheres (b) and P(NIPAM-*co*-BCAm) microspheres (c).

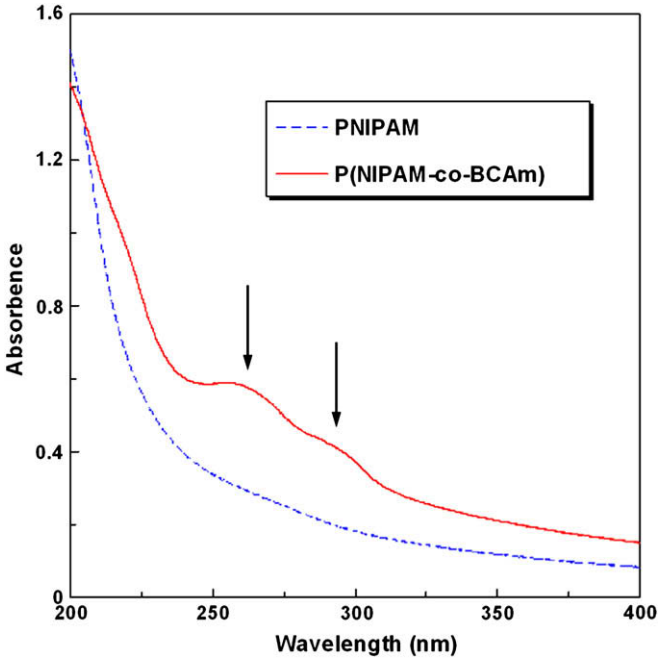

Fig. 3. UV–vis spectra of dispersions of PNIPAM microspheres and P(NIPAM-*co*-BCAm) microspheres in deionized water at 25 °C. [Microsphere] = 3.0×10^{-2} g/L.

peaks confirm a successful fabrication of P(NIPAM-*co*-BCAm) copolymeric microspheres.

Further evidence to copolymer formation is provided by UV analyses of P(NIPAM-*co*-BCAm) microsphere (Fig. 3). The absorption spectrum of dispersion of P(NIPAM-*co*-BCAm) microspheres in deionized water displays two absorption peaks at approximately 260 nm and 290 nm, which attribute to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of benzo-crown ether moiety and of course, are absent in the spectrum of PNIPAM microspheres.

Figs. 4 and 5 show SEM images of PNIPAM and P(NIPAM-*co*-BCAm) microspheres. As shown in Fig. 4, the colloidal microspheres exhibit nearly perfect spherical shape with good monodispersity. It can be clearly seen that the size of P(NIPAM-*co*-BCAm) microspheres is larger than that of PNIPAM microspheres. The average sizes of PNIPAM and P(NIPAM-*co*-BCAm) microspheres are 390 and 570 nm, respectively. The main reason for the difference sizes is that BCAm is a hydrophilic monomer, and introducing a hydrophilic secondary group leads to a larger particle size in the preparation of microspheres via precipitation polymerization [59]. Another reason is that, the steric hindered effect of BCAm groups also contributes to form larger microspheres.

P(NIPAM-*co*-BCAm) microspheres with different particle sizes are also prepared with different compositions (Fig. 5). The microsphere size can be controlled by altering the recipe for preparing the P(NIPAM-*co*-BCAm) microspheres. Increasing the content of NIPAM or BCAm monomer results in P(NIPAM-*co*-BCAm) microspheres with larger sizes. The spherical shape in dried state is also affected by the compositions of microspheres. Larger size would cause worse spherical shape, due to the soft characteristics of the microspheres. During the drying processing, the soft microgels

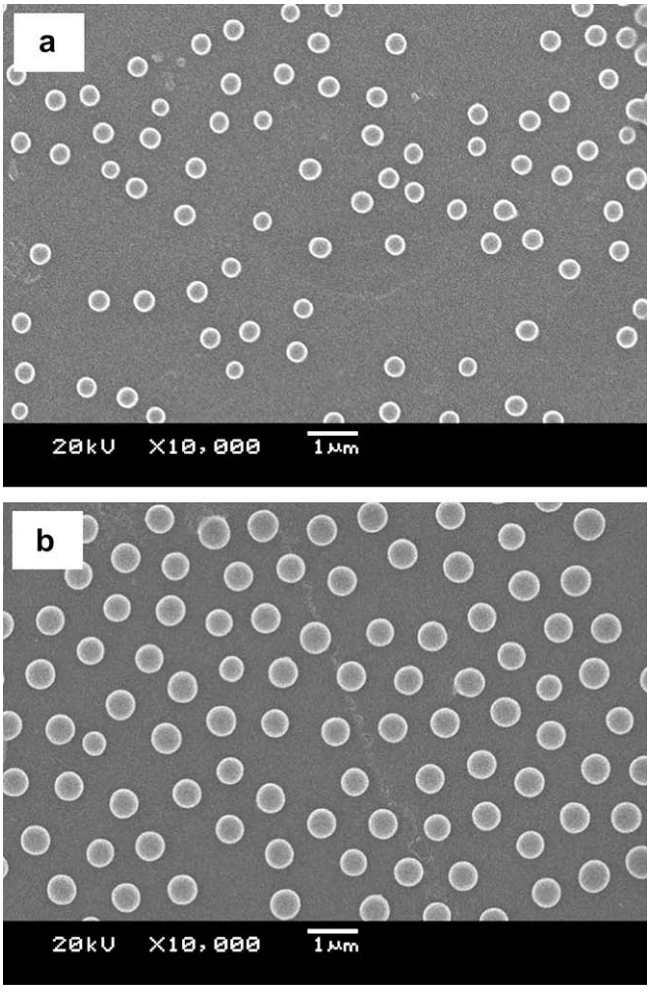

Fig. 4. SEM images of PNIPAM microspheres ([NIPAM] = 10 g/L) (a) and P(NIPAM-*co*-BCAm) microspheres ([NIPAM] = 10 g/L, [NIPAM]/[BCAm] = 4/1 (g/g)) (b). Scale bar 1 μm.

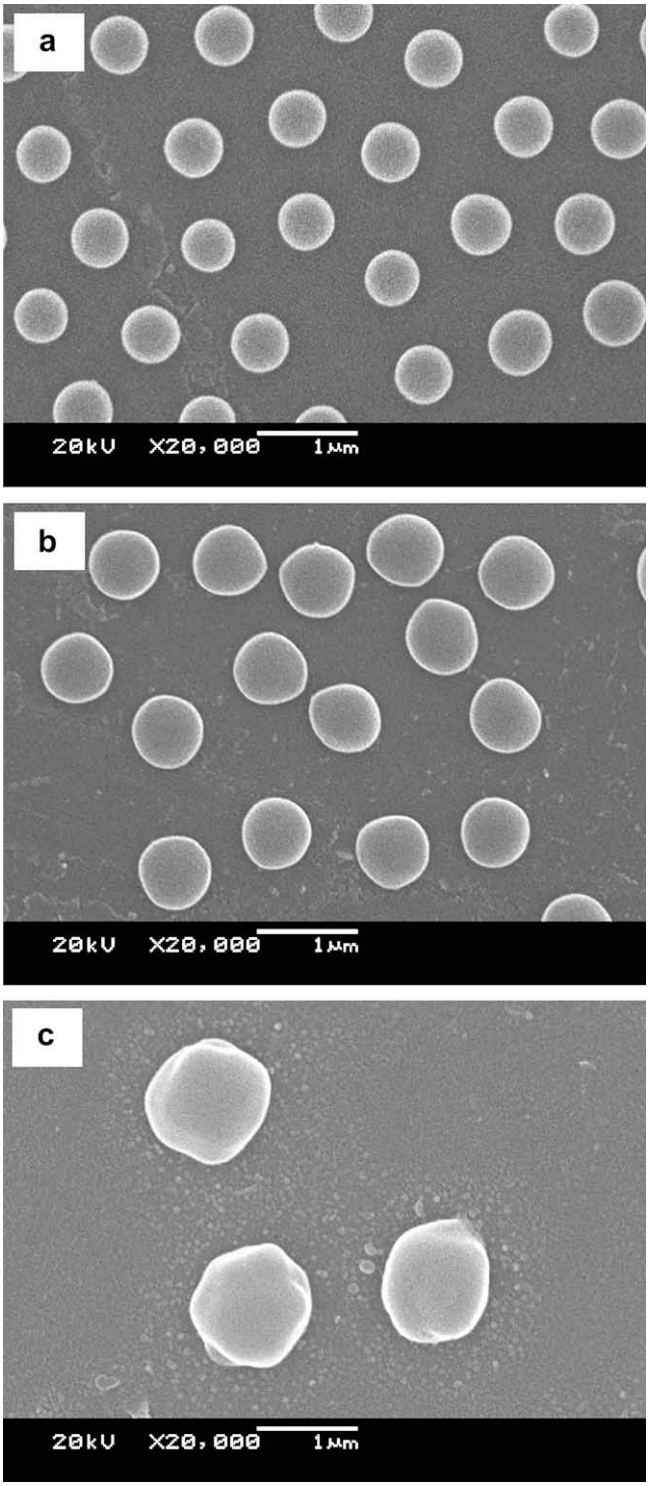

Fig. 5. SEM images of P(NIPAM-*co*-BCAm) microspheres prepared with different compositions. (a) [NIPAM] = 10 g/L, [NIPAM]/[BCAm] = 4/1 (g/g), (b) [NIPAM] = 20 g/L, [NIPAM]/[BCAm] = 4/1 (g/g), and (c) [NIPAM] = 20 g/L, [NIPAM]/[BCAm] = 8/3 (g/g). Scale bar 1 μm.

with larger size may easily be deformed and could not maintain their spherical shape well.

A small dimension is necessary for stimuli-responsive microspheres for drug delivery applications, because the distribution of the microspheres within the body and the interaction with biological cells are greatly affected by the particle size [32]. Furthermore, a small-sized particle minimizes any potential irritant reaction at the injection site. Therefore, the fabricated smallest P(NIPAM-*co*-BCAm) microspheres with average size of 570 nm will be used in the subsequent study.

3.3. Thermo-responsive behaviors of microspheres

Thermo-responsive properties of PNIPAM and P(NIPAM-*co*-BCAm) microspheres in water can be readily investigated by using DLS to determine the temperature-induced volume phase transition of these microspheres (Fig. 6). The DLS results show that both PNIPAM and P(NIPAM-*co*-BCAm) microspheres exhibit narrow size distributions. As expected, both PNIPAM and P(NIPAM-*co*-BCAm) microspheres exhibit good thermo-responsive characteristics and their volumes decrease dramatically as the environmental temperature increases across the LCST (around 33 °C). At the same temperature, the hydrodynamic diameter of P(NIPAM-*co*-BCAm) microspheres is larger than that of PNIPAM microspheres in water. The reason is that the hydrophilicity and steric hindered effect of introduced BCAm groups lead to a larger particle size in the precipitant copolymerization [59].

3.4. Ion-recognition behaviors of microspheres

The ion-recognition responsive behaviors of P(NIPAM-*co*-BCAm) microspheres are investigated by DLS technique in metal cationic solutions at different temperatures. Fig. 7 shows deswelling behaviors and dispersion stabilities of PNIPAM and P(NIPAM-*co*-BCAm) microspheres in the absence or presence of K^+ with different concentrations.

As expected, the LCST of P(NIPAM-*co*-BCAm) microspheres in 5 mM K^+ solution shifts to a higher temperature compared with that in deionized water (Fig. 7b), although this increase is not so remarkable. The diameter change trend of PNIPAM microspheres in 5 mM K^+ solution is almost the same as that in deionized water below 33 °C, at which PNIPAM microspheres begin to aggregate in K^+ solution. It is well known that dispersions of microspheres exhibit aggregation phenomena in the presence of electrolytes [60,61]. The addition of hydrated electrolytes to the dispersions causes competition for the water molecules hydrating PNIPAM chains. Such dehydration effects decrease the hydrophilicity of the colloidal particles and lead to microspheres' aggregation.

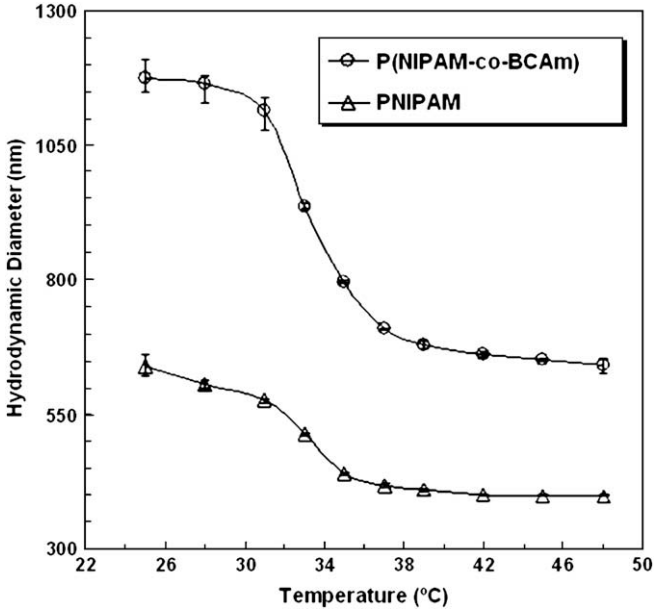

Fig. 6. Temperature dependence of the hydrodynamic diameter of PNIPAM and P(NIPAM-*co*-BCAm) microspheres in deionized water measured by DLS (temperature-raising process).

The dispersion stabilities of P(NIPAM-*co*-BCAm) microspheres in K^+ solutions are significantly different from that of PNIPAM microspheres. When the concentration of K^+ solution is 5 mM, PNIPAM microspheres begin to aggregate at temperatures above 33 °C; however, for P(NIPAM-*co*-BCAm) microspheres, the aggregation phenomenon appears only when the K^+ concentration is as high as 15 mM and temperatures are above 37 °C. When the K^+ concentration is 20 mM, the aggregation of P(NIPAM-*co*-BCAm) microspheres begins only when the temperature is higher than 35 °C.

The formation of crown ether/metal-ion complexes and the nonuniform crosslinked density in the microsphere structure could be the reasons for the above-mentioned phenomena.

It has been reported that PNIPAM-based microspheres prepared by precipitation polymerization using MBA as crosslinker have a nonuniform structure with a solid core and a loose shell [62,63]. Kinetic investigations reveal that in precipitation polymerizations the MBA crosslinker is consumed faster at beginning, resulting in a higher degree of crosslink density in inner part of the particle than in outer part [64,65]. As a result, towards the microsphere center the crosslink density is higher and the cavities of crown ethers are closer to each other. Therefore, the electrostatic repulsions among K^+ ions affect the formation of stable BCAm/K^+ complexes inside polymer chains with higher crosslinked density, which is the same as that in the P(NIPAM-*co*-BCAm) hydrogels we reported previously [56]. However, in outer layer of the microsphere, the polymer chains are more hairy-like and the cavities of crown ethers are not so close. Consequently, the BCAm receptors in outer layer of microspheres can capture K^+ ions and form stable BCAm/K^+ complexes. The polymer chains with appended ionic "host–guest" complexes near the surface of P(NIPAM-*co*-BCAm) microspheres behave like ionic polymeric chains. The repulsion among charged BCAm/K^+ complex groups counteracts the shrinkage of P(NIPAM-*co*-BCAm) microspheres with the increase of temperature, thereby resulting in that the LCST shifts to a higher temperature. However, due to the fact that formation of BCAm/K^+ complexes is mainly in the outer layer of P(NIPAM-*co*-BCAm) microspheres, the LCST shift is not so remarkable. Additionally, ionic "host–guest" complexes bring some positive charges onto the microsphere surface; therefore, the colloid stability of dispersion is increased. Fig. 8 shows the schematic illustration of ion-recognition behavior of P(NIPAM-*co*-BCAm) microspheres.

To confirm the "host–guest" complexation behavior, measurements with UV spectrometry are also performed with highly diluted P(NIPAM-*co*-BCAm) microsphere dispersions in 5 mM K^+ solution as well as in deionized water at 25 °C (Fig. 9). When K^+ is added, the absorbance spectrum around 290 nm, derived from the benzo-crown ether moiety, shows a blue-shift. The reason is that the oxygen atoms linked with benzo-ring participate in the formation of "host–guest" complex and K^+ withdraws the electrons of the oxygen atoms in the crown ether ring. Therefore, the p–π conjugated system between benzene and the oxygen atoms is disrupted and results in a blue-shift effect, which confirms the formation of BCAm/K^+ complexes [66,67].

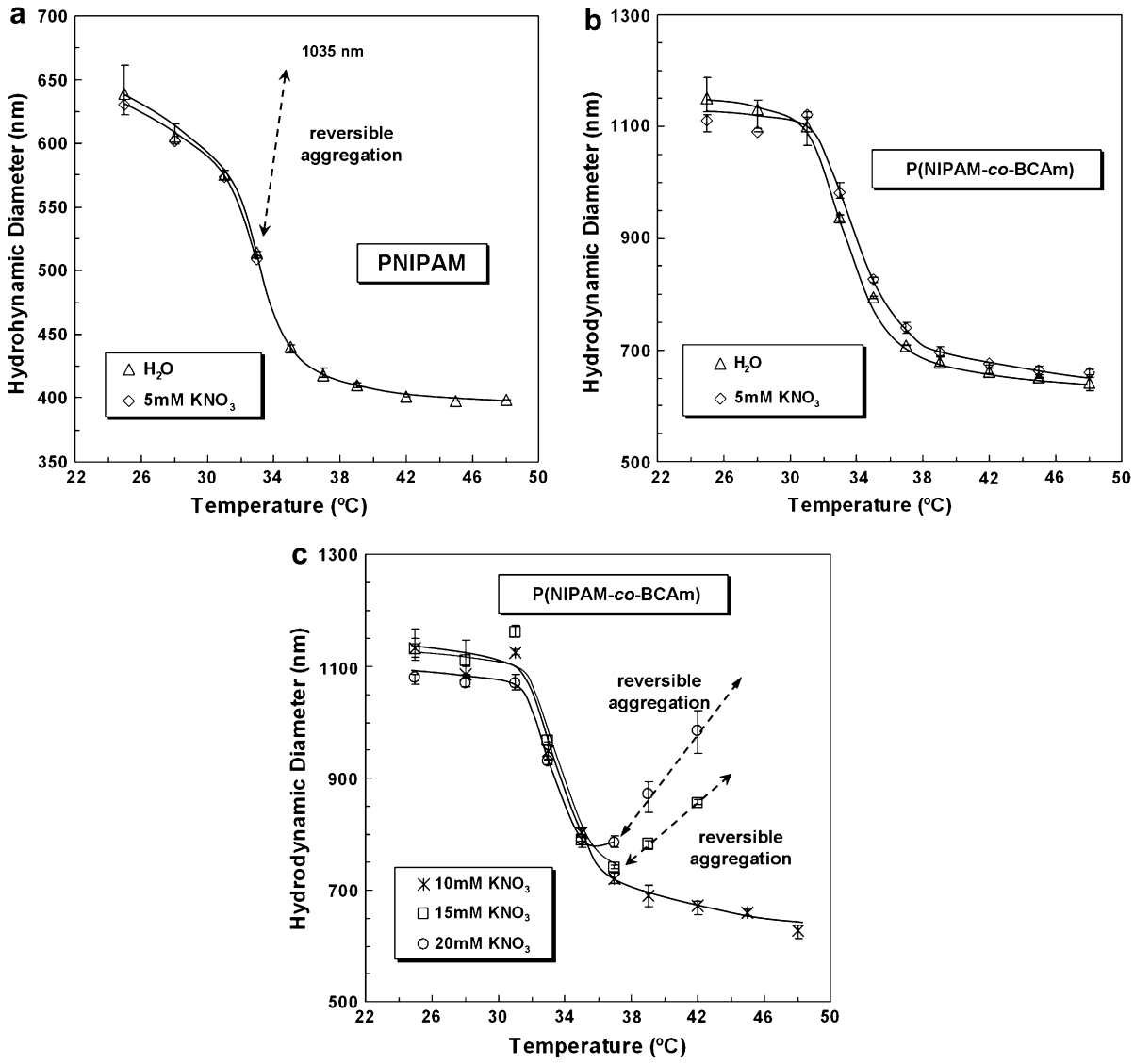

Fig. 7. The deswelling behaviors and dispersion stabilities of PNIPAM (a) and P(NIPAM-*co*-BCAm) (b and c) microspheres in the absence or presence of K^+ with different concentrations.

The optimal operating temperature for ion recognition of P(NIPAM-*co*-BCAm) microspheres is the temperature fixed between the LCST in deionized water and that in a corresponding ion solution, at which the P(NIPAM-*co*-BCAm) microspheres would swell or shrink in response to the special ions isothermally. That is, the so-called isothermal volume change shall be most significant at a temperature in the range from the LCST in deionized water to that in a corresponding ion solution. Therefore, the volume change of the microspheres is investigated at 33 °C. Fig. 10 shows the volumes of PNIPAM and P(NIPAM-*co*-BCAm) microspheres in solutions with different metal cations at 33 °C. The volume measurements are carried out three times and the data are in good agreement within a standard deviation of 2%. In the volume ratio of V_{ion}/V_{H_2O}, V_{ion} and V_{H_2O} are the volumes of microspheres in solutions containing different cations and in deionized water respectively. The volumes of PNIPAM microspheres in nitrate solutions decrease slightly compared with that in deionized water at 33 °C. The reason is that addition of hydrated anions provides competition for the water molecules with PNIPAM chains and causes dehydration of the polymer chains, which leads to a slight decrease in the volume of

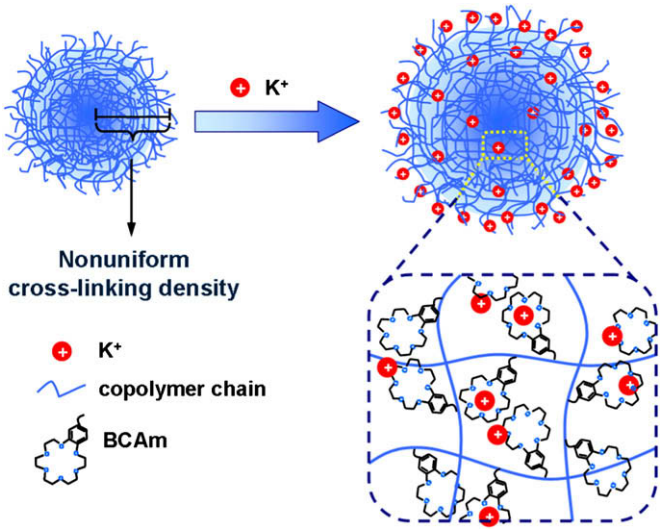

Fig. 8. The schematic illustration of ion-recognition behavior of P(NIPAM-*co*-BCAm) microspheres.

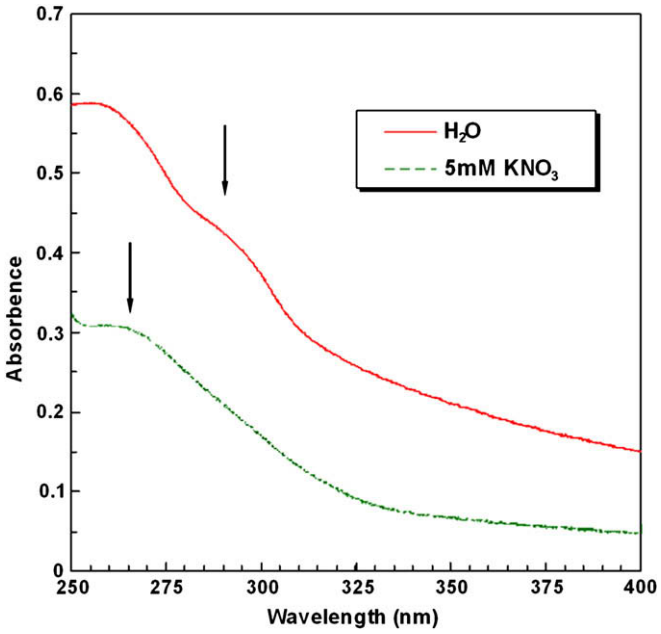

Fig. 9. UV–vis spectra of dispersions of P(NIPAM-*co*-BCAm) microspheres in deionized water and in 5 mM KNO_3 solution at 25 °C. [Microsphere] = 3.0×10^{-2} g/L.

PNIPAM microspheres [60]. On the other hand, the volumes of P(NIPAM-*co*-BCAm) microspheres in Ba^{2+} and K^+ solutions are larger than that in deionized water due to the formation of BCAm/ion complexes. The charge repulsion among the charged BCAm/ion complexes could cause larger interspaces so that more water may be contained inside the P(NIPAM-*co*-BCAm) microsphere, and consequently a larger volume is resulted. In addition, osmotic pressure within the P(NIPAM-*co*-BCAm) microsphere due to a Donnan potential also makes the P(NIPAM-*co*-BCAm) microsphere swells more [68,69]. It can be seen that the effects of Ba^{2+} and K^+ on the volumes of P(NIPAM-*co*-BCAm) microspheres are different. The reason is that the complex stability constant, log *K*, of

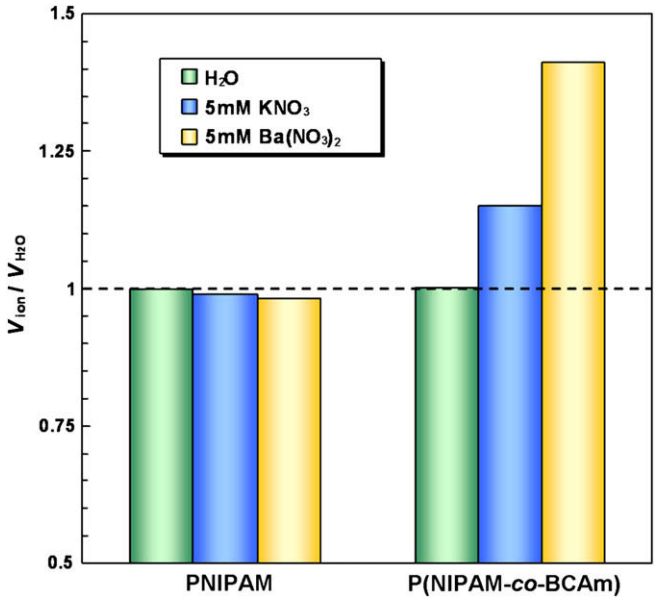

Fig. 10. Effect of various cations on the volume of PNIPAM and P(NIPAM-*co*-BCAm) microspheres at 33 °C.

benzo-18-crown-6 with Ba^{2+} is larger than that with K^+ [70]. As a result, more stable BCAm/ion complexes are formed inside the P(NIPAM-*co*-BCAm) microspheres in Ba^{2+} solution than in K^+ solution, so that the P(NIPAM-*co*-BCAm) microspheres swell more in Ba^{2+} solution.

The above results demonstrate the ion-recognition capability of the fabricated P(NIPAM-*co*-BCAm) microspheres, that is, the microspheres can isothermally change their volumes at a certain temperature by recognizing specific metal ions. In K^+ solutions, the LCST of the P(NIPAM-*co*-BCAm) microspheres shifts to a higher temperature and their colloidal stability increases. Such "smart" microspheres could be utilized as new functional materials for ion-responsive systems, which are highly attractive for targeting drug delivery systems, sensors, chemical carriers, and so on.

4. Conclusions

Monodisperse ion-recognizable P(NIPAM-*co*-BCAm) microspheres have been successfully fabricated via precipitation copolymerization of NIPAM with BCAm. In K^+ solutions, the LCST of the P(NIPAM-*co*-BCAm) microsphere increases slightly. On the other hand, the formation of BCAm/K^+ complexes in the outer layer of the P(NIPAM-*co*-BCAm) microspheres bring some charges onto the microsphere surfaces, which results in higher colloidal stability of the P(NIPAM-*co*-BCAm) microspheres in K^+ solution than that of PNIPAM microspheres. Besides, the repulsion among the charged BCAm/ion complexes and the osmotic pressure within the P(NIPAM-*co*-BCAm) microspheres cause swelling of the microspheres. This means that by adding specific metal ions in the environmental solution, the P(NIPAM-*co*-BCAm) microspheres can isothermally change their volumes at a certain temperature. That is, the P(NIPAM-*co*-BCAm) microspheres exhibit ion-recognition capability. The ion-recognition property of such monodisperse microspheres makes them be promising for various applications, especially for "smart" targeting drug delivery systems, sensors, actuators and chemical separations.

Acknowledgments

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