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Effect of polyelectrolyte on the lower critical solution temperature of poly(*N*-isopropyl acrylamide) in the poly(NIPAAm-*co*-acrylic acid) hydrogel

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Abstract

Temperature/pH sensitive hydrogels were prepared by copolymerizing *N*-isopropyl acrylamide (NIPAAm) and acrylic acid (AAc). The influence of polyelectrolyte on the lower critical solution temperature (LCST) of temperature/pH sensitive hydrogels was investigated in the pH range of 2 ~ 12. Swelling ratio of hydrogels as a function of pH at various temperatures was obtained by measuring the weight of the hydrogels in buffer solutions. Swelling ratio of the hydrogels in the presence of poly(allyl amine) (PAA) as a polyelectrolyte was also measured at the same conditions. The LCSTs of the poly(*N*-isopropyl acrylamide-*co*-acrylic acid) [P(NIPAAm–*co*–AAc)] hydrogels increased with pH value and disappeared above the pK_a value of poly(acrylic acid) (PAAc) except hydrogel containing 10 mol% of AAc. The LCSTs of the P(NIPAAm-*co*-AAc) hydrogels in the presence of PAA could be observed even above the pK_a value of PAAc. At same pH, the LCSTs of the P(NIPAAm-*co*-AAc) hydrogels in the presence of PAA were lower than those of the P(NIPAAm-*co*-AAc) hydrogels due to the polyelectrolyte complex formation between PAAc and PAA. The swelling ratio of P(NIPAAm-*co*-AAc) gel was the largest at 20 mol% of AAc content and decreased by polyelectrolyte complex formation with PAA. The swelling kinetics of P(NIPAAm-*co*-AAc) hydrogel was strongly dependent on pH value, temperature and polyelectrolyte solute. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Polyelectrolyte; Lower critical solution temperature; Temperature/pH sensitive hydrogel

1. Introduction

Recently, much attention has been focused upon phase transitions and critical phenomena in polymer gels [1–3]. Phase transitions accompanied by a reversible, discontinuous volume change as large as several hundred times the original volume, in response to infinitesimal changes in external conditions, have been universally observed in various gels made of synthetic and natural polymers [1–8]. A typical temperature-sensitive hydrogel, crosslinked poly(*N*-isopropyl acrylamide) (PNIPAAm) has a lower critical solution temperature (LCST) at 32 ~ 33°C [9,10]. Below that temperature, the gel is swollen, hydrated and hydrophilic, and above the LCST, the gel becomes collapsed, dehydrated and hydrophobic. Furthermore, its phase transition behavior can be controlled by incorporating more hydrophilic or hydrophobic monomer in the gel composition [11–13].

It has long been known that a crosslinked polymer gel bearing weakly acidic or weakly basic pendant groups absorbs water to an extent that depends on the pH and the ionic composition of the solution bathing the gel. If the temperature-sensitive gel contains acidic pendant groups, the swelling increases as the pH of solution increases [14,15]. Similarly, a weakly basic temperature-sensitive gel expands smoothly as the pH of solution decreases [16,17]. PNIPAAm and poly(acrylic acid) (PAAc) have characteristic temperature- and pH-sensitivity, respectively. Therefore, P(NIPAAm-*co*-AAc) hydrogel, where PAAc is introduced as a pH-sensitive component into the temperature-sensitive component, PNIPAAm, has both pH- and temperature-sensitivity [18,19]. However, for a higher pH than pK_a of PAAc and higher AAc content, the swelling transition phenomena of the hydrogel disappears [19]. In order to utilize the hydrogels for the drug delivery system, their temperature- and pH-sensitivity responding to small

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Table 1
Feed composition of P(NIPAAm-*co*-AAc) hydrogel

Code[a]	NIPAAm (g)	AAc (ml)	EGDMA[b] (ml)	AIBN[c] (g)	Dioxane[d] (ml)
PNIPAAm	6.00	0.00	0.10	0.026	5.79
P(NIPAAm-*co*-AAc-10)	5.40 (4.77 × 10^{-2} mol)	0.36 (5.30 × 10^{-3} mol)	0.10	0.026	5.59
P(NIPAAm-*co*-AAc-20)	4.80 (4.24 × 10^{-2} mol)	0.73 (1.06 × 10^{-2} mol)	0.10	0.026	5.38
P(NIPAAm-*co*-AAc-30)	4.20 (3.71 × 10^{-2} mol)	1.09 (1.59 × 10^{-2} mol)	0.10	0.026	5.17
P(NIPAAm-*co*-AAc-40)	3.60 (3.18 × 10^{-2} mol)	1.45 (2.12 × 10^{-2} mol)	0.10	0.026	4.96
P(NIPAAm-*co*-AAc-50)	3.00 (2.65 × 10^{-2} mol)	1.82 (2.65 × 10^{-2} mol)	0.10	0.026	4.75

[a] Mol% of AAc against NIPAAm.
[b] EGDMA as a crosslinker (1.0 mol% of monomers).
[c] AIBN as an initiator (0.3 mol% of monomers).
[d] Dioxane as a solvent (25 wt% of monomers).

change in physiological condition should be maintained. To retain the temperature-induced transition property over a broad and useful pH range, we used the method of polyelectrolyte complex formation.

In previous studies, the influence of polyelectrolytes on the cloud point (CP) of PNIPAAm in the linear P(NIPAAm-*co*-AAc)/water was investigated in the pH range of 2–12 [20,21]. It was found that the CPs of PNIPAAm in the presence of poly(allyl amine) (PAA) as a polyelectrolyte appeared above pK_a of PAAc and were lower than those of PNIPAAm without PAA due to the polyelectrolyte complex between PAAc and PAA [20]. Also, it was found that the influence of more hydrophobic poly(L-lysine) as a polyelectrolyte on the CP of PNIPAAm in the copolymer was stronger than that of PAA due to occurrence of much more dehydration around PNIPAAm [21].

Temperature/pH sensitive hydrogels attract greater interest than temperature/pH sensitive linear polymers for the drug delivery system [19,22], since they exhibit a volume phase transition in response to pH as well as temperature and allow the drug to be released in response to the change of pH and temperature.

In this study, it has been aimed to investigate the influence of polyelectrolyte solute on the swelling property of crosslinked P(NIPAAm-*co*-AAc) hydrogel for the application of drug delivery system.

Table 2
Monomer ratios in P(NIPAAm-*co*-AAc) gels compared to monomer feed ratios

Comonomer AAc feed molar composition (mol%)	Copolymer AAc molar composition (mol%)
0	0
10	14.0
20	24.2
30	36.6
40	45.2
50	54.0

2. Experimental

2.1. Materials

N-isopropyl acrylamide (NIPAAm, Polysciences Inc.) was purified in toluene/*n*-hexane (1/9, v/v%). Acrylic acid (AAc, Junsei Chem. Co.) was purified by distillation at 40°C/26 mm Hg. 2,2′-azobisisobutyronitrile (AIBN, Tokyo Kasei Kogyo Co.) was purified in chloroform/methanol (1/5, v/v%). 1,4-dioxane (Duksan Co.) was purified by distillation. Poly(allyl amine) (PAA, Aldrich), ethylene glycol dimethacrylate (EGDMA, Junsei Chem. Co.), sodium hydroxide standard solution (Katayama Chem.), hydrochloric acid standard solution (Katayama Chem.), buffer salts, sodium chloride (Katayama Chem.) and other solvents were used as received.

2.2. Synthesis of hydrogel

Hydrogels composed of NIPAAm and AAc were prepared by free radical solution polymerization in the presence of a crosslinking agent, EGDMA (1.0 mol% of total monomers). The crosslinked hydrogels were prepared using various monomer ratios in 1,4-dioxane (50 wt%). Feed composition is given in Table 1. Dried nitrogen was bubbled into the monomer/solvent mixtures for 10 min to remove the oxygen dissolved in the reaction mixture. AIBN as an initiator (0.3 mol% of total monomers) was added to the mixture, which was transferred to cylindrical polypropylene vials, sealed and placed in a 70°C temperature-regulated water bath for 24 h during the reaction. The resulting hydrogels were recovered and dried at ambient conditions until they were rigid enough to be sliced into thin disks using a cutter. The cylindrical disk-shaped hydrogels soaked

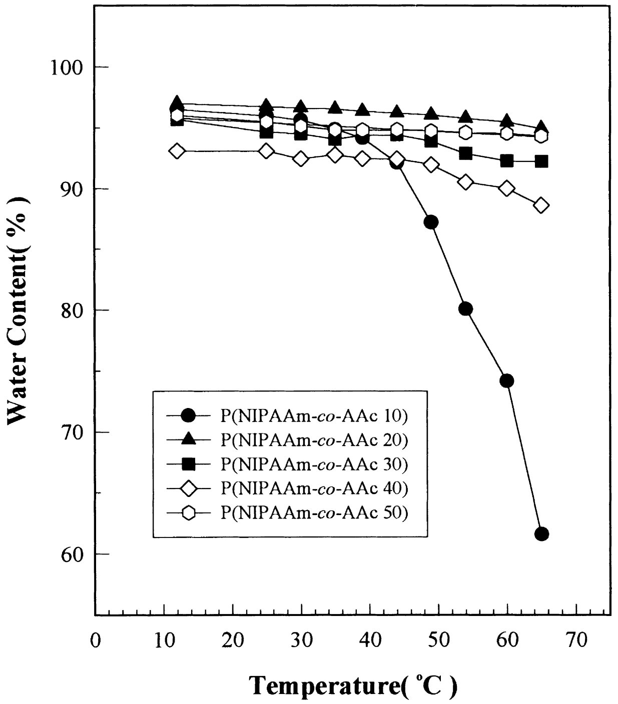

Fig. 1. Temperature dependent water content of P(NIPAAm-*co*-AAc-*X*) gel series at pH 6 (*X* is mol% of PAAc in the gels).

in 100/0, 75/25, 50/50 and 25/75 v/v% methanol/water mixtures for 1 day each, and in deionized water for 4 days to remove unreacted compounds. After drying in air for 3 days, the gels were vacuum dried at 37°C for 5 days. The compositions of the formed polymers were determined by elemental analysis. The results are shown in Table 2.

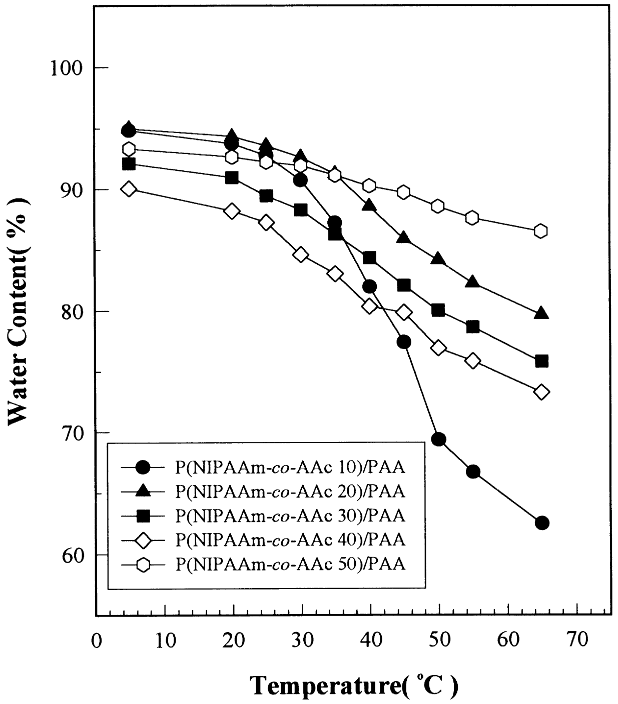

Fig. 2. Temperature dependent water content of P(NIPAAm-*co*-AAc-*X*) gel series with PAA at pH 6 (*X* is mol% of PAAc in the gels).

2.3. Swelling measurement

For the pH dependent swelling studies, gels in triplicate were incubated in buffer solutions ranging from pH 2 to 11 at a particular temperature. 0.2 M KCl/0.2 M HCl buffer was used for pH 2, 0.2 M acetic acid/0.2 M sodium acetate buffer for pH 4, 5 and 6, and borate buffer for the rest of pH values. The total ionic strength of each buffer was adjusted to 0.2 M with calculated amount of NaCl. The incubation time was approximately 24 h. It was confirmed that 24 h equilibration was enough to reach the equilibrium swelling of the gel (data not shown). For the temperature dependent swelling studies, gels were swollen in the particular buffer solution at various temperatures in the expected range of the LCST phase transition. Periodically, the gels were withdrawn from the buffer solution and weighed after removal of excessive surface water by lightly blotting with a filter paper. After equilibration at one condition, gels were re-equilibrated at the other temperature. The weight-swelling ratio was calculated by W_s/W_p, where W_s and W_p were the fully swollen gel and dried gel weights, respectively. The water content (wt%) was also calculated by the following equation, water content (wt%) $= [(W_s - W_p)/W_s \times 100]$. To investigate the effect of polyelectrolytes on the LCST, the gels were immersed in 20 ml buffer solutions containing a calculated amount of PAA and swelling ratio was determined by weighing gels as described above.

3. Results and discussion

3.1. Temperature dependent swelling behavior

Temperature dependence on the water content of P(NIPAAm-*co*-AAc) gel series at pH 6 is shown in Fig. 1. P(NIPAAm-*co*-AAc) gel with only 10 mol% AAc exhibited swelling transition, though the swelling transition became broad with temperature. On the other hand, LCST behavior of PNIPAAm in the P(NIPAAm-*co*-AAc) gels with 20, 30, 40 and 50 mol% AAc disappeared because the amount of a hydrophilic charged PAAc increased with AAc content in the copolymeric hydrogels. It is thought that the ionized PAAc component confers sufficient hydrophilicity to offset the aggregation of the hydrophobic temperature sensitive component.

Temperature dependence on water content of P(NIPAAm-*co*-AAc) gel series in the presence of PAA at pH 6 is shown in Fig. 2. The LCSTs of PNIPAAm in the P(NIPAAm-*co*-AAc) gels appeared above the pK_a value of PAAc, which was not observed in the absence of PAA as shown in the Fig. 1, and were lower than those of the PNIPAAm in the gels without PAA. As the PAAc content in the copolymer gel increased, the swelling transition more broadly occurred and shifted progressively to higher

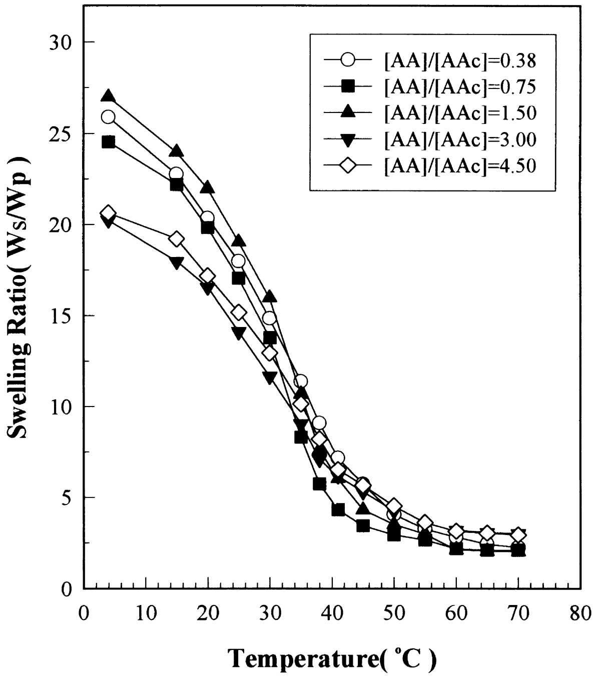

Fig. 3. Temperature dependent equilibrium swelling ratio of P(NIPAAm-*co*-AA-10) gel with PAA against functional unit mole ratio at pH 6.

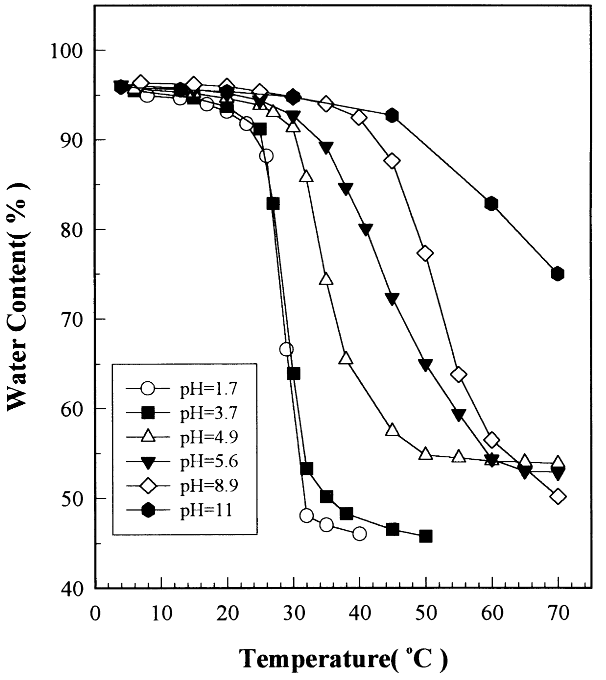

Fig. 5. Temperature dependent water content of P(NIPAAm-*co*-AAc-10) gel with PAA according to pH.

temperatures. A possible explanation for these results is the following. In the pH region from pK_a of PAAc (partly or completely ionized) to pK_b of PAA (partly or completely protonated), the hydrogels bind with polyelectrolyte through ionic interaction between opposite charges on both polymer chains. This may lead to a decreased LCST due to the reduced ionic repulsion and accessibility of water surrounding the gel. Fig. 3 shows the LCSTs of the P(NIPAAm-*co*-AAc) gels with 10 mol% of PAAc against unit mole ratio at pH 6. This result indicates that LCSTs of PNIPAAm in the hydrogels are scarcely affected by unit molar ratio, [AA]/[AAc], but the swelling ratio decreases with increasing one. The first phenomenon is explained as the polyelectrolyte complex between PAAc and PAA, which is formed stoichiometrically. The second phenomenon can be explained as follows: swelling ratio of the ionic gel is determined by two major forces, that is, the electrostatic repulsion between the carboxylic acid polymer side chain and ions present in the buffer solution, and the ionic osmotic pressure generated from mobile counterions to charged ions in the network (Donnan equilibrium) [23,24]. These two forces are influenced by the ionic strength of solution. An increase of ionic strength shields the charged groups in the network and reduces the Donnan effect, so the degree of swelling is decreased by the weakened electrostatic repulsion and the lowered ionic osmotic pressure. Ionic strength of the external buffer solution increases with an amount of PAA dissolved in one, i.e. unit mole ratio, [AA]/[AAc]. Therefore, swelling ratio of the gel decreases with an increase of unit mole ratio, [AA]/[AAc].

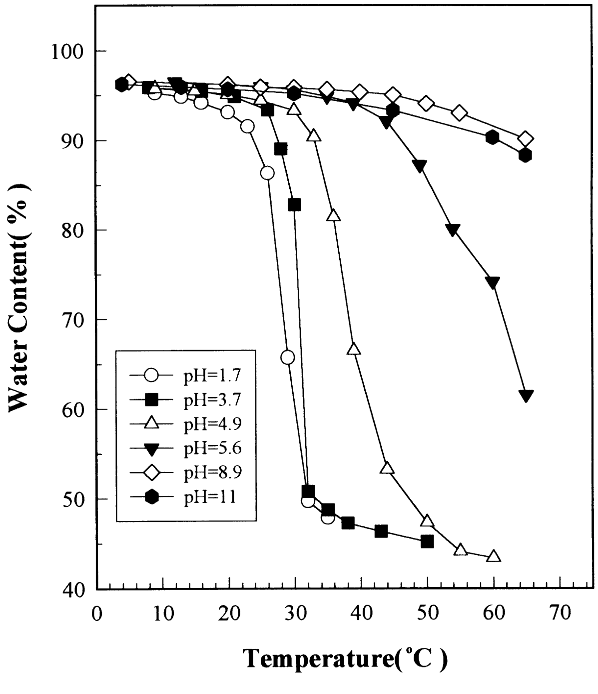

Fig. 4. Temperature dependent water content of P(NIPAAm-*co*-AAc-10) gel according to pH.

3.2. pH dependent swelling behavior

Fig. 4 shows water content of the P(NIPAAm-*co*-AAc) gel with 10 mol% of PAAc as a function of pH. As the pH is increased, the LCST of PNIPAAm in the gel is shifted

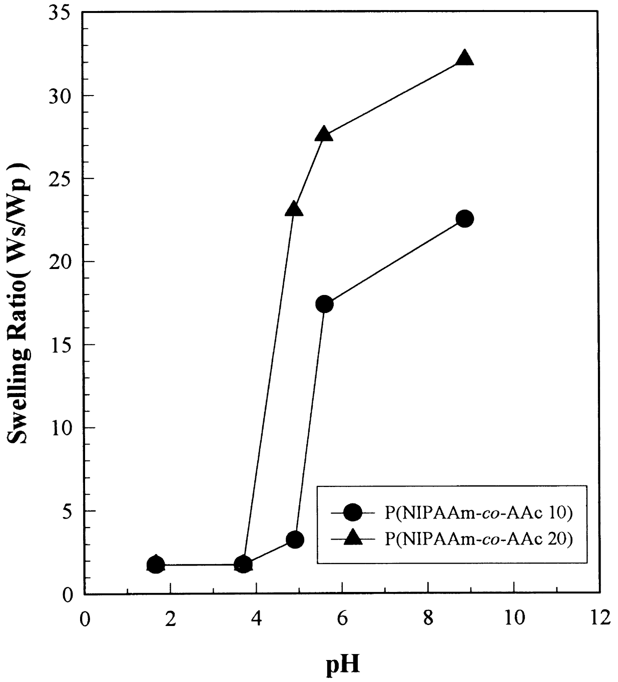

Fig. 6. pH dependent swelling ratio of P(NIPAAm-*co*-AAc-*X*) gels in buffer solution at 39°C (*X* is mol% of PAAc in the gels).

progressively to higher temperature and broadened. Distinct swelling transitions were observed below pH 4.9 and its transition temperatures were 30.0, 30.0 and 40.0°C for the pH values of 1.7, 3.7 and 4.9, respectively. Besides, broader swelling transition was observed at pH 5.6 and its transition temperature was 51.5°C. At a fixed gel composition and a particular temperature, the variation of the bulk pH changes the degree of ionization, which results in the change of the hydrophobicity of the gel. The increased amount of charged groups in the gel decreases the hydrophobicity of the gel, so its LCST raises. Consequently, the ionization of charged groups is easily accomplished with a higher pH, and ended up with a higher phase transition pH [15].

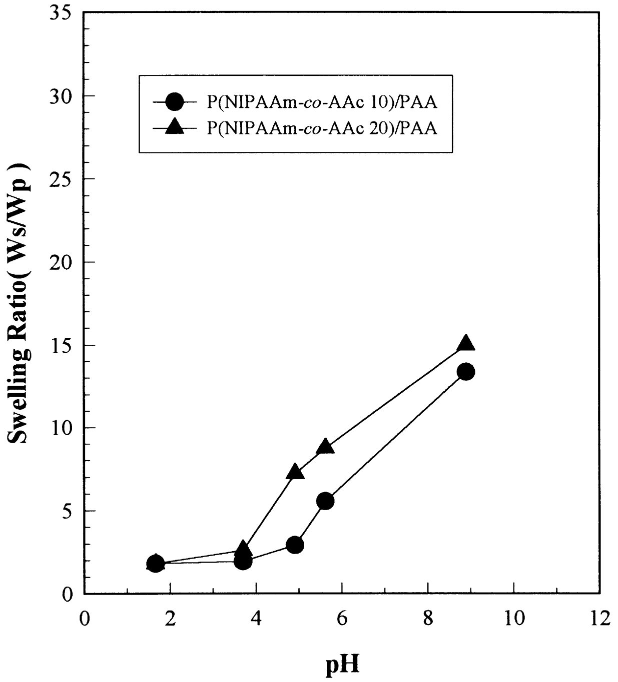

Fig. 7. pH dependent swelling ratio of P(NIPAAm-*co*-AAc-*X*) gels with PAA in buffer solution at 39°C (*X* is mol% of PAAc in the gels).

Fig. 5 shows water content of the P(NIPAAm-*co*-AAc) gels with 10 mol% of PAAc in the presence of PAA as a function of pH. Distinct swelling transitions were observed below pH 8.9 and its transition temperatures were 30.0, 29.5, 36.5, 40.0 and 44.0°C for the pH values of 1.7, 3.7, 4.9, 5.6 and 8.9, respectively. Furthermore, a broader swelling transition was observed even at pH 11 and its transition temperature was 53.0°C. It is thought that the hydrogels in the presence of PAA became expanded at higher pH in comparison with the hydrogels in the absence of PAA because the carboxylate ions on the polymer network were reduced by formation of polyelectrolyte complex with PAA. Not much difference of swelling transition temperature for the P(NIPAAm-*co*-AAc) gel with 10 mol% of PAAc itself was found below pH 3.7 since the polyelectrolyte complex was not formed under acidic conditions. On the other hand, the swelling transition temperatures of gels with PAA were more sharper and lower than ones without PAA in the neutral condition of pH 4.9~8.9 due to polyelectrolyte complex. It is thought that the hydrogels in the presence of PAA dehydrate more easily than those without PAA because the binding sites of water are decreased by formation of polyelectrolyte complex with PAA.

Fig. 6 shows pH dependence of swelling ratio for the P(NIPAAm-*co*-AAc) gels with 10 and 20 mol% of PAAc at 39°C. These two hydrogels demonstrated a sharp swelling transition according to pH. The equilibrium-swelling ratio of P(NIPAAm-*co*-AAc) gel with 10 mol% of PAAc greatly increased between pH 5.0 and 6.0, whereas that of P(NIPAAm-*co*-AAc) gel with 20 mol% of PAAc greatly increased between pH 4.0 and 5.0. It is thought that these swelling transitions were related to pK_a values determined by titration curve in previous study [21]. Fig. 7 shows pH dependence of the swelling ratio of P(NIPAAm-*co*-AAc) gels with 10 and 20 mol% of PAAc in the presence of PAA at 39°C. The pH sensitivity of these two hydrogels with PAA at a particular pH decreased in comparison with P(NIPAAm-*co*-AAc) gels itself. The equilibrium-swelling ratio of the gels increased between pH 5.6 and 8.9. It may be regarded that the electrostatic interaction between P(NIPAAm-*co*-AAc) gels and PAA weakens around pH 9 which is pK_b value of PAA. By comparison of Figs. 6 and 7, it can be seen that though the swelling pH range became widely from 5.6 to 8.9, the value of W_s/W_p became smaller. It may be supposed as follows: in the case of P(NIPAAm-*co*-AAc) gel, there is a much difference between the swelling ratio below pK_a of PAAc (about 4.8) [25] and above one due to the difference of carboxylate side chains. However, in

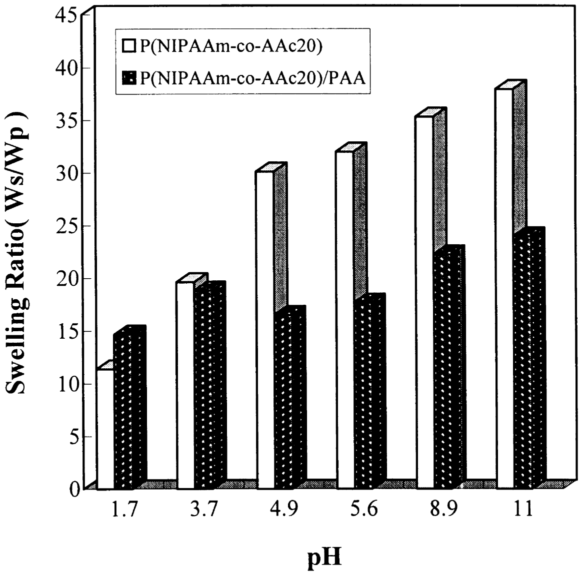

Fig. 8. Comparison of swelling ratio of P(NIPAAm-*co*-AAc-20) with that of P(NIPAAm-*co*-AAc-20)/PAA according to pH.

the case of P(NIPAAm-*co*-AAc) gel with PAA, the polyelectrolyte complex is formed in the pH range from 5.6 to 8.9. This lead to a reduced swelling ratio, since the expansion of ionized hydrogel is hindered by mutual blocking of oppositely charged ionic groups and the accessibility and mobility of water surrounding the hydrogel is decreased. Therefore, the value of W_s/W_p became smaller in spite of the wider pH range.

3.3. Effect of pH and PAAc content on the swelling ratio

Fig. 8 shows swelling ratios of P(NIPAAm-*co*-AAc) gels with 20 mol% of PAAc and those of the gels in the presence of PAA as a function of pH. It was found that the swelling ratios increased with pH due to electrostatic repulsion between the carboxylic acid polymer side chain and ions present in the buffer solution. At high pH values, the carboxylate side-chains are repelled by the anions in the solution, minimizing the charge concentration by expanding [22]. Also, the swelling ratios of the hydrogels in the presence of PAA were lower than those of the gels without PAA, except pH 1.7. Particularly, more difference of swelling ratio among them was found in the pH region above pK_a of PAAc, since the expansion of ionized hydrogel was hindered by formation of the polyelectrolyte complex, resulting in mutual blocking of oppositely charged ionic groups. Fig. 9 shows swelling ratios of P(NIPAAm-*co*-AAc) gels and those of the gels in the presence of PAA as a function of PAAc content at pH 6. The swelling ratio of the hydrogels decreased in order of P(NIPAAm-*co*-AAc-20) > P(NIPAAm-*co*-AAc-10) > P(NIPAAm-*co*-AAc-50) > P(NIPAAm-*co*-AAc-30) > P(NIPAAm-*co*-AAc-40). It is difficult to explain the reason because a clear tendency according to PAAc content did not appear. However, this order was kept in the range of pH 3.7~11 as well as pH 6 and was reproducible. It is supposed that the water absorption is enlarged when the composition of NIPAAm and AAc is 80 and 20 mol%, respectively, because both amide group of NIPAAm and carboxyl group of AAc affect the swelling ratio of the gel.

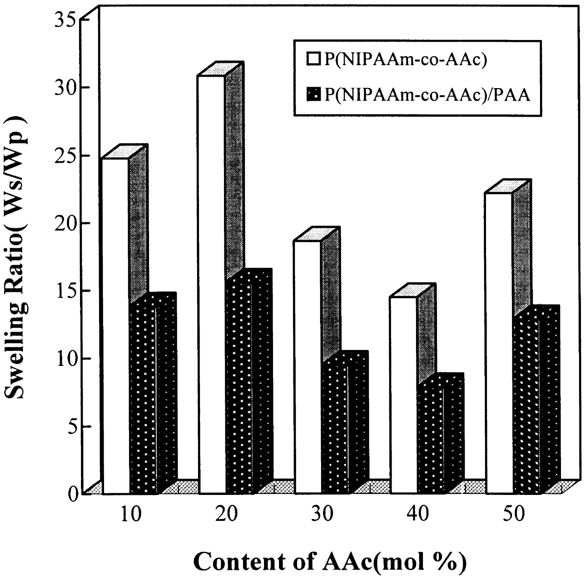

Fig. 9. Comparison of swelling ratio of P(NIPAAm-*co*-AAc) with that of P(NIPAAm-*co*-AAc)/PAA as a function of AAc content at pH 6.

In conclusion, P(NIPAAm-*co*-AAc) hydrogels were synthesized from comonomer feed compositions ranging from 0 to 50 mol% of AAc. Copolymer composition were 0, 14.0, 24.2, 36.6, 45.2 and 54.0 mol% of PAAc. The LCSTs of the P(NIPAAm-*co*-AAc) hydrogels increased with pH value and disappeared above the pK_a value of PAAc, except the hydrogel containing 10 mol% of PAAc. The LCSTs of the P(NIPAAm-*co*-AAc) hydrogels in the presence of PAA were observed even above the pK_a value of PAAc. At the same pH, the LCSTs of the P(NIPAAm-*co*-AAc) hydrogels were lower than that of the hydrogel in the absence of PAA due to the polyelectrolyte complex formation. Below the pK_a value of PAAc, the LCSTs of hydrogels decreased with an increase of PAAc content in the hydrogel. On the other hand, the LCSTs of hydrogels increased with PAAc content above pK_a value of PAAc. Furthermore, the swelling ratio of P(NIPAAm-*co*-AAc) gel was the largest at 20 mol% of PAAc content and decreased by polyelectrolyte complex formation with PAA. The swelling kinetics of poly(NIPAAm-*co*-AAc) hydrogels were strongly dependent on pH value, temperature, and polyelectrolyte solute.

Acknowledgements

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References

[1] Tanaka T. Phys Rev Lett 1978;40:820.
[2] Dusek K, Patterson DJ. J Polym Sci, A-2 1968;6:1209.
[3] Tanaka T, Fillmore DJ, Sun ST, Nishio I, Swislow G, Saha S. Phys Rev Lett 1980;45:1636.
[4] Hirokawa Y, Tanaka T, Matsuo ES. J Chem Phys 1984;81:6379.
[5] Katayama S, Hirokawa Y, Tanaka T. Macromolecules 1984;17:2641.
[6] Tanaka T, Nishio I, Sun ST, Ueno-Nishio S. Science 1982;218:467.
[7] Sisido M, Inai Y, Imanishi Y. Macromolecules 1990;24:1605.
[8] Otake K, Inomato H, Konno M, Saito S. Macromolecules 1990;23:283.
[9] Schild HG. Progress in polymer science, 17. Oxford: Pergamon Press, 1992. pp. 163.
[10] Bae YH, Okano T, Sakurai Y, Kim SW. Pharam Res 1991;8:624.
[11] Dong LC, Hoffman AS. J Controlled Release 1986;4:223.
[12] Park TG, Hoffman AS. J Biomed Mater Res 1990;24:21.
[13] Park TG, Hoffman AS. Biotech Bioeng 1990;35:152.
[14] Cussler EL, Stokar MR, Varberg JE. AIChE J 1984;30:578.
[15] Grignon J, Scallan AM. J Appl Polym Sci 1980;25:2829.
[16] Kost J, Horbett TA, Ratner BD, Singh MJ. Biomed Mater Res 1985;19:1117.
[17] Ishihara K, Kobayashi M, Ishimaru N, Shinohara I. Polym J (Tokyo) 1985;16:625.
[18] Dong LC, Hoffman AS. J Controlled Release 1991;15:141.
[19] Chen G, Hoffman AS. Nature 1995;373(5):49.
[20] Yoo MK, Cho CS, Lee YM, Sung YK. Polymer 1997;38:2759.
[21] Yoo MK, Cho CS, Lee YM, Sung YK. Polymer 1998;39:3703.
[22] Brazel CS, Peppas NA. J Controlled Release 1996;39:57.
[23] Flory PJ. Principles of Polymer Chemistry, Ithaca, NY: Cornell University Press, 1953.
[24] Tanaka T, Fillmore D, Sun S, Nishio I, Swislow G, Shsh A. Phys Rev Lett 1980;45:1636.
[25] Zezin AB, Kargin VA. Vysokomol Soyed 1972;A14(4):772.