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Dual thermo- and pH-sensitive poly(*N*-isopropylacrylamide-co-acrylic acid) hydrogels with rapid response behaviors

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Abstract

Novel dual temperature- and pH-sensitive comb-type grafted poly(*N*-isopropylacrylamide-co-acrylic acid) (P(NIPAM-co-AAc)) hydrogels were successfully prepared by grafting PNIPAM chains with freely mobile ends onto the backbone of a cross-linked P(NIPAM-co-AAc) network. The prepared comb-type grafted P(NIPAM-co-AAc) hydrogels exhibited a more rapid deswelling rate than normal-type P(NIPAM-co-AAc) hydrogels in ultrapure water in response to abrupt changes from 25 °C to 60 °C. The same was true in buffer solution with a pH jump from 7.4 to 2.0 at 25 °C. Unexpectedly, the comb-type grafted P(NIPAM-co-AAc) hydrogels showed abnormal shrinkage behaviors in a buffer solution when the temperature increased from 25 °C to 60 °C with a pH value fixed at 7.4 or 2.0. In a buffer solution of pH 7.4, when the environmental temperature jumped from 25 °C to 60 °C, the grafted comb-type hydrogels shrank slower than the normal-type hydrogels, while at pH 2.0, the gels shrank faster than the normal-type gels in the beginning, which was followed by a slower shrinking. Interestingly, the much quicker shrinkage of the comb-type grafted P(NIPAM-co-AAc) hydrogels was observed because of the cooperative thermo-/pH-responses when the simultaneous temperature and pH stimuli met from pH 7.4/25 °C to pH 2.0/60 °C. The results of this study provide valuable information regarding the development of dual stimuli-sensitive hydrogels with fast responsiveness.

Keywords: Hydrogels; pH/temperature sensitive; Rapid response

1. Introduction

In recent years, intelligent stimuli-sensitive hydrogels, a new-style polymer material able to change their volume and properties in response to environmental stimuli such as temperature [1,2], pH [3,4], and certain chemicals [5], have generated considerable research interest. Poly(*N*-isopropylacrylamide) (PNIPAM) gel is a typical and widely-investigated temperature-sensitive polymer that undergoes a volume phase transition around the lower critical solution temperature (LCST, approximately 32 °C) in aqueous solution [6,7]. PNIPAM swells at temperatures below the LCST and shrinks above the LCST. Gels respond to pH changes due to the presence of ionizable groups like carboxyl groups or amino groups. One of the frequently studied pH-sensitive polymers is poly(acrylic acid) (PAAc), which extends and shrinks at pH values above and below the p*K*a of PAAc (about pH 4.75), respectively [8–11]. Based on their dramatic swelling and deswelling behaviors, these hydrogels are being utilized for new potential applications in numerous fields including chemical transducer [12], chemical separation [13,14], drug delivery [15,16], and artificial organ [17].

From applications' point of view, hydrogels would be much favorable if they could respond to several stimuli simultaneously. Along these lines, temperature- and pH-sensitive

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hydrogels have been commonly investigated during the last decade, because both parameters are important environmental factors in biomedical and other systems [18–24]. Dual thermo- and pH-responsive hydrogels may be prepared by combining PNIPAM with a pH-sensitive polymeric component, such as acrylic acid (AAc) [22–28], and copolymerization is a common method used to make such compounds.

For several potential hydrogel applications, a fast response is necessary for their practical usage. Some target drug delivery systems need hydrogels to release drugs immediately in a specific time and location, while an acting actuator requires an instantaneous feedback after receiving signals. However, the swelling and deswelling behaviors of conventional hydrogels are dominated by diffusion-controlled transport through the polymer networks, and the response rate for hydrogels is inversely proportional to the square of the smallest dimension of the gel [29,30]. A conventional PNIPAM homopolymer gels shrink very slowly after the temperature is increased from 10 °C to 40 °C due to the formation of dense skin layers, requiring more than a month to reach equilibrium [31]. As previously reported, for dual thermo- and pH-responsive hydrogels, the combination of pH-sensitive materials might reduce or even eliminate the thermo-sensitivity of the resulting hydrogels [32–34]. Thus, it was proposed that impregnating hydrogels with AAc would increase the hydrophilicity and break the continuous thermo-sensitive isopropylamide pendant groups of PNIPAM [35].

Several methods have been developed to enhance the response rate of hydrogels to the surrounding environment. Incorporating hydrophilic polymers into the PNIPAM hydrogel network by interpenetrating polymer network (IPN) or semi-interpenetrating polymer network (semi-IPN) technologies has been reported to be an effective approach [36–38]. Zhang et al. [39,40] synthesized rapid thermo-sensitive hydrogels with macroporous structures using a pore-forming strategy and expanded network structures. Okano et al. achieved rapid deswelling volume changes in a comb-type grafted PNIPAM hydrogel with freely mobile chains grafted on a backbone network [31,41–43]. To increase the response rate of dual thermo- and pH-responsive hydrogels, several distinctive methods have also been reported. For instance, Lee et al. [44–46] generated a series of rapidly responsive comb-type hydrogels by grafting thermo-responsive PNIPAM chains onto the backbone of alginate networks and chitosan chains. Asoh et al. [47] developed rapid response porous semi-IPNs composed of PNIPAM networks and PAAc linear chains. Kishi et al. [48] prepared fast responsive and pH-/thermo-responsive copolymer hydrogels by creating micro-porous structures with γ-ray irradiation treatment. However, because of their appeal, dual thermo- and pH-sensitive hydrogels with rapid responsivity continue to increasingly attract attention. Thus, in order to promote new applications, it remains essential to develop dual stimuli-sensitive hydrogels with new architectures by new synthetic strategies.

In this paper, we aimed to develop a novel method for creating dual thermo- and pH-sensitive hydrogels with rapid response behavior. Considering a rapid deswelling single thermo-sensitive comb-type grafted PNIPAM hydrogel reported by Okano et al. [31], we developed a novel strategy to improve the response rate of dual stimuli-responsive hydrogels through a modification of the molecular structure. We prepared a dual temperature- and pH-sensitive P(NIPAM-co-AAc) hydrogel with comb-type grafted chains. The PNIPAM graft chains were introduced into the cross-linked network by copolymerization of PNIPAM macromonomers with NIPAM monomers and AAc monomers. The effect of the graft chains with freely mobile ends on the deswelling changes was compared with the behavior of normal-type gels containing random copolymers of NIPAM and AAc in given temperature and pH conditions. Moreover, we investigated for the first time the effects of simultaneous changes of both temperature and pH value on the prepared dual thermo- and pH-sensitive hydrogels.

2. Experimental section

2.1. Materials

N-Isopropylacrylamide (NIPAM) was purchased from Kohjin Co., Japan, and was recrystallized from a mixture of acetone and *n*-hexane. Acrylic acid (AAc) was purchased from Tianjin Bodi Chemical Engineering Co., Ltd. and was purified by vacuum distillation at 40 °C and 10 mmHg. Tetrahydrofuran (THF) was purchased from Chongqing Chuandong Chemical Engineering Co., Ltd., 2-hydroxyethanethiol (HESH) was purchased from Sanland-chem International Inc., Japan, benzoyl peroxide (BPO) was purchased from Tianjin Jingxing Chemical Reagents, diethyl ether and acetone were purchased from Tianjin First Chemical Reagents, acryloyl chloride was purchased from Haimen Beisite Jingxi Chemical Engineering Co., Ltd., chloroform was purchased from Tianjin Bodi Chemical Engineering Co., Ltd., *N*,*N*′-methylenebisacrylamide (BIS) was purchased from Chengdu Kelong Chemical Reagents, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) was purchased from Shanghai Qianjin Nongchang Reagents, and ammonium peroxide (APS) was purchased from Shanghai Chemical Reagents. All these reagents were used as received. Fresh deionized water from a Milli-Q Plus water purification system (Millipore, Bedford, with a 0.2 μm filter) was used throughout this work.

2.2. Macromonomer synthesis

The NIPAM macromonomer was synthesized as previously described by the literature [42]. First, a PNIPAM polymer with a terminal hydroxyl end group (PNIPAM-OH) was prepared. NIPAM (16.95 g, 0.15 mol), 2-hydroxyethanethiol (0.117 g, 1.5 mmol), and benzoyl peroxide (0.0242 g, 0.1 mmol) were dissolved in THF (50 mL). The sample containing the monomer solution was degassed by a freeze–thaw cycle and sealed in vacuum. Polymerization was carried by heating the reaction mixture at 70 °C for 15 h. To precipitate PNIPAM-OH, the reactant was poured into diethyl ether. PNIPAM-OH was collected by filtration and was purified by repeated precipitation

in diethyl ether from acetone. The polymer was isolated by freeze-drying the aqueous solution. The purified PNIPAM-OH was dissolved in chloroform, acryloyl chloride was instilled, and the reaction mixture was stirred at 40 °C for 2 h under nitrogen atmosphere. NIPAM macromonomer was isolated using the procedure described above for PNIPAM-OH.

^{1}H NMR spectra were recorded on a Bruker-300 spectroscopy using D_2O as the solvent. The molecular weight of semi-telechelic PNIPAM-OH was estimated by gel permeation chromatography (GPC, Waters 515 pump with Waters 2410 refractive-index detector) using THF as the mobile phase and polystyrene as the standard.

2.3. Synthesis of P(NIPAM-co-AAc) hydrogels

To synthesize the comb-type grafted P(NIPAM-co-AAc) hydrogels, the NIPAM and AAc monomers, NIPAM macromonomer, cross-linker BIS, and accelerator TEMED were dissolved in 20 mL of ultrapure water (18.2 MΩ cm) and bubbled with nitrogen gas for 10 min, at which time APS was added as an initiator. The solution was then injected between two glass plates covered with PE films and separated by a glass gasket (3.6 mm). The feed compositions of the monomers and other reactants are listed in Table 1. Polymerization was carried out at room temperature for 1 day, and the resulting hydrogels were cut into disks (7 mm in diameter) with a cork borer. To leach out unreacted compounds and allow the hydrogels to equilibrium, the gel disks were immersed in ultrapure water, which was changed twice every day, for at least 6 days at room temperature. The P(NIPAM-co-AAc) hydrogels with grafted chains and normal-type P(NIPAM-co-AAc) hydrogels were denoted as GNA and NNA, respectively.

2.4. Measurements of equilibrium swelling ratio

A gravimetric method was used to measure the equilibrium swelling ratio. The equilibrium swelling weights were measured at room temperature for the gel samples in water or in buffer solutions (the ionic strength was adjusted to 0.1 M beforehand) after wiping excess water from the gel surface with moistened filter paper. The effect of temperature on the equilibrium swelling ratio was measured in the temperature range from 25 °C to 60 °C. At each particular temperature, gel samples were incubated in ultrapure water for 24 h, wiped with moistened filter paper to remove excess water from the gel surface, and weighed. The weight data presented are an average of three samples. The swelling ratio was defined as the weight of water absorbed in the swollen gel (W_s) divided by the weight of the dried gel (W_d).

2.5. Measurements of the deswelling kinetics of hydrogels

The deswelling kinetics of the hydrogels were measured gravimetrically after the sample surfaces had been wiped with moistened filter paper to remove water in different conditions designed for the measurements. The temperature was maintained at 25 °C or 60 °C, at pH values of 7.4 or 2.0. The gel samples were allowed to reach equilibrium in ultrapure water or buffer solutions at 25 °C and were then transferred to a given condition. At regular time intervals, the gel samples were retrieved and weighed. The weight datum was an average of three samples. Water retention was defined as $100 \times (W_t - W_d)/W_s$, where W_t was the weight of hydrogel at time t and the other symbols are the same as those described above.

3. Results and discussion

3.1. Preparation of PNIPAM macromonomer

The NIPAM macromonomer was prepared by radical telomerization of NIPAM monomer using HESH as a chain transfer agent. A spectrum of NIPAM macromonomer obtained with ^{1}H NMR spectroscopy measurements exhibited peaks at 1.1 ppm ($-CH_3$) and 3.9 ppm ($-CH-$), while two broad peaks at 1.5 and 2.0 ppm due to methylene proton and methyne proton on the main chains were observed. Significantly, the peaks of vinyl proton at 5.7–6.4 ppm were detected, indicating that a polymerizable end group was introduced into the hydroxyl semi-telechelic PNIPAM.

The weight-average and number-average molecular weights of NIPAM macromonomer were, respectively, determined to be 8778 and 4579 by gel permeation chromatography.

3.2. Synthesis of comb-type grafted P(NIPAM-co-AAc) hydrogels

Normal-type P(NIPAM-co-AAc) copolymer hydrogels are usually prepared by free-radical polymerization with existing monomers, cross-linkers, redox initiators, and accelerators. As a result of the incorporation of the ionizable groups of the comonomer AAc, the P(NIPAM-co-AAc) hydrogel can respond to changes in both temperature and pH. Comb-type grafted PNIPAM gels were prepared by radical copolymerization of

Table 1
Feed compositions for the preparation of P(NIPAM-co-AAc) gels

Component	Sample ID					
	NNA20	GNA20-1	GNA20-2	NNA30	GNA30-1	GNA30-2
NIPAM (g)	1.0	0.6	0.5	1.0	0.6	0.5
Macromonomer (g)	0	0.4	0.5	0	0.4	0.5
AAc (μL)	20	20	20	30	30	30

Note: BIS as a cross-linker = 0.02 g; TEMED as an accelerator = 50 μL; 5 wt% APS as an initiator = 0.2 mL; solution (ultrapure water) = 20 mL.

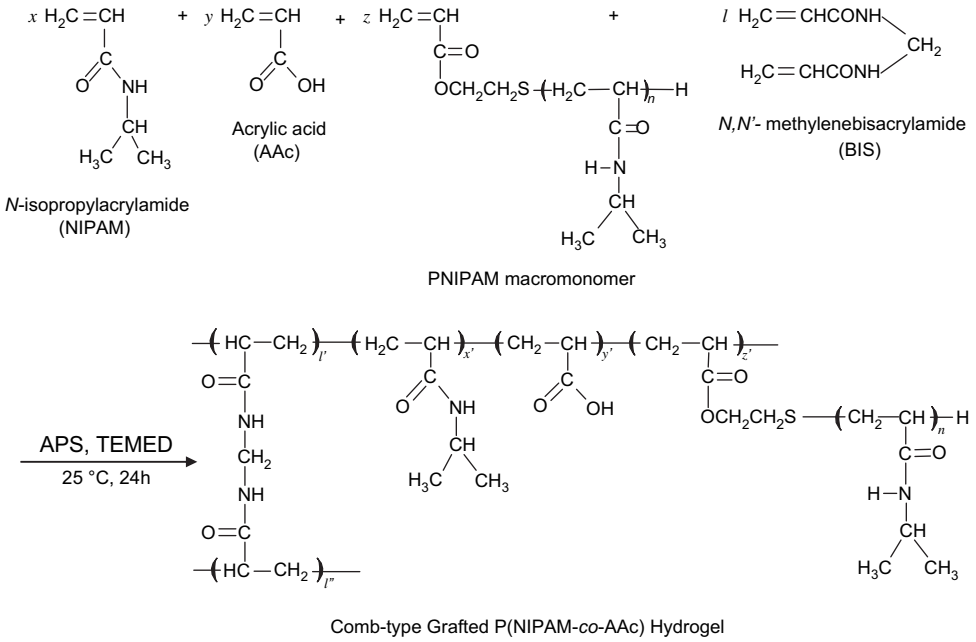

Fig. 1. Synthetic scheme for the preparation of comb-type grafted P(NIPAM-co-AAc) hydrogels by radical copolymerization.

PNIPAM macromonomer with NIPAM in the presence of BIS as a cross-linker [31]. Unlike the process used to prepare normal-type copolymer hydrogels, the comb-type grafted P(NIPAM-co-AAc) hydrogels were synthesized by radical copolymerization of PNIPAM macromonomer with NIPAM and AAc, as illustrated in Fig. 1. The backbone networks were made up of the NIPAM and AAc components, and the linear PNIPAM polymers served as the freely mobile chains and were grafted onto the backbone by fixing one end structurally. Within the gel, the grafted chains had freely mobile ends, distinct from the typical network structure in which both ends of chains are cross-linked and relatively immobile. Schematic structures of comb-type PNIPAM, normal-type P(NIPAM-co-AAc) and comb-type P(NIPAM-co-AAc) hydrogels are shown in Fig. 2. As listed in Table 1, the grafted P(NIPAM-co-AAc) gels constructed with different contents of AAc and macromonomer were designated as GNA20-1, GNA30-1, GNA20-2, and GNA30-2; normal-type P(NIPAM-co-AAc) gels without grafted chains were designated as NNA20 and NNA30 with a different content of AAc. The total weight of NIPAM and the PNIPAM macromonomer was kept constant, although their ratio was varied, ensuring that the quantity of thermo-sensitive components was constant.

3.3. Equilibrium swelling ratio in different aqueous solutions at room temperature

Obviously, the swell and shrink behaviors of hydrogels are driven by the main network structure (backbone) that is made up of the cross-linked chains. Fig. 3 shows the equilibrium swelling ratios of hydrogels in ultrapure water at room temperature. Compared with the PNIPAM hydrogel, the hydrophilicity of the gel improved with increasing amounts of the hydrophilic monomer AAc introduced into the backbone of the gel, which in turn led to an increase in water content at room temperature [40]. The water uptake for the hydrogels rose with increasing AAc content, and the GNA hydrogels had higher equilibrium swelling ratios than the NNA gels containing the same amount of AAc. The mobility of the grafted chains allowed them to be structurally separated from the backbone cross-linked network, permitting strong hydration, which may have been carried over to the hydrogel, resulting

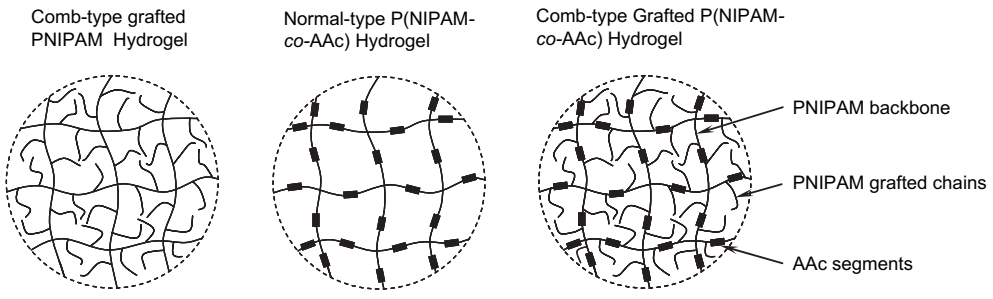

Fig. 2. Schematic illustration of the structures of comb-type grafted PNIPAM and normal-type P(NIPAM-co-AAc) hydrogels, as well as a comb-type grafted P(NIPAM-co-AAc) hydrogel.

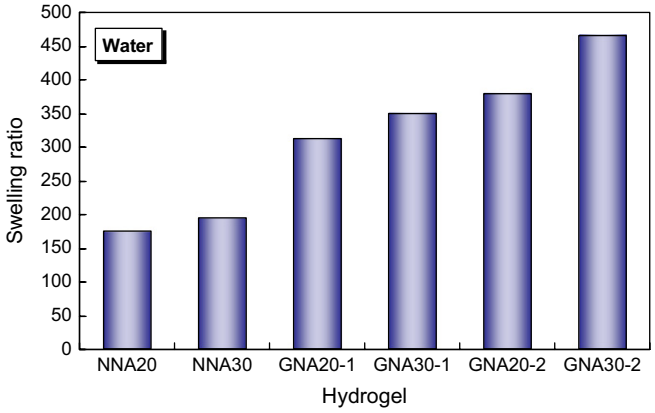

Fig. 3. Equilibrium swelling ratios of normal-type and comb-type grafted P(NIPAM-co-AAc) hydrogels in water at room temperature (25 °C).

in increased hydration of the grafted hydrogels. Indeed, because of the inherent mobile nature of the grafted chains with free ends, the comb-type gels showed a greater extent of swelling [31]. In the recipe for the preparation of hydrogels (as listed in Table 1), the total weight of thermo-sensitive NIPAM and macromonomer in GNA was equal to the weight of NIPAM in NNA. As a result, the percentage of thermo-sensitive materials in the backbone of the GNA gels might be lower than those of the NNA gels, but the AAc dosages were the same. In other words, the density of the pH-sensitive AAc in the backbone of the GNA gels was higher than that of NNA gels, and the hydrophilicity of them increased. Then, an increased number of grafted chains was related to a higher equilibrium swelling ratio at room temperature.

Fig. 4 shows the equilibrium swelling ratios of normal-type and comb-type P(NIPAM-co-AAc) hydrogels in pH buffers at room temperature. Due to the effects of ionic strength, the equilibrium swelling ratios of the hydrogels in pH buffers were universally smaller than those in ultrapure water. It is well known that while NIPAM does not respond to changes in pH, AAc is a typical pH-sensitive polymeric material that can deprotonate its carboxyl moieties in alkaline solution and protonate them in acidic solution. All of the hydrogels were swollen in pH 7.4 buffer and were relatively shrunk in pH 2.0 buffer; the pH sensitivity was proportional to the AAc content of the hydrogels. In pH 7.4 buffer, an electrostatic repulsive force operating between the charged carboxyl groups of acrylic acid increased the hydration of the hydrogels, causing swelling. On the contrary, the hydration of the hydrogels decreased in pH 2.0 buffer because the electrostatic repulsive force was vanished between the uncharged carboxyl groups. The copolymerization of the macromonomer also affected gel swelling behavior. Compared with NNA, GNA was more swollen in pH 7.4 buffer, but less in pH 2.0 buffer. Because of the higher density of the pH-sensitive AAc in the backbone than the NNA gels, the GNA gels had a significantly higher sensitivity to pH. Furthermore, the grafted gels were relatively less rigid, which resulted from the increased hydration; this in turn improved the pH sensitivity of the GNA hydrogels.

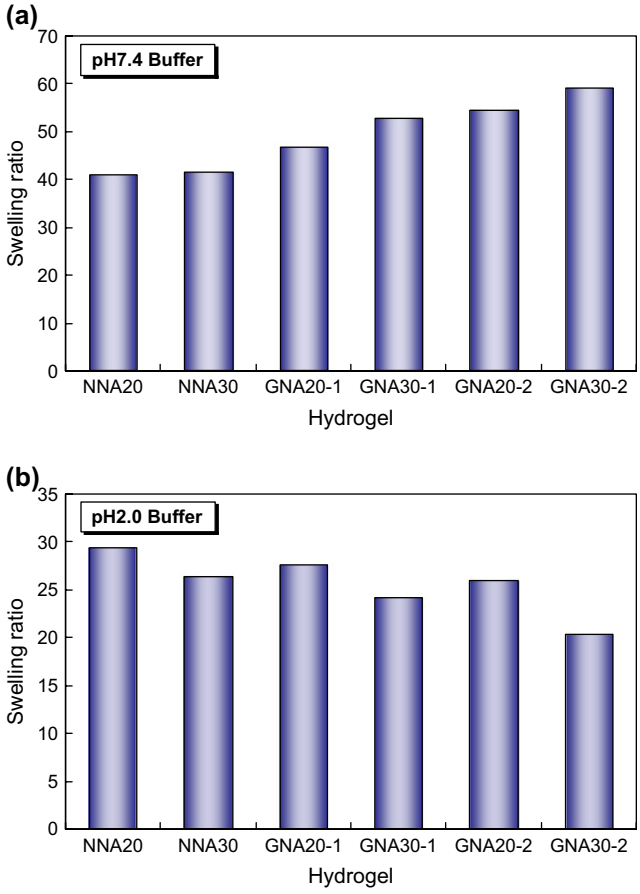

Fig. 4. Equilibrium swelling ratios of normal-type and comb-type grafted P(NIPAM-co-AAc) hydrogels in different pH buffer solutions at room temperature (25 °C). (a) pH 7.4, (b) pH 2.0.

3.4. Temperature dependence of the equilibrium swelling ratio in ultrapure water

Equilibrium swelling ratios of normal-type and comb-type P(NIPAM-co-AAc) hydrogels in ultrapure water are plotted as a function of temperature in Fig. 5. It is a well-known fact that PNIPAM hydrogels have LCST behavior [6,7]. At temperatures below the LCST, hydrogen bonds between water molecules and hydrophilic groups give the hydrogels good solubility. When the external temperature is increased to the LCST, the hydrogen bonds are overwhelmed by the hydrophobic interactions among the hydrophobic group, causing a phase separation and shrinkage of the gel matrix [49–51]. Similar to the PNIPAM hydrogels, the prepared P(NIPAM-co-AAc) gels became swollen at temperatures below the LCST, but underwent a deswelling process when the external temperature was increased. Some steep falls in hydrogel swelling were observed when the temperatures were close to the relative LCSTs observed around 38 °C, 40 °C, 42 °C and 43 °C, 45 °C, 46 °C for NNA20, GNA20-1, GNA20-2 and NNA30, GNA30-1, GNA30-2 hydrogels, respectively. Increasing AAc content caused the LCSTs of the hydrogels to increase, as a higher temperature was needed to drive the disruption of hydrogen bonds strengthened by the increased hydrophilicity. Shifts to higher temperatures were identified in a comparison of the

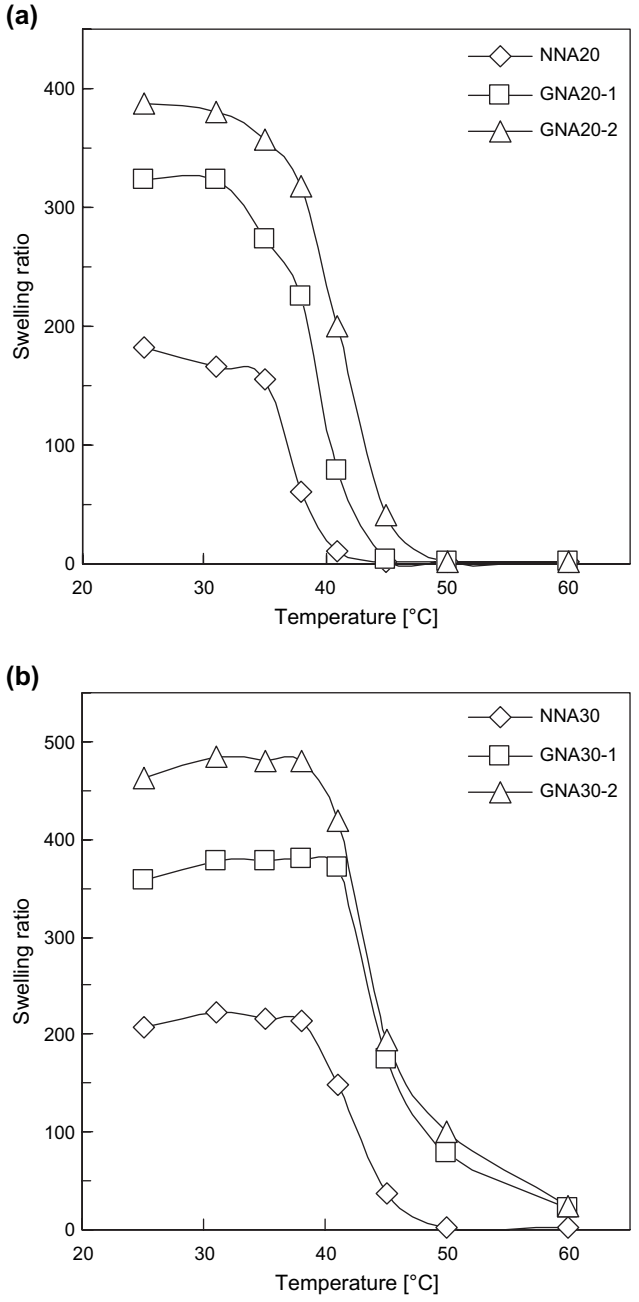

Fig. 5. Temperature dependence of the equilibrium swelling ratio of normal-type and comb-type grafted P(NIPAM-co-AAc) hydrogels in the temperature range from 25 °C to 60 °C.

LCSTs of GNA and NNA hydrogels with the same AAc content, and this was probably due to the higher density of hydrophilic materials in the backbone of the GNA gels. The interactions between the hydrophobic groups in response to temperature changes could not easily overwhelm the stronger hydrogen bonds between the hydrophilic carboxyl groups of AAc units, and thus the LCSTs were increased. Because of these factors, the dimensional shrinkage of the GNA gels from a large equilibrium swelling ratio to a much smaller volume during phase separation was much greater than those of the NNA gels. A similar phenomenon was reported by Zhang et al. [40]. One can also observe that the GNA gels have more freely mobile chains, the greater deswelling the gels undergo in the process. These indicate that the sensitivity of the GNA gels with grafted chains to temperature was enhanced.

3.5. Deswelling kinetics of hydrogels in various conditions

3.5.1. Deswelling behavior of hydrogels in ultrapure water with temperature changes

Fig. 6 shows the deswelling kinetics of NNA and GNA gels after a temperature jump from the equilibrium state in ultrapure

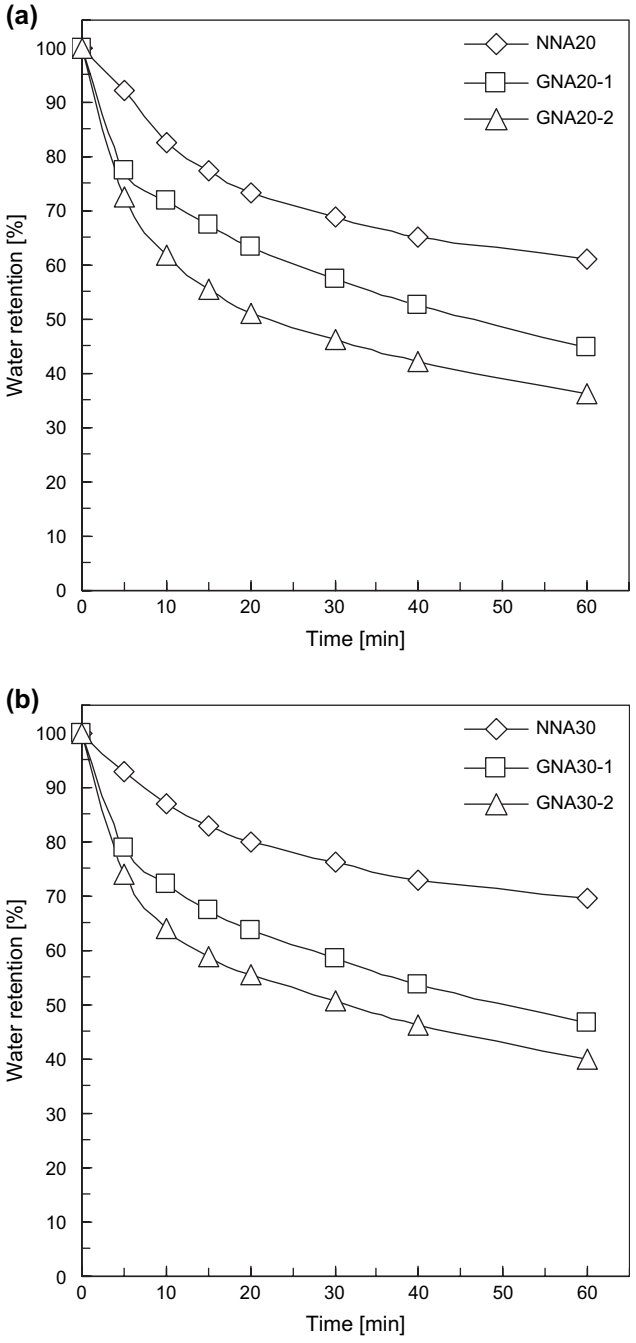

Fig. 6. Deswelling kinetics of hydrogels at 60 °C as measured from an equilibrium swelling condition at 25 °C in water.

water at 25 °C to above the LCST at 60 °C. The graft-type hydrogels shrunk rapidly on the time scale and entrapped water was rapidly squeezed out from the gels interior for the experiment, and the quick response was ranked in the order of the feed weight of macromonomers in response to temperature changes. In contrast, shrinking of the normal-type P(NIPAM-co-AAc) hydrogels was much slower and were hardly shrunk after 60 min. In this process, such rapid shrinking of the GNA gels is due to the immediate dehydration of freely mobile grafted chains in the gel matrixes, followed by subsequent hydrophobic interactions between dehydrated grafted chains preceding shrinkage of the whole network [31]. On the other hand, surface stable dense shrunken layers within polymer networks containing the hydrophilic AAc comonomer were not formed due to decreased hydrophobic aggregation forces [32]. Therefore, a rapid expulsion of water from the GNA gel matrixes was observed, while this was not the case with pure PNIPAM gel [52]. When NIPAM units aggregated at higher temperatures, incorporated segments which maintained hydration also restricted the shrinkage of gels synchronously. Even though the two forces are contradictory, the hydrophobic forces overwhelmed the hydrophilic forces in the matrixes, especially in the graft-type gels with freely mobile ends. Clearly, greater hydrophobic aggregation forces were engendered within the GNA gels having a greater number of branches of grafted chains. In addition, because of decreased work needed to cause shrinkage by hydrophobic interactions, the hydrogels with less AAc exhibited a faster rate of deswelling than those with more AAc.

3.5.2. Deswelling behavior of hydrogels in pH buffers at room temperature with pH changes

Fig. 7 shows the deswelling behavior of hydrogels from a swollen equilibrium in a pH 7.4 buffer solution at room temperature to a pH 2.0 buffer solution. In this process, only a change in pH, with no change of temperature, was measured. The deswelling rate of all gels was relatively slow due to the mild surroundings and lack of a rapid dehydration phenomenon responded to temperature change. The deswelling occurred because of the pH sensitivity of the AAc incorporated in the backbone of hydrogels [9,10]. With the same AAc content, GNA deswelled faster than NNA, and the deswelling rate increased with an increasing number of grafted chains. For the grafted comb-type gels, the AAc units in the backbone may have been closer, owing to the higher density of pH-sensitive comonomers. Therefore, the ability of the hydrogel to respond to pH changes was enhanced, thereby reducing the response time. As expected, an increased amount of AAc units in the hydrogels also resulted in a faster deswelling rate.

3.5.3. Deswelling behavior of hydrogels in pH 7.4 buffer undergoing temperature changes

Large differences were observed in the deswelling process of hydrogels that had been pre-equilibrated in pH 7.4 buffer solutions at 25 °C and were subsequently elevated to a temperature of 60 °C. The deswelling kinetics results are illustrated in Fig. 8. Unlike the deswelling behaviors of hydrogels mentioned above, the order of response rates was ranked the other

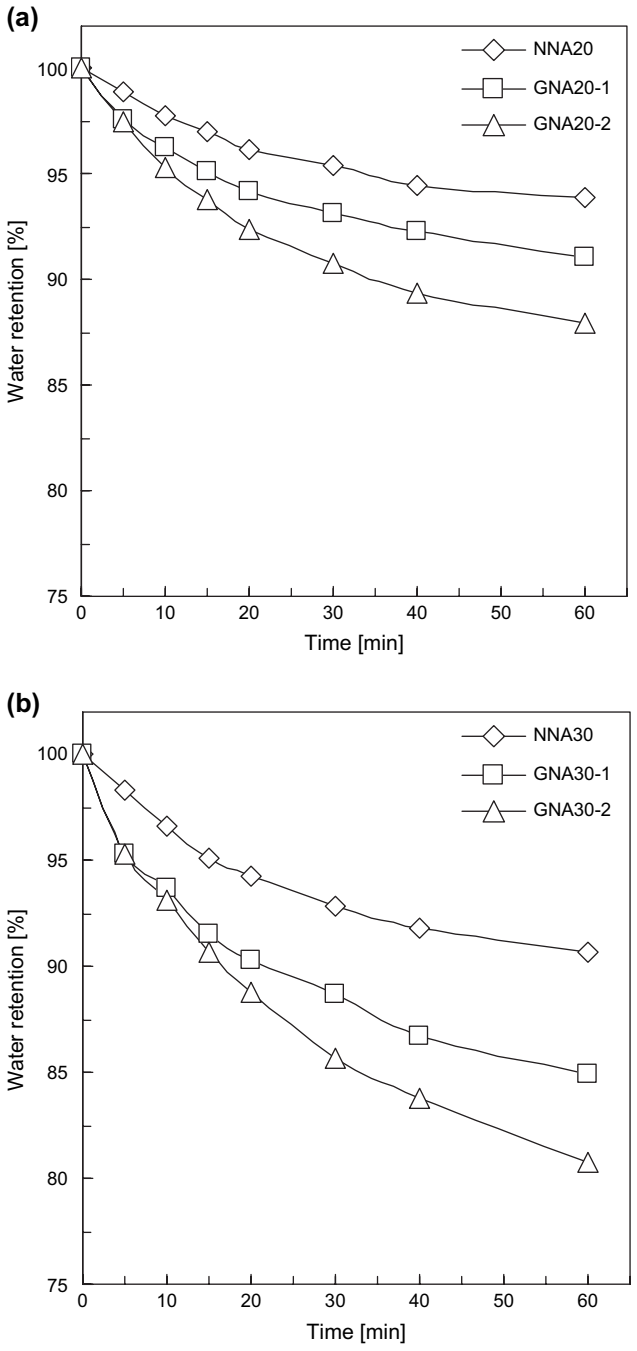

Fig. 7. Deswelling kinetics of hydrogels in buffer at pH 2.0 as measured from an equilibrium swelling condition in buffer at pH 7.4 at room temperature (25 °C).

way round. The abnormal phenomenon described above might occur for the following reasons. According to their pH-sensitive nature, the polymer chains (backbone) expand because of strong electrostatic repulsions among the charged carboxyl groups of AAc in alkaline solution. Upon an external temperature increase, the freely mobile grafted chains would collapse and the backbone of gels would shrink due to their NIPAM component at the same time. For the NNA gels, the holistic shrinking forces on the backbone aroused by NIPAM would be greater than the expanding forces aroused by AAc. On the

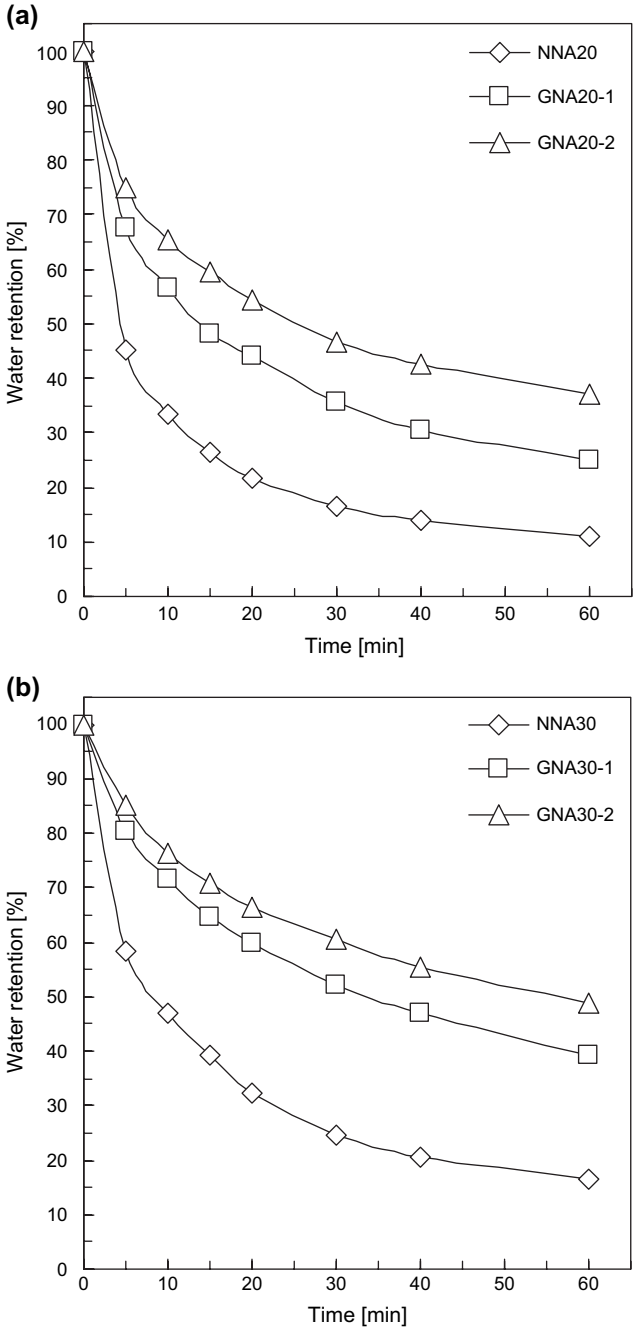

Fig. 8. Deswelling kinetics of hydrogels at 60 °C as measured from an equilibrium swelling condition at 25 °C in buffer solution (pH 7.4).

other hand, trapped water could be easily squeezed from the gel interior through channels formed by the hydrophilic AAc units. Thus, the gels constructed in this study shrunk rapidly under such conditions, which are consistent with the results observed by Kaneko et al. [43]. In the GNA gels, where there could be a potential high density of pH-sensitive AAc units in the backbone networks, the largest expanding forces would counteract with shrinking forces to a certain extent, despite the presence of strong aggregated forces among the grafted chains. As a result, the backbone networks were unable to shrink to a large extent. Obviously, the density of AAc in the backbone networks increased either indirectly with the increase of macromonomers, or directly with the increase of AAc, and thus the shrinkage of the gels with more grafted chains or AAc was much slower.

3.5.4. Deswelling behavior of hydrogels in pH 2.0 buffer with temperature changes

Fig. 9 shows the shrinking kinetics of the hydrogels in a pH 2.0 buffer solution after a temperature jump from the equilibrated state at 25 °C to 60 °C. It can be clearly seen that the shrinking rates of all the gels were much larger than those described above. One interesting trend was that the GNA gels deswelled slightly faster than the NNA gels in the beginning, but were slower to reach a new equilibrium. Upon reaching a new equilibrium, the water retention of GNA was greater than NNA. The hydrogels were pre-equilibrated in an acidic environment at 25 °C and were thus in a contracted state. Upon experiencing an external temperature shift above the LCST, for the GNA gels, the immediate response to temperature occurred and could be attributed to the freely mobile grafted chains, which would cause a much faster contraction in the absence of the counteraction caused by AAc. Likewise, AAc would produce contracting forces in an acidic solution, but the forces would be milder than those caused by the temperature response. Thus, the rapid shrinking would destroy the layers formed by AAc units for packing water, leading to a rapid release of water from the gels' interior. Subsequently, the rate of deswelling slowed because of weakened thermo-sensitive effects when the hydrophobic aggregation reached an utmost, and the ceaselessly formed layers could not be destroyed, resulting in the formation of some uneven bubbles containing aqueous solution. The NNA gels shrunk slower than GNA gels in the early phase of the deswelling process because of a lack of grafted chains, and then more aqueous solution is released through the not-well-compacted skin layers due to the lower density of AAc in the backbone networks, whereas they reached a smaller contracted state finally owing to the aggregation effects of the NIPAM main chains. On the other hand, an obvious effect of AAc quantity in the hydrogels was not detected, as the rate of deswelling of all gels occurred too rapidly for such measurements.

3.5.5. Deswelling behavior of hydrogels in pH buffer with dual temperature and pH changes

In the above-mentioned experiments and results, only one of the environmental elements (temperature or pH) was changed, and the other was fixed to measure the deswelling kinetics of hydrogels in different conditions. In fact, environmental elements always change together in potential applications. As far as we know, investigations on hydrogels in response to simultaneous dual temperature and pH changes have reported for the first time. Fig. 10 shows the time course of deswelling for hydrogels undergoing shrinking in pH 2.0 buffer at 60 °C after an abrupt change from pH 7.4 and 25 °C. The NNA gels shrunk slowly like their behaviors in ultrapure water at 60 °C. On the other hand, the GNA gels shrunk rapidly, exceeding the shrink rates of them in response to either temperature or pH alone, on the minute time scale. The actual shrinking processes of

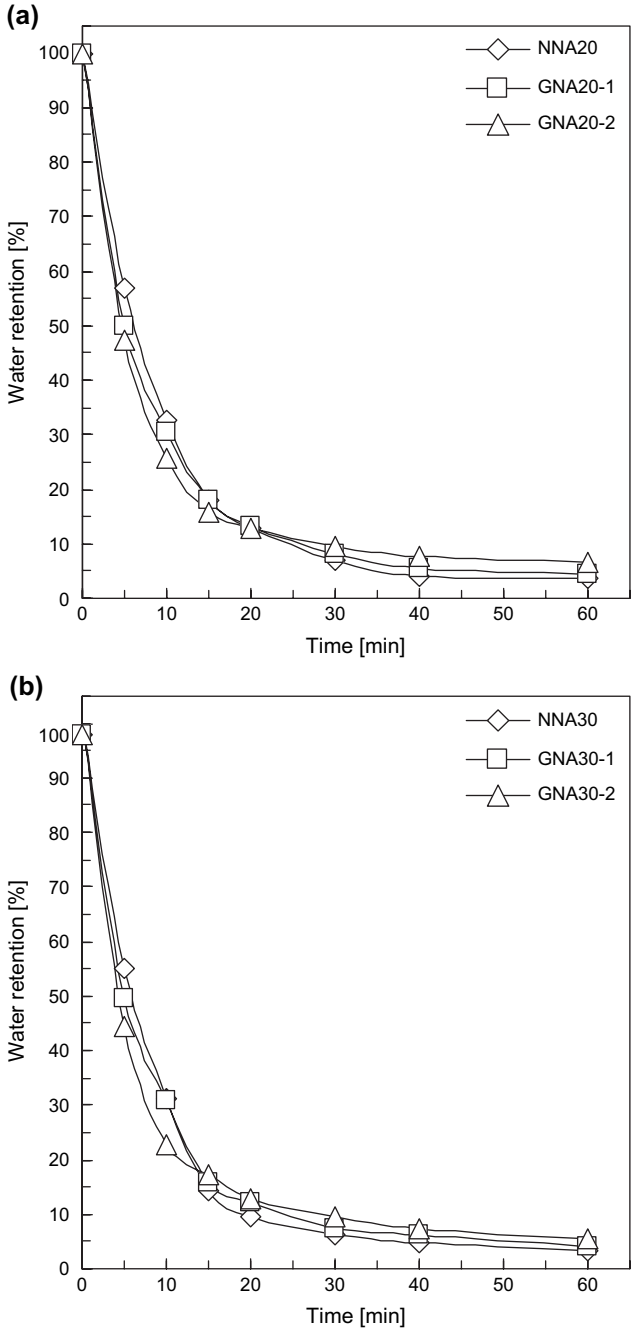

Fig. 9. Deswelling kinetics of hydrogels at 60 °C as measured from an equilibrium swelling condition at 25 °C in buffer solution (pH 2.0).

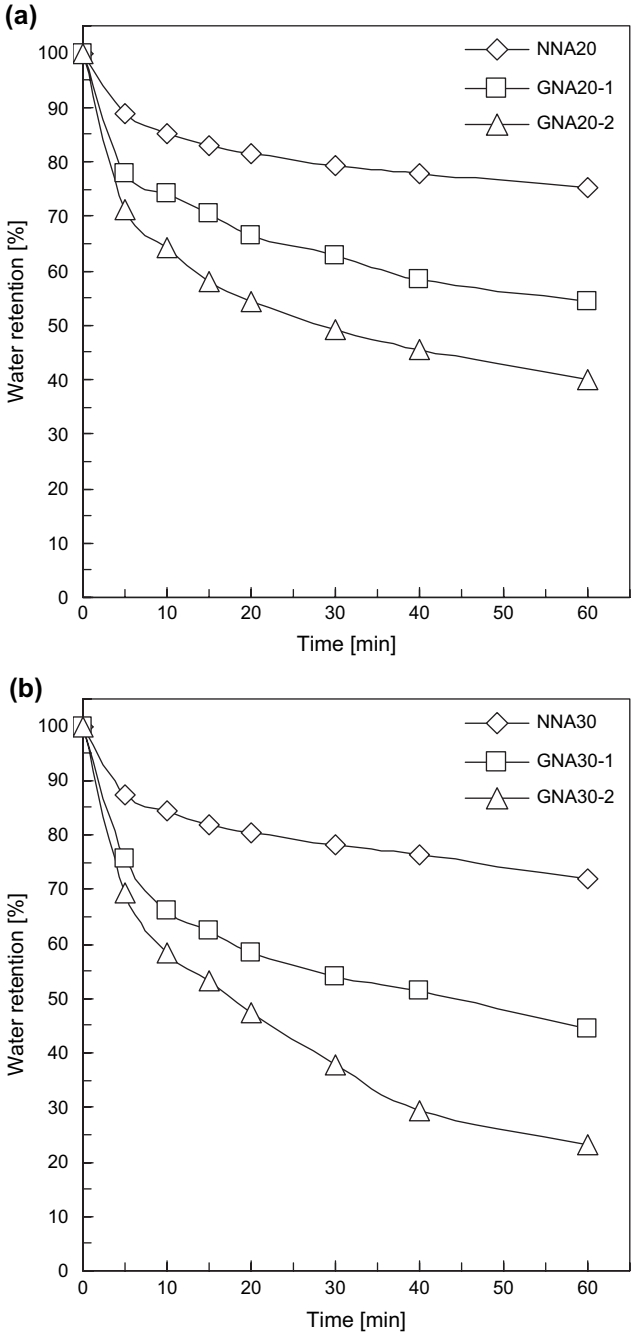

Fig. 10. Deswelling kinetics of hydrogels in buffer at pH 2.0 and 60 °C as measured from an equilibrium swelling condition in buffer at pH 7.4 and 25 °C.

disk-shaped NNA30, GNA30-1 and GNA30-2 gels are demonstrated in the series of photographs in Fig. 11. The gels swelled in pH 7.4 buffer solutions at 25 °C and the volume was ranked in order of the number of grafted chains, as forenamed. Transparent blister formation was immediately observed on the surfaces of the hydrogels after an abrupt environmental change [41,53], and then, these bubbles broke continuously during the collapse. This temporal formation of surface layers was probably engendered by the firstly occurred hydrophobic aggregation and constriction of the gels in response to the abrupt pH change to 2.0 at the interface.

The GNA gels, GNA30-1 and GNA30-2, had smaller bubbles than those of NNA30. The strong aggregation accumulated large internal pressure to create the bubble formation on the surface structure [41], and the power of these strong aggregation forces surpassed the influences of the flimsy surface layers on the gel's collapse. Meanwhile, contracting forces brought about by the changes in pH further enhanced the hydrostatic pressures within the gels. Thus, in a few barrages, the entrapped water was rapidly released through the broken bubbles. In particular, GNA30-2 gel did exhibit mechanical

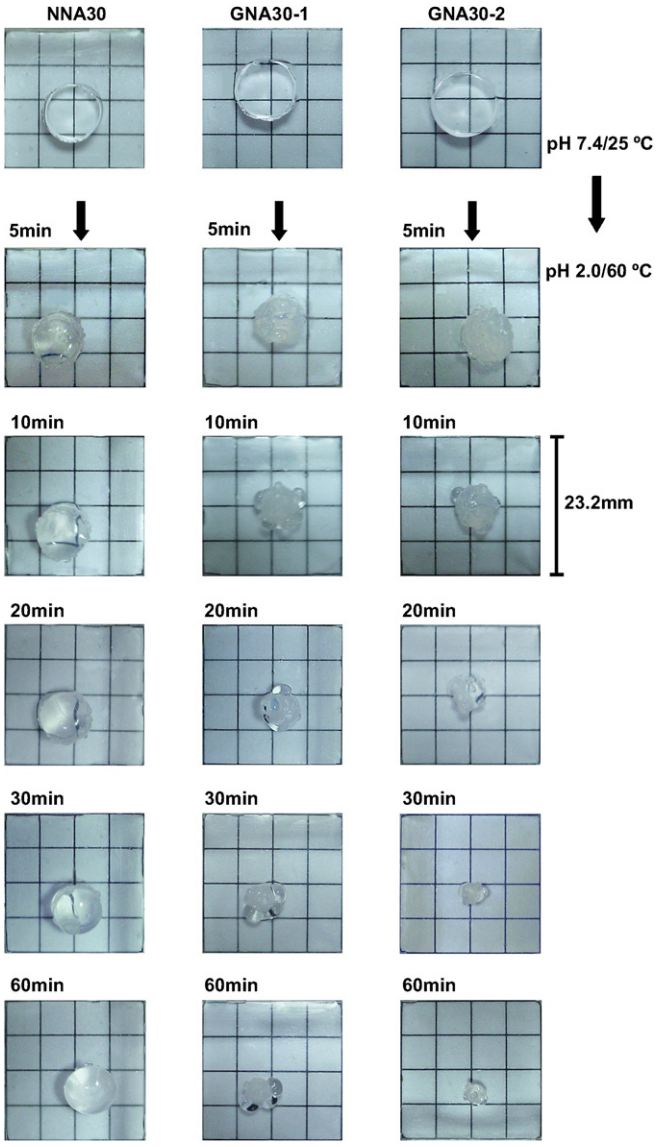

Fig. 11. Photographs of the deswelling process of a disk-shaped normal-type hydrogel (NNA30) and comb-type grafted hydrogels (GNA30-1 and GNA30-2) undergoing shrinking at pH 2.0 and 60 °C after being removed from an equilibrium condition of pH 7.4 at 25 °C.

bucking. After a brief time, the gels exhibited a dramatically decreased volume. The deswelling mechanism was close to that of the comb-type grafted PNIPAM gels [41]. However, there were no strong aggregations within the normal-type gels due to the bubbles that were not broken and the water which was prevented from entering the bulk polymer networks. In fact, to some extent, all of hydrogels shrunk faster in the beginning (several minutes) of the change in conditions, but this rate became slower subsequently. One possible explanation for this phenomenon could be that the bubbles were formed incompletely in the beginning of shrinkage so that the water was repulsed rapidly with less delay; however, after the formation of intact bubbles, water was restricted in the bubbles resulting in slower shrinkage of the gels. As mentioned above, the pH sensitivity of gels was also one of the factors responsible for shrinking of the gels. Therefore, faster deswelling rates were observed for hydrogels that had a higher AAc content.

4. Conclusions

Comb-type grafted P(NIPAM-co-AAc) hydrogels with varying numbers of grafted chains were successfully prepared. The molecular mobility of polymers was improved and rapid responses to temperature and pH were obtained as a result of the introduction of freely mobile grafted chains into the polymer framework. The equilibrium properties and rate of deswelling of hydrogels were controlled by the number of the grafted chains. Introduction of comb-type grafted chains into a dual stimuli-responsive hydrogel might enhance thermo-sensitive rates of hydrogels directly and pH-sensitive rates indirectly by increasing the density of pH-sensitive materials in the backbone network. A larger number of the grafts allowed larger swelling ratios in ultrapure water and more obvious pH sensitivity in pH buffers. Therefore, comparing with the normal-type gels, rapid deswelling dynamics of comb-type grafted gels were observed in most given conditions except the one that in pH 7.4 buffer undergoing temperature changes. This study is the first to investigate the effects of simultaneously changing both the temperature and pH values on the response rate of hydrogels. The grafted gels exhibited higher deswelling rates in an acid solution above the LCST after being abruptly changed from alkaline solution below the LCST. This was attributed to the effects of the thermo-sensitive PNIPAM main chains and grafted chains and that pH-sensitive AAc segments reacted cooperatively at the same time.

An effective method for improving the response rate of dual stimuli-responsive hydrogels was demonstrated with the hydrogels containing freely mobile grafted chains prepared for this study. Based on this strategy, it may be possible to obtain many new hydrogels with improved responses to environment stimuli. The proposed grafted comb-type gels with rapid deswelling rates in response to dual temperature and pH stimuli may find potential applications as sensors, actuators, and vehicles or carriers in various conditions.

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