Release Property of Microgels Formed by Electrostatic Interaction Between Poly(*N*-isopropylacrylamide-*co*-methacrylic acid) and Poly(*N*-isopropylacrylamide-*co*-dimethylaminoethylmethacrylate)

Mi Kyoung Kang, Sung Kyeong Hong, Jin-Chul Kim

Division of Biotechnology and Bioengineering and Institute of Bioscience and Biotechnology, Kangwon National University, 192-1, Hyoja 2 dong, Chunchon 200-701, Kangwon-do, Korea

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ABSTRACT: Microgels were prepared by taking advantage of electrostatic interaction between poly(N-isopropylacrylamide-*co*-methacrylic acid) and poly(*N*-isopropylacrylamide-*co*-dimethylaminoethylmethacrylate). The maximum interaction, investigated by measuring the size of complex and the turbidity of the mixture, took place at pH = 6.5. The microgel prepared at pH = 6.5 using the copolymer ratio of 1/1 (w/w) was globular on scanning electron microscopy, and the size was a few to tens of micrometer. The phase transition of the microgel, observed by turbidometry and differential scanning calorimetry, occurred around 31°C. % Release, in 24 h at room temperature, of FITC-dextran from the microgel was higher under an acidic (64% at pH = 4.0) and an alkali condition (69 % at pH = 9.0) than the % release at pH = 6.5 (41%). The disintegration of microgels would be responsible for the higher % release. The % releases, in 24 h at pH = 6.5, were lower at higher temperatures (53% at 35°C, 50% at 40°C) than at lower temperatures (71% at 25°C, 61% at 30°C). The suppressed release at higher temperatures is possibly due to the skin formation on the surface of microgel. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 125: 1993–1999, 2012

Key words: microgel; *N*-isopropylacrylamide; dimethylaminoethylmethacrylate; methacrylic acid; release

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAM) is well known as a thermosensitive polymer.[1,2] The polymer in the aqueous solution exhibited a lower critical solution temperature (LCST) around 32°C. Below the LCST, the polymer is fully hydrated and water-soluble, so it takes an expended form. Above the LCST, the polymer is dehydrated and water-insoluble, so it takes a contracted form.[3] Owing to the thermal property, PNIPAM has been exploited to develop drug carriers, which release their content in response to environmental temperature. Chemically crosslinked PNIPAM hydrogels released their content more extensive when the temperature increased across LCST, because the content was squeezed-out by the thermal contraction.[4] It was also reported that the dense layer was formed on the surface of hydrogels on the thermal contraction, and it could suppress the release from the hydrogel.[5] PNIPAM has also been used as an actuator to develop temperature-sensitive lipid-based carriers. To develop a temperature sensitive liposome, the surface was modified with hydrophobicized PNIPAM. The thermal contraction was reported to impose a mechanical strength on the liposomal membrane, leading to an extensive release.[6,7] In order to design a temperature-responsive cubic phase, hydrophobicized PNIPAM was included in the nanosized water channel of monoolein cubic phase. On the thermal contraction of PNIPAM, the diffusion rate through the water channel was altered, and the release rate form the cubic phase could be controlled.[8]

Microgels are crosslinked hydrogel particles. They are confined to smaller dimensions and they have the structure of macroscopic network.[9] Recently, microgels have attracted much attention as a drug carrier because they show high water content, biodegradability, biocompatibility, and adjustable chemical and mechanical properties. Microgels have been developed by chemical and physical crosslinking methods. Physical crosslinking methods (e.g., electrostatic interaction) are relatively simple. A polyelectrolyte complex microgel was prepared by just mixing the

Correspondence to: J.-C. Kim (jinkim@kangwon.ac.kr).
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solution of positively charged chitosan and that of negatively charged dextran sulfate.[10] In addition, the microgels were formed by electrostatic interaction and the hydrophobic interaction of naphthaleneacetic acid (NAA) with β-cyclodextrin-grafted polyethyleneimine.[11] NAA was included in the cavity of βCD and it could also interact with PEI by an electrostatic interaction, resulting in the formation of microgels.

In this study, poly(*N*-isopropylacrylamide-*co*-methacrylic acid) (PNIPAM-*co*-MAA) and poly(*N*-isopropylacrylamide-*co*-dimethylaminoethylmethacrylate) (PNIPAM-*co*-DMAEMA) were prepared by a free-radical reaction, and microgel was prepared by taking advantage of salt bridges formed between methacrylic acid (MAA) residues and DMAEMA ones. The microgel is not only temperature-responsive but also pH-responsive in terms of release, because the integrity of microgel is maintained by salt bridges, which are stable under a neutral condition but labile under an acidic and an alkali condition. So, an extensive release could take place under an acidic and an alkali condition due to the dissolution of microgel. The degree of interaction between the copolymers was investigated in the range of pH = 4.0–9.0 by turbidometry and dynamic light scattering. The microgel was prepared by combining each copolymer solution at certain pH where maximum interaction took place. The shape and the phase transition of microgels were observed by scanning electron microscopy (SEM) and differential scanning calorimetry. In order to investigate the pH- and temperature-dependent release property of microgels, the release of FITC-dextran (MW = 4,000) was observed for 24 h with changing the pH and the temperature of release medium.

EXPERIMENTAL

Materials

MAA, 2-(dimethylamino)ethyl methacrylate (DMAEMA), fluorescein isothiocyanate-dextran (FITC-dextran, MW = 4000), and tris-hydroxymethylaminomethane (Trizma® base) were purchased from Sigma Chemical. Glycine was obtained from Bio Basic (NY). *N*-isopropylacrylamide (NIPAM) was obtained from Tokyo Kasei Kogyo (Japan). 2-(*N*-morpholino)-ethane sulfonic acid (MES) was purchased from Biopure (Canada). α-α′-Azobis(isobutyronitrile) (AIBN) was obtained from Junsei Chemical (Japan). All other reagents were in analytical grade.

Synthesis and characterization of P(NIPAM-*co*-MAA) and P(NIPAM-*co*-DMAEMA)

Poly(*N*-isopropylacrylamide-*co*-methacrylic acid) (P(NIPAM-*co*-MAA)) was prepared by a free radical reaction.[12] The molar ratio of NIPAM to MAA in the reaction mixture was 85/15. The content of acidic comonomer (MAA) residue in P(NIPAM-*co*-MAA) was determined by a titration method.[13] Poly(*N*-isopropylacrylamide-*co*-dimethylaminoethylmethacrylate) (P(NIPAM-*co*-DMAEMA)) was also prepared by a free radical reaction,[14] and the molar ratio of NIPAM to DMAEMA in the reaction mixture was 85/15. The content of alkali comonomer (DMAEMA) residue in P(NIPAM-*co*-DMAEMA) was determined by H^1-NMR spectroscopy. The copolymer was dissolved in $CDCl_3$ and the spectrum was obtained on a Bruker Avance 400 (Karlsruhe, Germany) spectrometer.

Interaction of P(NIPAM-*co*-MAA) and P(NIPAM-*co*-DMAEMA)

P(NIAPM-*co*-MAA) and P(NIAPM-*co*-DMAEMA) are dissolved in distilled water so that the concentration of each solution was 0.5%. The pH of the copolymer solution was adjusted to 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, and 9.0 using 1*N* HCl or 1*N* NaOH. When the pH for maximum interaction was determined, P(NIPAM-*co*-MAA) solution of certain pH and P(NIAPM-*co*-DMAEMA) solution of the same pH were mixed in the volumetric ratio of 1/1. When the copolymers ratio for maximum interaction was determined, two kinds of solutions were mixed together in the ratio of 1/7. 1/6. 1/5, 1/4, 1/3, 1/2, 1/1, 2/1, 3/1, and 4/1. The transmittances of mixture solutions were measured at 600 nm on a UV spectrophotometer (JENWAY 6505) at 25°C. The mean diameters of complexes formed in the mixture solution were measured on dynamic light scattering equipment (ZetaPlus 90, Brookhaven Instrument).

Preparation of microgels

Microgel was prepared under a condition where maximum interaction between P(NIPAM-*co*-MAA) and P(NIAPM-*co*-DMAEMA) took place. Each copolymer was dissolved in distilled water so that the concentration of each solution was 2.0%. The pH of each copolymer solution was adjusted to 6.5, and two kinds of copolymer solutions were combined in 1/1 ratio by volume to obtain microgels. After the suspension of microgels was freeze-dried (TFD 5508), the shapes of freeze-dried microgels were investigated on SEM (Jeol JSM-840A). Dry microgels were mounted on metal stubs with double-sided tape, sputtered with gold. When microgels containing FITC-dextran were prepared for a release experiment, the fluorescence dye and each copolymer were codissolved in distilled water so that the concentrations of the dye and the copolymer were 0.05 and 2.0%, respectively. After the pH of each solution was adjusted to 6.5 and two copolymer solutions

were combined in 1/1 volumetric ratio, the microgel suspension was gently stirred for 24 hr. In order to remove unloaded-dye, the suspension was centrifuged at 2588 × *g* for 20 min, and the supernatant was decanted. After the microgels were washed with distilled water (adjusted to pH = 6.5), they were freeze-dried for a release experiment.

Observation of phase transition of microgels

The phase transitions temperatures of each copolymer and mixture of P(NIPAM-*co*-MAA) and P(NIPAM-*co*-DMAEMA) (1/1) in an aqueous phase were determined by observing the turbidity change of the aqueous solutions (0.25%) in distilled water (pH = 6.5). A total of 1.0 ml of copolymer solution contained in 2-mL cuvette was heated from 25 to 50°C, and the turbidity of the solution was recorded at 600 nm on a UV-spectrophotometer (JENWAY 6505). In addition, microgel in suspension was thermally scanned on a differential scanning calorimeter (TA instruments DSC 2010). An aliquot of suspension was put into aluminum DSC pans, and it was scanned from 20 to 60°C at a heating rate of 0.5°C/min.

Releases of FITC-dextran from microgels

The release of FITC-dextran was investigated by a dialysis method. When the effect of pH on the release was observed, dye-loaded dry microgel, 0.05 g, was suspended in 1 mL of Glycine buffer (pH = 4.0), MES buffer (pH = 5.5, pH = 6.5), and HEPES buffer (pH = 7.5, pH = 9.0), the suspension was put in dialysis bag (MWCO 300,000), and it was dialyzed against 80 mL of the same buffer solution at room temperature. When the effect of temperature on the release was observed, the microgels were suspended in MES buffer, and it was dialyzed at 25, 30, 35, and 40°C. Buffer solution, 1 mL, was taken at predetermined time intervals for the determination of the released amount of FITC-dextran. The same volume of fresh buffer solution was put in the dialysis system to keep the total volume constant. The amount of FITC-dextran was determined on fluorescence spectrometer (F-2500, HITACHI) at 520 nm with excitation of 495 nm. The % release is defined as the percentage of the released amount versus the total amount loaded in the microgels.

RESULTS AND DISCUSSION

Determination of contents of MAA residues and DMAEMA residues

The molar ratio of NIPAM residue to MAA one in P(NIPAM-*co*-MAA) was about 84.5/15.5, and the molar ratio of NIPAM monomer to MAA one in the feed for the polymerization was 85/15. There was no significance difference between the residue ratio in the copolymer and the monomer ratio in the feed. According to the result of a previous report, the molar ratios of the NIPAM residue to MAA one in the copolymers were almost the same as the feed ratios when the feed ratios of NIPAM to MAA were in the range of 85/15–15/85.[13,15] On the other hand, the molar ratio of NIPAM residues to DMAEMA ones in P(NIPAM-*co*-DMAEMA) was calculated on the H^1-NMR spectrum. The —CH= of isopropyl group of NIPAM residue was found around 4.0 ppm, and the $—CH_2—$ adjacent to dimethylamino group of DMAEMA residue was observed around 2.5 ppm. By taking advantage of the areas of those peaks, the molar ratio of NIPAM residue to DMAEMA one was calculated to be 85.7/14.3. The molar residue ratio in the copolymer insignificantly deviated from the monomer ratio in the feed, indicating that the reactivity of NIPAM is almost the same as that of DMAEMA.

FTIR spectrometry

In the spectrum of P(NIPAM-*co*-MAA), the characteristic peaks of NIPAM residues were found at 1459, 1544, and 1635 cm^{-1}, along with the signal of carbonyl group of MAA residues at 1712 cm^{-1}. In the spectrum of P(NIPAM-*co*-DMAEMA), the characteristic peaks of NIPAM residues were observed at the same positions as in the spectrum of P(NIAPM-*co*-MAA), and the signals of ester bonds of DMAEMA residues were observed at 1153 and 1718 cm^{-1}.

Interaction of P(NIPAM-*co*-MAA) and P(NIPAM-*co*-DMAEMA)

Figure 1 shows the transmittances of mixtures of P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) (1/1, w/w) in distilled water in the range of pH 4.0–9.0. The mixtures were almost transparent at pH = 4.0 and pH = 5.0. Under an acidic condition, most of carboxylic groups of MAA residues are in unionized form, so no significant electrostatic interaction between P(NIAPAM-*co*-MAA) and P(NIAPM-*co*-DMAEMA) would take place. When the pH of medium increased to 5.5, 6.0, 6.5, and 7.0, the mixture became turbid. At those pH values, the carboxylic group is likely to be ionized enough to electrostatically interact with P(NIPAM-*co*-DMAEMA), leading to the formation of complexes. Further increase of the pH value to 8.0 and 9.0 resulted in the transparent solutions, indicating that large complexes disappeared on dissolution. Under an alkali condition, most of amino groups of DMAEMA residues are in

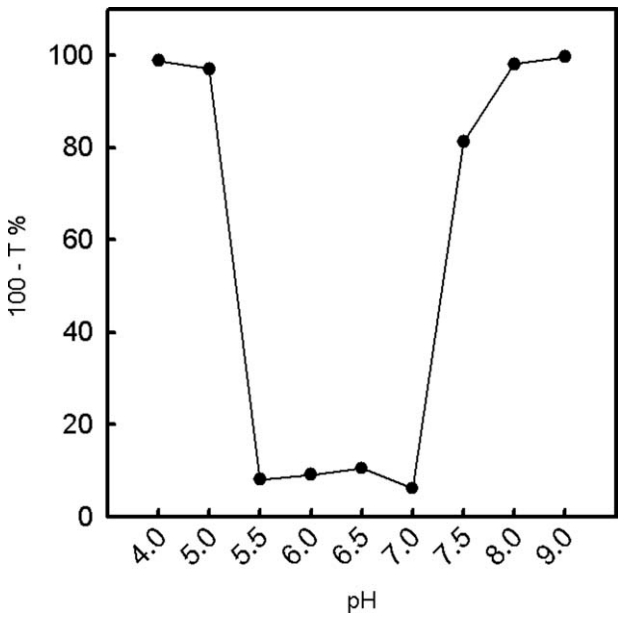

Figure 1 Transmittances of mixtures of P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) (1/1, w/w) in distilled water in the range of pH= 4.0–9.0, measured at 25°C. *T*% in vertical axis is the percent of transmission of the mixture solution.

unionized form, so no significant interaction between two kinds of copolymers could occur. Figure 2 shows the mean diameter of complexes in the mixtures of P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) (1/1, w/w) in distilled water in the range of pH = 4.0–9.0. The size at pH = 4.0 and pH = 5.0 was relatively small (194.2 and 96.2 nm, respectively), possibly because of weak electrostatic interaction. The diameter markedly increased when the pH of medium increased from 5.0 to 5.5, 6.0, 6.5, and 7.0, possibly due to a strong electrostatic interaction between two kinds of copolymers. The maximum size was observed around pH = 6.5, and the value was 4.06 μm. The further increase of the pH led to the outstanding reduction in the mean size, possibly because of reduction in the attraction between two copolymers. According to the results of the transmittance measurement (Fig. 1) and those of the size measurement (Fig. 2), it is believed that the pH for maximum interaction is around pH = 6.5. As the maximum interaction will take place when the number of positive charge is equal to that of negative charge, the number of ionized MAA residues, at pH = 6.5, is believed to be equal to that of ionized DMAEMA residues when the copolymers ratio is 1/1 (w/w). In order to make sure that pH = 6.5 is a value for the maximum interaction at the copolymer ratio of 1/1, the copolymers ratio for maximum interaction was determined at pH = 6.5. Figure 3 shows the turbidities of mixtures (pH = 6.5) where the copolymers ratios were 1/7–4/1. As the ratio increased from 1/7 to 1/1, the transmittance decreased. At a lower ratio (e.g., 1/7), the number of MAA residues is much less than that of DMAEMA ones so the amount of complex formed by electrostatic interaction will be relatively low. As the ratio increases to 1/1, MAA residues increase in number so the amount of complex will increase. The increase in complex formation could account for the decrease in the transmittance in the range of 1/7–1/1. On the contrary, as the ratio increased in the range of 1/1–

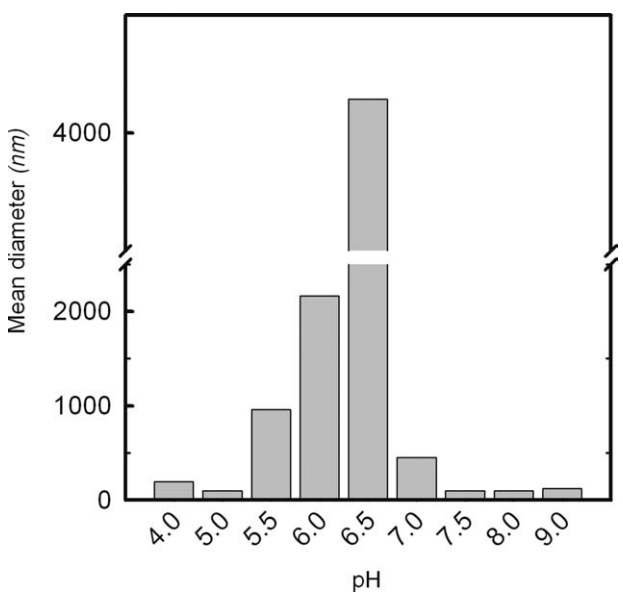

Figure 2 Mean diameter of complexes in the mixtures of P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) (1/1, w/w) in distilled water in the range of pH = 4.0–9.0, measured at 25°C.

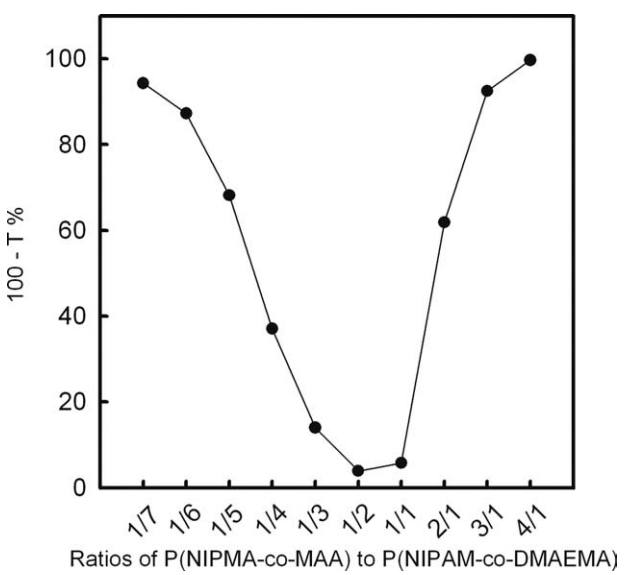

Figure 3 Transmittances of mixtures (pH = 6.5) where P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) ratios were 1/7 to 4/1, measured at 25°C. *T*% in vertical axis is the percent of transmission of the mixture solution.

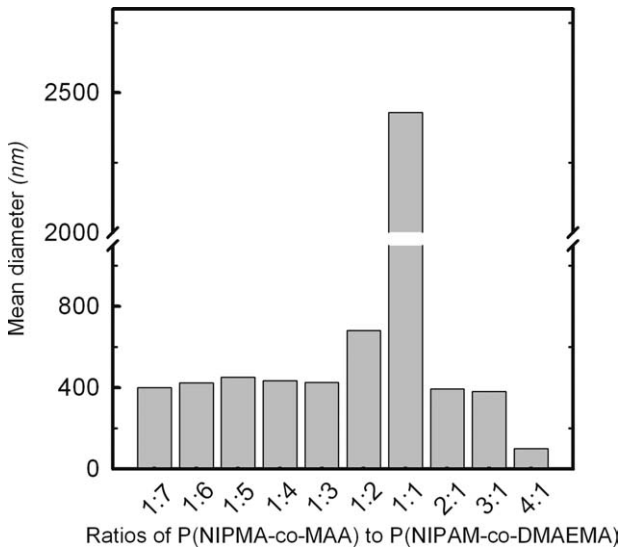

Figure 4 Mean diameters of complexes in the mixtures (pH = 6.5) where P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) ratios were 1/7 to 4/1, measured at 25°C.

4/1, the transmittance increased. In the range of 1/1–4/1, the number of DMAEMA residues may be less than that of MAA ones so the complexation will decrease with increasing the ratio. Figure 4 shows the mean diameter of complexes in the mixtures (pH = 6.5) where the copolymers ratios were 1/7–4/1. The mean size was sub-micrometer except when the ratio was 1/1 where the mean size was about 2.43 μm in diameter. According to the results of the transmittance measurement (Fig. 3) and those of the size measurement (Fig. 4), it is confirmed that, when the copolymer ratio was 1/1, pH = 6.5 is a right value for the maximum interaction.

SEM of the microgels

Figure 5 shows the SEM photos of microgels composed of P(NIPAM-*co*-MAA) and P(NIAPM-*co*-DMAEMA) (1/1, w/w) prepared at pH = 6.5. The globular particles were observed together with some irregular ones, and the size of microgel was a few to tens of micrometers. The driving force for the formation of particulate gel is an electrostatic interaction between MAA residues and DMAEMA ones. When the copolymer solutions were mixed under an acidic condition (e.g., pH = 4.0) and under an alkali condition (e.g., pH = 9.0), no particles were formed possibly due to the lack of electrostatic interaction.

Observation of phase transition of microgels

Figure 6 shows the phase transitions of each copolymer, and of microgel in distilled water (pH = 6.5). Both copolymers exhibited low temperature sensitivity around 43°C. As the pH value of 6.5 is greater

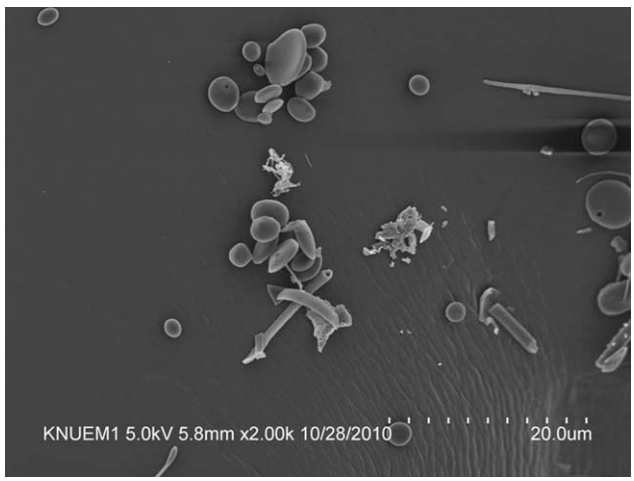

Figure 5 SEM photos of microgels composed of P(NIPAM-*co*-MAA) and P(NIAPM-*co*-DMAEMA) (1/1, w/w) prepared at pH = 6.5.

than pK_a of MAA residues (4.7) and less than pK_b of DMAEMA ones (8.4), both of copolymers are likely to be in an ionized form. So, the intramolecular electrostatic repulsion will act as a force against the thermal collapse of the copolymer chains. On the other hand, the turbidity change of microgel suspension was found around 30°C, and the temperature sensitivity was outstanding. Because the maximum interaction between two kinds of polymer took place at pH = 6.5 (Figs. 1 and 2), the microgel was prepared at the same pH. Accordingly, when each copolymer was in the microgel, the charges of copolymers

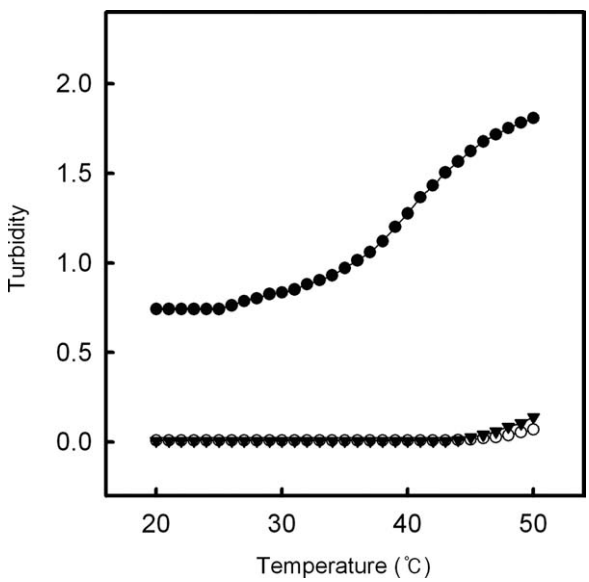

Figure 6 Phase transitions of each copolymer, and of microgel in distilled water (pH = 6.5). Microgel (●), P(NIAPM-*co*-DMAEMA) (○), P(NIPAM-*co*-MAA) (▼). Turbidity in vertical axis is the absorbance of microgel suspension measured at 600 nm, and it is proportional to the cloudiness degree of the suspension.

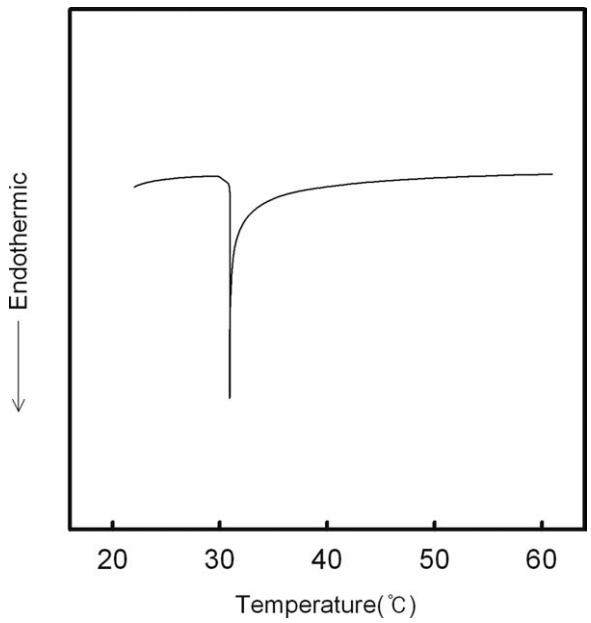

Figure 7 Thermogram of microgels. P(NIPAM-*co*-MAA)/P(NIPAM-*co*-DMAEMA) ratio of microgel was 1/1, and the pH of microgel suspension was 6.5.

would have been neutralized and the intramolecular electrostatic repulsion of each copolymer would much less than that of the copolymer in its pure solution. As a result, the thermal collapse of each copolymer in microgel could be hindered less than that of the copolymer could in its pure solution. This may be a reason for why the temperature sensitivity of the microgel was higher than that of each copolymer. Figure 7 shows the thermogram of microgels. A sharp endothermic peak was observed around 31°C, and this is due to the phase transition of the microgels. The phase transition temperature determined by the thermogram is in a good agreement with the phase transition temperature observed on the temperature-dependent turbidity (Fig. 6).

Releases of FITC-dextran from microgels

Figure 8 shows the effect of pH on the release of FITC-dextran from microgel at room temperature. The degree of release increased in a saturation manner for 24 h and the release seems to be a first-order release. The microgel has no reservoir for the entrapment of FITC-dextran but they entrap the dye throughout their matrix. The dye in the outer part of the matrix would be exhausted in the early stage of release and then the dye in the inner part would. In this circumstance, the traveling distance of dye to diffuse out of the matrix will increase with time, so the mass transfer resistance will also increase. This would explain the reason why the release seems to be a first order release. The degree of release in 24 h decreased from 64 to 41% when the pH of release medium increased from 4.0 to 6.5. On the contrary, the degree of release increased from 41 to 69% when the pH of release medium increased from 6.5 to 9.0. Under an acidic condition (e.g., pH = 4.0), the salt bridge formed between MAA residues and DMAEMA ones will break down since MAA residues are likely to be in unionized form. As a result, the microgel could be disintegrated, leading to an extensive release. Under an alkali condition (e.g., pH = 9.0), the microgel could be disintegrated, leading to an extensive release, because DMAEMA residues are likely to be in unionized form. On the other hand, the degree of release was the lowest at pH = 6.5. The maximum interaction was found at the pH = 6.5, so the microgels would be stable at the pH value, resulting in a suppressed release. In fact, the size of particles observed at pH = 4.0 and pH = 9.0 was much lower than that of particles at 6.5 (Fig. 2). Figure 9 shows the effect of temperature on the release of FITC-dextran from microgel at pH = 6.5. The release increased in a saturation manner at all temperatures tested. The % releases in 24 h at 25°C, 30, 35, and 40°C were 71, 61, 53, and 50%, respectively. The release was suppressed at temperatures (35 and 40°C) higher than the phase transition temperature of the microgel (around 31°C). It was reported that two mechanisms were involved in the thermally induced release from the PNIPAM hydrogels.[4] When the temperature increases across its LCST, the release is promoted by squeezing-out, or the release is suppressed by skin formation. In case of the microgel developed in this study, the effect of skin formation seems to be more dominant than that of squeezing-out. FITC-dextran (4000) could act as a

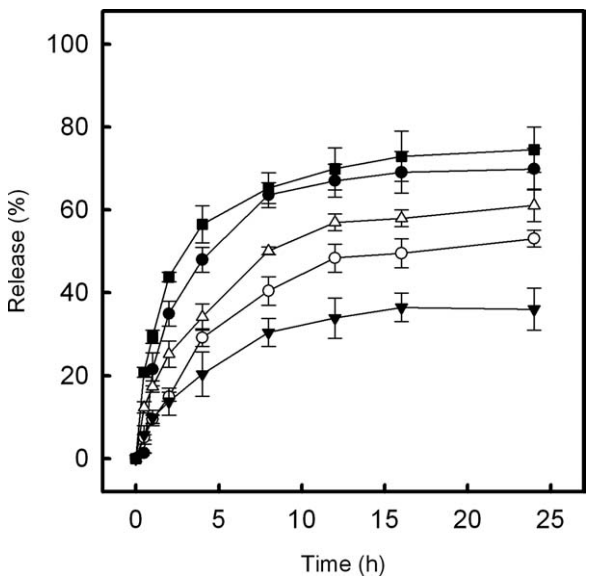

Figure 8 Effect of pH on the release of FITC-dextran from microgel at room temperature. pH 4.0 (●), pH = 5.5 (○), pH = 6.5 (▼), pH = 7.5 (△), pH = 9.0 (■).

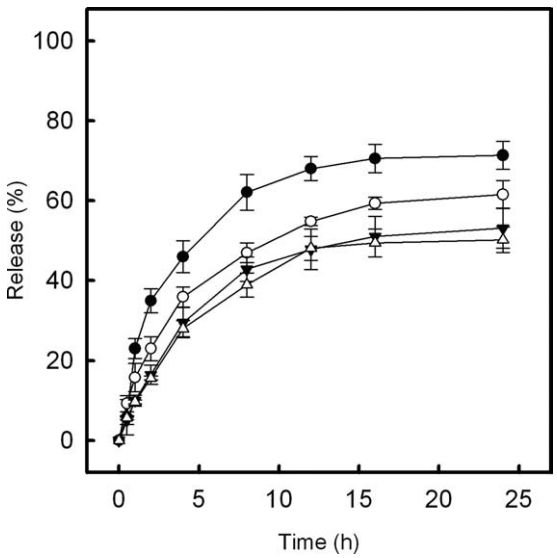

Figure 9 Effect of temperature on the release of FITC-dextran from microgel at pH = 6.5. 25°C (●), 30°C (○), 35°C (▼), 40°C (△).

model for peptide drugs because the molecular weight is not significantly different from those of peptide drugs. There would be no thermo- or pH-sensitive release with a small molecular drug model. Because of its large mesh size, the collision frequency of the microgel network with a small molecular model would be low whether the microgel is in swollen state or not.

CONCLUSIONS

Stable microgel composed of P(NIPAM-*co*-MAA) and P(NIPAM-*co*-DMAEMA) in 1/1(w/w) ratio could be prepared at pH = 6.5. Under an acidic and an alkali condition, the microgel could be hardly prepared due to the lack of electrostatic interaction. The microgel was globular and there were also some irregular ones. The size of microgel was from a few to tens of micrometers, and the phase transition temperature of microgel, determined by differential scanning calorimetry, was about 31°C. The FITC-dextran release from the microgel was pH- and temperature-dependent. The microgel developed in this study could be used as a carrier for pH- and temperature-controlled release of water-soluble compounds.

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