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Rapid pH/temperature-responsive cationic hydrogels with dual stimuli-sensitive grafted side chains

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ABSTRACT

Dual temperature- and pH-sensitive comb-type grafted cationic hydrogels are successfully synthesized by grafting polymeric chains with freely mobile ends, which are composed of both *N*-isopropylacrylamide (NIPAM) segments and *N*,*N*-dimethylamino ethyl methacrylate (DMAEMA) segments, onto the backbone of crosslinked poly(NIPAM-*co*-DMAEMA) networks. Equilibrium and dynamic swelling/deswelling properties of the prepared hydrogels responding to pH and/or temperature are investigated. The prepared hydrogels demonstrate a lower critical solution temperature (LCST) at about 34 °C and a pK_a value at about pH 7.3. At lower pH and lower temperature, both the swelling degree and the swelling rate of the comb-type grafted hydrogel are larger than those of the normal-type crosslinked hydrogel. The comb-type grafted poly(NIPAM-*co*-DMAEMA) hydrogel exhibits a more rapid deswelling rate than that of the normal-type hydrogel in response to a pH jump from 2.0 to 11.0 at a fixed temperature. The volume changes of the poly(NIPAM-*co*-DMAEMA) hydrogels are acute in a series of fixed buffer solutions with an abrupt increase of environmental temperature from 18 °C to a temperature higher than the LCST. The comb-type grafted poly(NIPAM-*co*-DMAEMA) hydrogels show quite fast shrinking behaviors in response to simultaneous dual temperature and pH stimuli. Drug-release in vitro from the prepared poly(NIPAM-*co*-DMAEMA) hydrogels is carried out when the environmental temperature and pH are changed synchronously. The results show that the model drug Vitamin B_{12} is released much more rapidly from the comb-type grafted hydrogel than that from the normal-type hydrogel. The proposed dual temperature/pH-sensitive comb-type grafted cationic poly(NIPAM-*co*-DMAEMA) hydrogel in this study may find various potential applications, *e.g.*, for fabricating rapid-response smart sensors, actuators, and chemical/drug carriers and so on.

1. Introduction

A hydrogel system that swells and shrinks in response to environmental stimuli such as temperature [1–3], pH [4,5], ionic strength [6], and certain chemicals [7] has attracted much attention in the past 20 years, and has potential applications in numerous fields including sensors, actuators, chemical separation and drug delivery systems [8–15]. Poly(*N*-isopropylacrylamide) (PNIPAM) gel is a typical temperature-sensitive gel exhibiting volume phase transition at approximately 34 °C and their temperature sensitivity has been extensively studied both for its fundamental interest and technological application [16–19]. In many cases, multiple environmental stimuli may occur at the same time. Therefore, from an application point of view, it is much more favorable that hydrogels could respond to more than one stimulus simultaneously. Temperature and pH are two important environmental factors in typical physiological, biological and/or chemical systems, and can be manipulated easily in many applications; consequently, temperature- and pH-sensitive hydrogels have been widely investigated [4,20–26].

Up to now, most dual temperature- and pH-sensitive hydrogels are prepared by incorporating pH-responsive anionic components bearing carboxyl groups into PNIPAM-based networks [27–29]. Such anionic dual stimuli-responsive hydrogels swell in alkaline pH surrounding but deswell in acidic pH environment [30–33]. However, hydrogels that can swell in acidic pH surrounding and deswell in alkaline pH are necessary in certain cases, such as drug release and dye adsorption [34–37]. For example, the drug (chloramphenicol) should be released more rapidly from hydrogel in a pH 1.4 (close to the pH of the stomach) buffered solution than in a pH 7.4 (close to the pH of the intestine) one [34], in which the drug release is controlled by the swelling/deswelling behavior of the hydrogel. To achieve such functions, cationic hydrogels are needed.

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Since the dynamics property of environmental stimuli-responsive hydrogels is vital to their applications, their response rates are usually expected to be as fast as possible. For instance, for fabricating 'smart' actuators, hydrogels are required to respond to environmental stimuli with instantaneous feedback after receiving stimulus signals. However, the swelling and deswelling behavior of normal-type crosslinked hydrogel is dominated by diffusion-controlled transport through polymer networks, and the response rate is reported to be inversely proportional to square of the smallest dimension of the hydrogel [38,39]. In order to improve the response rate of such hydrogels, a lot of investigations have been carried out [40–43]. Remarkably, a novel type of hydrogel, namely comb-type hydrogel, has been developed. Compared with normal-type hydrogels merely possessing network structures, comb-type hydrogels have freely mobile chains grafted on the backbone networks. Okano et al. achieved a comb-type grafted PNIPAM hydrogel having thermo-responsive grafted chains, which showed a rapid deswelling volume change in response to temperature variation [12,44,45]. They also reported comb-type grafted hydrogels composed of poly(ethylene oxide) (PEO) grafted chains and PNIPAM crosslinked networks [46].

As far as dual thermo- and pH-responsive hydrogels are concerned, introducing grafted chains onto backbone network is also an effective method to improve the response rate. Lee et al. fabricated a series of rapidly responsive comb-type hydrogels by grafting thermo-responsive PNIPAM chains onto the pH-responsive backbone of alginate networks or chitosan chains [47–49]. These comb-type grafted hydrogels exhibited fast response to pH/temperature change, and rapidly reached swelling/deswelling equilibrium. Utilizing the methodology of grafting, we synthesized a comb-type copolymer hydrogel exhibiting rapid thermo- and pH-responsive phase-transition rate [50]. The thermo-sensitive PNIPAM grafted chains were introduced onto the crosslinked network by copolymerization of PNIPAM macromonomers with *N*-isopropylacrylamide (NIPAM) and acrylic acid (AAc) monomers. For the dual stimuli-responsive hydrogel, the comb-type grafted chains could enhance thermo-sensitive rates directly and pH-sensitive rates indirectly by increasing the density of pH-sensitive segments in the backbone network [50]. Up to now, very few investigations have been reported about thermo- and pH-sensitive cationic hydrogels with rapid response rate [51].

In this study, we report on the preparation of a novel type of dual thermo- and pH-sensitive comb-type grafted cationic hydrogels with rapid response rate. In the proposed hydrogel, both crosslinked network backbones and grafted chains with freely mobile ends are composed of both NIPAM and *N*,*N*-dimethylamino ethyl methacrylate (DMAEMA) segments, *i.e.*, the chemical compositions of both of them are poly(*N*-isopropylacrylamide-*co*-*N*,*N*′-dimethylamino ethyl methacrylate) (poly(NIPAM-*co*-DMAEMA)). DMAEMA is a typical cationic component with tertiary amine groups and its homopolymer is dual pH- and thermo-sensitive [52,53]. The poly(NIPAM-*co*-DMAEMA) grafted chains with freely mobile ends are fabricated from a self-made poly(NIPAM-*co*-DMAEMA) macromonomer in this study. Effects of the novel comb-type structure on swelling/deswelling properties of hydrogels are investigated systematically with different environmental temperature and pH stimuli. Besides, the stimuli-responsive drug-release property of the prepared hydrogel is also studied. The proposed novel dual thermo- and pH-sensitive comb-type cationic hydrogels show great potentials in various applications, *e.g.*, smart sensors, actuators, and chemical/drug carriers.

2. Experimental section

2.1. Materials

N-Isopropylacrylamide (NIPAM) is kindly provided by Kohjin Co. Ltd., Japan and was recrystallized from a mixture of acetone and *n*-hexane. *N*,*N*-Dimethylamino ethyl methacrylate (DMAEMA, Wuxi Xinyu Chemical Co., Ltd., China) was distilled under reduced pressure and stored in a refrigerator before use. *N*,*N*-Azobisisobutyronitrile (AIBN, Tianjin Kermel Chemical Reagent Co., Ltd., China) was recrystallized within ethanol. 2-Hydroxyethanethiol (HESH, Sanland-chem International Inc., USA), acryloyl chloride (Alfa Chemicals, USA), *N*,*N*′-methylene-bis-acrylamide (BIS), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), ammonium peroxide (APS), and Vitamin B_{12} (VB_{12}, Shanghai Yuanju Bioengineering Co., Ltd., China) were used as received. All solvents and other chemicals were of analytical grade and used as received. Ultrapure water (18.2 MΩ) used in all experiments was from Millipore Milli-Q purification system.

2.2. Synthesis of macromonomer

Before fabrication of comb-type hydrogels, a poly(NIPAM-*co*-DMAEMA) macromonomer was synthesized. The synthesis route is shown in Fig. 1. At first, poly(NIPAM-*co*-DMAEMA) polymer with a terminal hydroxyl group (poly(NIPAM-*co*-DMAEMA)–OH) was prepared by radical telomerization of NIPAM monomer and DMAEMA monomer using HESH as a chain transfer agent. NIPAM (0.054 mol), DMAEMA (0.0088 mol), HESH and AIBN were dissolved in THF (20 mL). The molar percentages of HESH and AIBN in the total monomers were 3 and 0.8 mol%, respectively. The monomer solution was degassed by a freeze–thaw cycle and sealed in vacuum. Polymerization was carried out at 70 °C for 15 h. After the reaction finishes, the mixture solution was poured into diethyl ether to precipitate semitelechelic poly(NIPAM-*co*-DMAEMA)–OH. Then the precipitation was collected by filtration and was purified by repeated precipitation in diethyl ether from acetone. Secondly, after isolation by freeze-drying from aqueous solution, the purified powder was dissolved in chloroform and acryloyl chloride (excess) under stirring and nitrogen atmosphere at 40 °C for 2 h. Finally, the poly(NIPAM-*co*-DMAEMA) macromonomer was collected and purified using the same procedure described above.

The molecular weight of macromonomer 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. FT-IR and ^{1}H NMR spectra were recorded on a NICOLET-560 spectroscopy and on a Bruker-400 spectroscopy using D_2O as the solvent respectively.

2.3. Synthesis of poly(NIPAM-co-DMAEMA) hydrogels

Both normal-type and comb-type grafted poly(NIPAM-*co*-DMAEMA) hydrogels were synthesized in this study. The feed compositions of the monomers and other reactants are listed in Table 1. The total weight of NIPAM and DMAEMA monomers and poly(NIPAM-*co*-DMAEMA) macromonomer was kept constant. To synthesize comb-type grafted poly(NIPAM-*co*-DMAEMA) hydrogels (PND-50), NIPAM and DMAEMA monomers (50 wt%), prepared macromonomer (50 wt%), crosslinker BIS (1.9 wt% to monomers), and accelerator TEMED were dissolved in ultrapure water, which has been bubbled with nitrogen gas for 20 min, and then APS was added as an initiator. The solution was then injected between two glass plates covered with PE films and separated by a Teflon gasket (2 mm in thickness). Polymerization was carried out at room temperature for 24 h, and the resulting hydrogels were cut into disks (8 mm in diameter) with a cork borer. Then, the gel disk samples were immersed in ultrapure water to leach out unreacted chemical residues for at least 3 days at room temperature, and the water was changed twice every day. Swollen gel discs were initially dried under ambient condition for 3 days followed by thorough drying under vacuum at room temperature for fear that hydrogels' structure was destroyed by directly being exposed to vacuum.

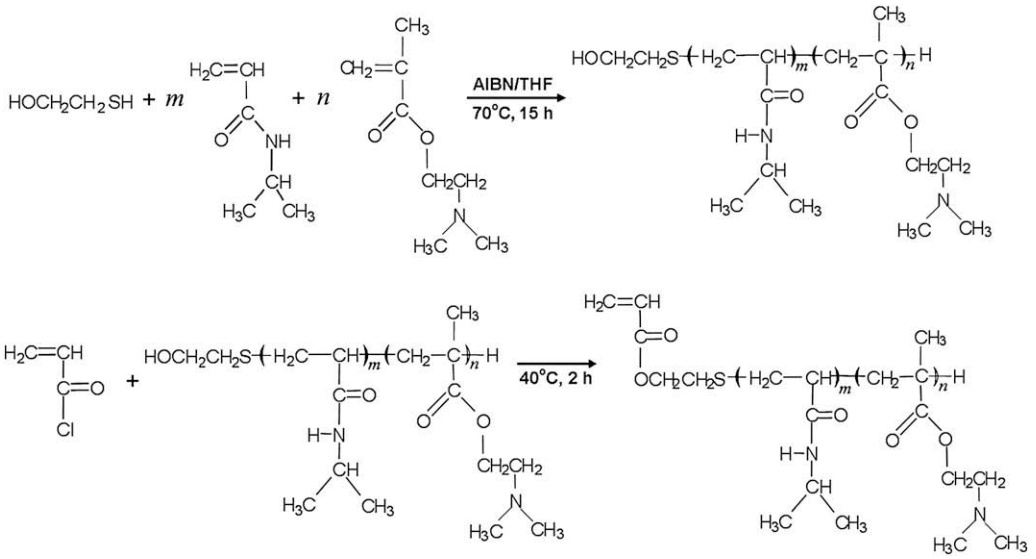

Fig. 1. Synthetic scheme for the preparation of the P(NIPAM-*co*-DMAEMA) macromonomer by radical telomerization.

Normal-type hydrogels (PND-00), which served as a reference, were also prepared using the protocol described above, except that macromonomer was not included in the recipe. To focus on the response properties of hydrogels due to different physicochemical structures, the ratio of BIS to total monomers (monomer and macromonomer) was fixed the same for preparing both comb-type and normal-type hydrogels by referring to previous researches [12,44,45].

2.4. Measurements of equilibrium swelling ratios of hydrogels

The swelling ratio was defined as the weight of water absorbed in the equilibrium swollen gel (W_s) divided by the weight of dried gel (W_d) (Eq. (1)).

$$\mathrm{SR} = \frac{W_s}{W_d} \tag{1}$$

Due to the natural body temperature and physiological pH was about 37 °C and pH 7.4, the equilibrium swelling ratio (SR) of cationic hydrogel discs was measured gravimetrically after wiping excess water from the gel surface with moistened filter paper as a function of pH values at constant temperature of 37 °C or as a function of temperatures at constant pH of 7.4. Each weight datum of hydrogels presented in the paper was an average value of three samples. The ionic strength of all pH buffers was adjusted to 0.1 M beforehand. In the case of constant temperature, dried gel discs had been immersed in a series of pH buffers for 24 h at 37 °C before the measurement. In the case of constant pH, dried gel discs were first equilibrated in pH 7.4 buffer solutions at 20 °C for 12 h and after being weighted, equilibrated again at another temperature until 48 °C. The transition temperature and pH values of the hydrogels were determined as the corresponding temperature and pH values at which the swelling ratio decreases to half of the original values.

Table 1
Recipe for the preparation of poly(NIPAM-*co*-DMAEMA) hydrogels.

Component	Sample code	
	PND-00	PND-50
NIPAM monomer (g)	1.8306	0.9153
DMAEMA monomer (g)	0.2826	0.1413
Macromonomer (g)	0	1.0566

Note: Crosslinker BIS = 40 mg; accelerator TEMED = 100 μL; initiator APS = 0.015 g; solution (ultrapure water) = 18 mL. The molar ratio of NIPAM to DMAEMA in macromonomer was about 90:10 according to the result of ^{1}H NMR spectroscopy, and the total molar ratio of NIPAM to DMAEMA in the whole monomers was also kept to 90:10.

2.5. Measurements of dynamic swelling/deswelling behaviors of hydrogels

The dynamic swelling behaviors of hydrogels were investigated by measuring SR variation along with time at room temperature (18 °C) after dried gels were suddenly immersed in the pH solutions. At regular time intervals, the gel sample was retrieved, wiped and weighed. The dynamic deswelling behaviors of hydrogels were investigated by measuring the water retention of hydrogel in different designed conditions at different time intervals, which was calculated using the following equation,

$$\text{Water retention} = \frac{(W_t - W_d) \times 100\%}{W_s} \tag{2}$$

where W_t is the weight of hydrogel in certain pH buffer solution at time t, and the other symbols are the same as those described above. Firstly, the gel sample was allowed to reach equilibrium in given buffer solutions at a given temperature; then, the equilibrated gel sample was quickly transferred to another condition with pH and/or temperature stimuli. At regular time intervals, the weight datum was measured. The SR and water retention were determined by the weight datum with an average of three samples.

2.6. Drug-release experiments of hydrogels

Dried gel discs had been immersed in 0.8 mmol L^{-1} VB_{12} buffer solutions of pH 7.4 at room temperature (18 °C) for at least 72 h before drug release experiments. The VB_{12} buffer solution was refreshed periodically to ensure the VB_{12} concentration inside the hydrogels reaches 0.8 mmol L^{-1}. Before release experiment, hydrogels were weighted after the sample surfaces have been wiped with moistened filter paper, the total drug-loading (M_0) was defined as

$$M_0 = \frac{\left(W_s' - W_d\right) \times 8 \times 10^{-4}}{\rho_L} \tag{3}$$

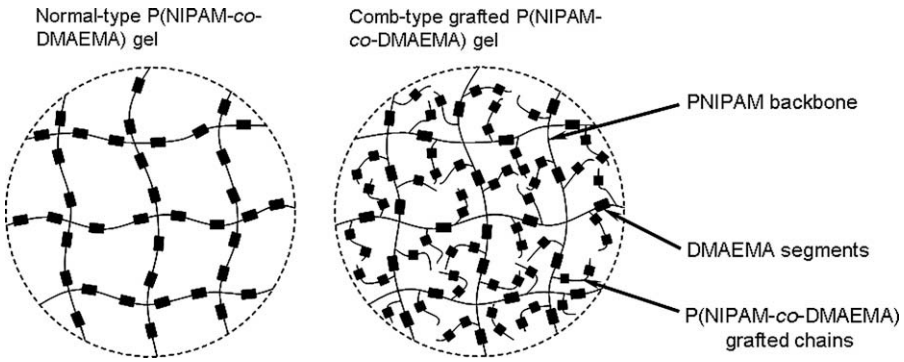

Fig. 2. Schematic illustration of the structures of the normal-type and comb-type grafted P(NIPAM-*co*-DMAEMA) hydrogels.

where W'_s and W_d are the weights of drug-loading hydrogel and dried gel, respectively; and ρ_L is the density of VB_{12} buffer solution. After being weighted, the drug-loading hydrogel disks were quickly transferred into pH 11.0 buffer solution without VB_{12} at a constant 44 °C using a thermostatic unit. At regular time intervals, VB_{12} concentration in the solution was measured by using a UV–vis recording spectrophotometer (UV9600, Beijing Rayleigh Analytical Instrument Co., China) at a wavelength of 361 nm. VB12 release behaviors from three samples were tested and the average value was used.

3. Results and discussion

3.1. Characterization of macromonomer

The weight-average and number-average molecular weights of macromonomer are respectively determined to be 3415 Da and 1952 Da by GPC (see Fig. S1 in the Supporting information). This confirms successful synthesis of macromonomer. In FT-IR spectroscopy, as expected, two characteristic peaks of NIPAM at both 1642.6 cm^{-1} (amide I) and 1550.8 cm^{-1} (amide II) appear and the characteristic peaks of DMAEMA at 1729.6 cm^{-1} are also detected, which indicates that both NIPAM and DMAEMA are introduced into the macromonomer (see Fig. S2 in the Supporting information). A ^1H NMR spectrum of poly(NIPAM-*co*-DMAEMA) macromonomer exhibits peaks at 1.1 ppm (–CH_3) and 3.9 ppm (–CH–), and two broad peaks at 1.6 and 2.0 ppm assigned to methylene proton and methyne proton on the main chains are observed. Meanwhile, two peaks at 3.5 and 4.3 ppm assigned to two methylene protons and the peak at 3.0 ppm (–CH_3) from the DMAEMA moieties are observed. Significantly, the peaks of vinyl proton at 5.9–6.5 ppm are detected, which indicates that a polymerizable end group is introduced into the hydroxyl semitelechelic poly(NIPAM-*co*-DMAEMA) (see Fig. S3 in the Supporting information). The results of GPC, FT-IR and ^1H NMR verify that, poly(NIPAM-*co*-DMAEMA) macromonomer bearing vinyl groups is successfully prepared out of monomers NIPAM and DMAEMA. The molar ratio of NIPAM and DMAEMA in the macromonomer is determined to be 90 to 10 according to the area ratio of respective characteristic peaks in ^1H NMR spectrum. To match the component ratio of NIPAM to DMAEMA in the macromonomer, the molar ratio of NIPAM monomer to DMAEMA monomer in the feed compositions is also initialized to be 90:10 for either normal-type or comb-type grafted hydrogel.

3.2. Synthesis of comb-type grafted poly(NIPAM-co-DMAEMA) hydrogels

Unlike normal-type copolymer hydrogel prepared by direct radical copolymerization of monomers NIPAM and DMAEMA, comb-type grafted hydrogel is synthesized by radical copolymerization of poly(NIPAM-*co*-DMAEMA) macromonomer with monomers NIPAM and DMAEMA. Cross-linked network backbones of the hydrogel are made up of the monomers NIPAM and DMAEMA, and poly(NIPAM-*co*-DMAEMA) chains with freely mobile ends are grafted onto the backbones. Within comb-type hydrogels, the grafted chains have freely mobile ends, which are distinct from typical network structures of normal-type crosslinked hydrogels. Schematic structures of normal-type and comb-type poly(NIPAM-*co*-DMAEMA) hydrogels are illustrated in Fig. 2.

3.3. Effects of pH and temperature on the equilibrium swelling ratio (SR)

To investigate the effect of pH on the equilibrium swelling ratio, the hydrogels are equilibrated in buffer solutions at pH ranged from 2.0 to 11.0 at 37 °C. Fig. 3 shows the dependence of equilibrium SR of synthesized normal-type and comb-type poly(NIPAM-*co*-DMAEMA) hydrogels on pH values at 37 °C. Both hydrogels have higher SR values at an acidic pH than at a basic pH, and the critical pH values of two hydrogels for the transition are approximately 7.3. Amino groups in cationic poly(NIPAM-*co*-DMAEMA) hydrogels are ionized in the lower pH region and positively charged. As a result, poly(NIPAM-*co*-DMAEMA) hydrogels become more extended because of the increased osmotic pressure among hydrogels. On the other hand, it is difficult for poly(NIPAM-*co*-DMAEMA) hydrogels to produce enough ionized amino groups in the higher pH condition

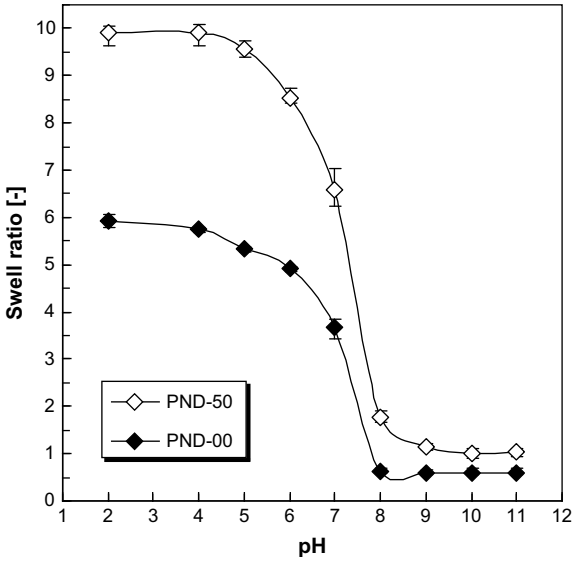

Fig. 3. Equilibrium swelling behaviors of hydrogels at 37 °C as a function of pH.

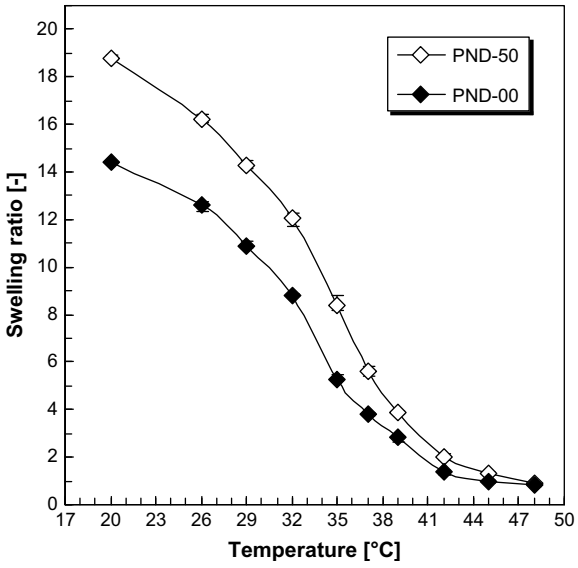

Fig. 4. Equilibrium swelling behaviors of hydrogels at pH 7.4 as a function of temperature.

so that the hydrogels take a contracted form [34]. The accordant critical pH values for the transition of PND-00 and PND-50 hydrogels confirm that the ratio of NIPAM to DMAEMA is same in both hydrogels. Although the equilibrium SR difference between two types of hydrogels at alkaline pH is not so significant, PND-50 hydrogel has much larger SR value at acidic pH than PND-00 hydrogel. As far as PND-50 hydrogel is concerned, the acidic pH makes the dual sensitive grafted linear chains having freely mobile ends more extended because of the electrostatic repulsion between ionizable groups, which tows the whole networks to a more swollen state. On the other hand, PND-00 hydrogel has no additional aid for swelling. Therefore, comb-type poly(NIPAM-*co*-DMAEMA) hydrogels have higher equilibrium SR values at acidic pH than normal-type hydrogels.

The effect of temperature on the equilibrium SR of hydrogels in a buffer solution (pH 7.4) is shown in Fig. 4. The comb-type -poly(NIPAM-*co*-DMAEMA) grafted hydrogel has the same phase transition temperature (about 34 °C) as the normal-type poly(NIPAM-*co*-DMAEMA) hydrogel. This result confirms again that two types of hydrogels are composed of copolymers with the same ratio of NIPAM to DMAEMA. Because amino groups of NIPAM and DMAEMA in hydrogels form intermolecular hydrogen bond with surrounding water at low temperature, hydrogels extend and obtain large SR; while hydrogen bonds are overwhelmed by hydrophobic interactions among hydrophobic groups over the LCST, which cause phase separation and shrinkage of hydrogel matrix [54–56]. However, PND-50 hydrogel shows more swollen state than PND-00 below the LCST. As the grafted chains are structurally separated from the backbone crosslinked network, stronger hydration may be possible [57]. The inherent mobile nature of dual sensitive grafted chains in PND-50 hydrogel makes them readily exposed to water [12]. This chain expansion is considered to result in increased hydration in the comb-type grafted polymeric hydrogels.

3.4. Dynamic swelling/deswelling behaviors in pH buffer solutions at fixed temperature

Fig. 5 illustrates SR variation of dried poly(NIPAM-*co*-DMAEMA) gels with time after being immersed in different pH buffer solutions at room temperature (18 °C). For the same type of hydrogels, they have trends to swell faster and to higher degree at an acidic solution than at an alkaline solution. In the dual thermo-/pH-sensitive poly(NIPAM-*co*-DMAEMA) hydrogels, NIPAM segments respond to temperature and DMAEMA segments respond to pH. According to the above-mentioned results in Figs. 3 and 4, poly(NIPAM-*co*-DMAEMA) hydrogels are swollen at lower temperature (below 34 °C) and acidic pH (lower than 7.3), and become shrunken at higher temperature (above 34 °C) and alkaline pH (higher than 7.3). At lower temperature (18 °C) and acidic pH (pH 2.0), both swelling effects derived from thermo- and pH-sensitive components make hydrogels expanded sufficiently; while at lower temperature (18 °C) and alkaline pH (pH 10.0), swelling effects derived from the hydration of thermo-sensitive components and shrinking effects from decreased electrostatic repulsion attributing to pH-sensitive components counteract mutually to some extent, which leads to insufficient swollen state. As a result, the swelling rate and degree of each type of hydrogels are larger at acidic pH solution than at

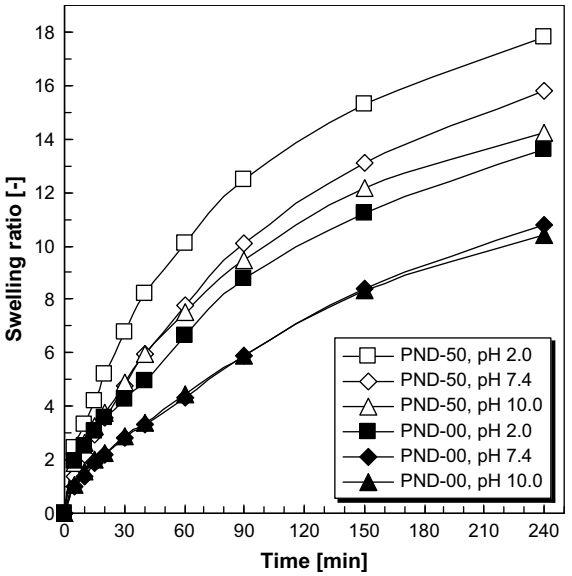

Fig. 5. Dynamic swelling behaviors of hydrogels at 18 °C in different pH buffer solutions.

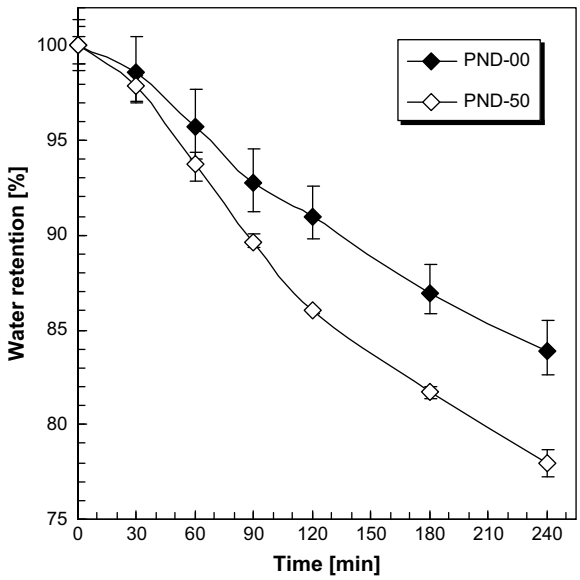

Fig. 6. Dynamic deswelling behaviors of hydrogels at 22 °C with a sudden pH jump from 2.0 to 11.0. The hydrogels are immersed in pH 2.0 buffer solution to the equilibrium state before the test.

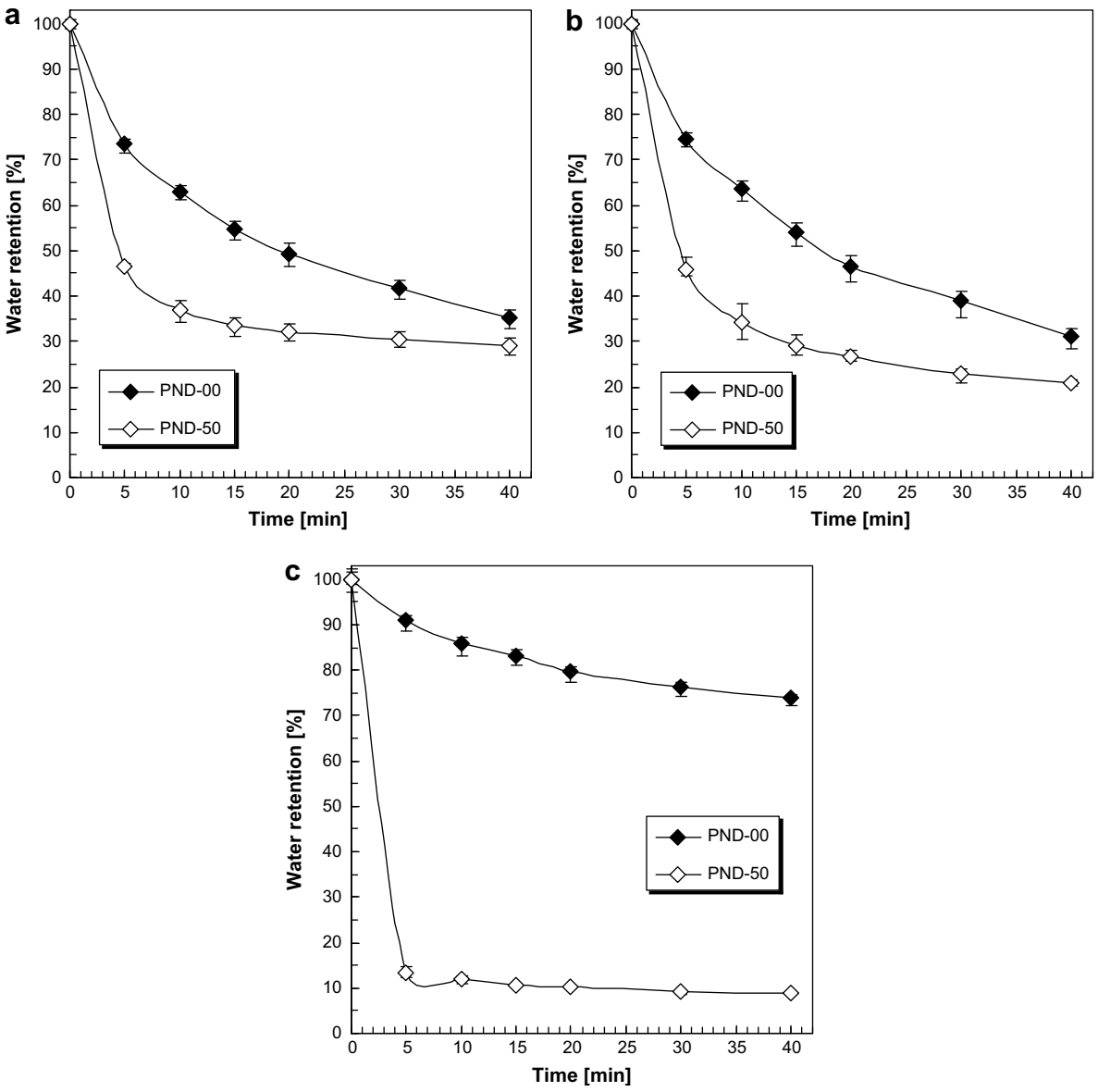

Fig. 7. Dynamic deswelling behaviors of hydrogels in three pH buffer solutions with a sudden temperature increase. (a) pH 2.0, $T = 49$ °C (increased suddenly from 18 °C); (b) pH 7.4, $T = 44$ °C (increased suddenly from 18 °C); (c) pH 11.0, $T = 44$ °C (increased suddenly from 18 °C). The hydrogels before the test are immersed in the same buffer solutions to the equilibrium state at 18 °C.

alkaline pH solution at the same temperature of 18 °C. Moreover, although hydrogels receive adverse interactions at 18 °C and pH 10.0, they still exhibit swelling tendency, which shows the effect of environmental temperature overwhelming that of pH. The molar ratio of NIPAM to DMAEMA is 90 to 10 for both types of hydrogels, *i.e.*, the amount of pH-sensitive component in hydrogels is much smaller than that of thermo-sensitive component. Therefore, the pH-response ability of hydrogels is milder than that of thermo-responsibility. For the same type of hydrogels, however, the higher the pH is, the slower the swelling rate. This confirms that the shrinking effect at alkaline pH restricts the swelling behavior of hydrogels to a certain extent. In addition, PND-50 hydrogel swells much more rapidly and to a higher degree at all pH investigated (*i.e.*, pH = 2.0, 7.4 and 10.0) than PND-00 hydrogel (Fig. 5). In PND-50 hydrogels, the dual sensitive grafted chains, which could hydrate with little restriction, could tow the whole networks to swell quickly. On the other hand, the shrinking effect of the dual sensitive grafted chains at alkaline pH may be concealed by the expanded effect owing to the strong hydration. Since the interactions in PND-50 hydrogels are larger than that in PND-00 hydrogels, PND-50 hydrogels have higher swelling rates and swollen degree than PND-00 hydrogels.

Fig. 6 shows the dynamic deswelling behaviors of hydrogels at 22 °C with a sudden pH jump from 2.0 to 11.0. The hydrogels are immersed in pH 2.0 buffer solution to the equilibrium state before the test. The deswelling rate of two hydrogels is slow due to the swelling effects of thermo-sensitive components at low temperature of 22 °C. Although the molar ratios of NIPAM to DMAEMA in the hydrogels are the same, the PND-50 hydrogel deswells faster than the PND-00 hydrogel. In the PND-50 hydrogel, DMAEMA segments are distributed throughout the backbone networks and the grafted chains. The pH-sensitive mobile side chains in the comb-type PND-50 hydrogel could shrink with little restriction at alkaline solution and tow the whole networks to deswell quickly. Therefore, the shrinking rate of comb-type hydrogels in response to pH change is enhanced compared with normal-type hydrogels.

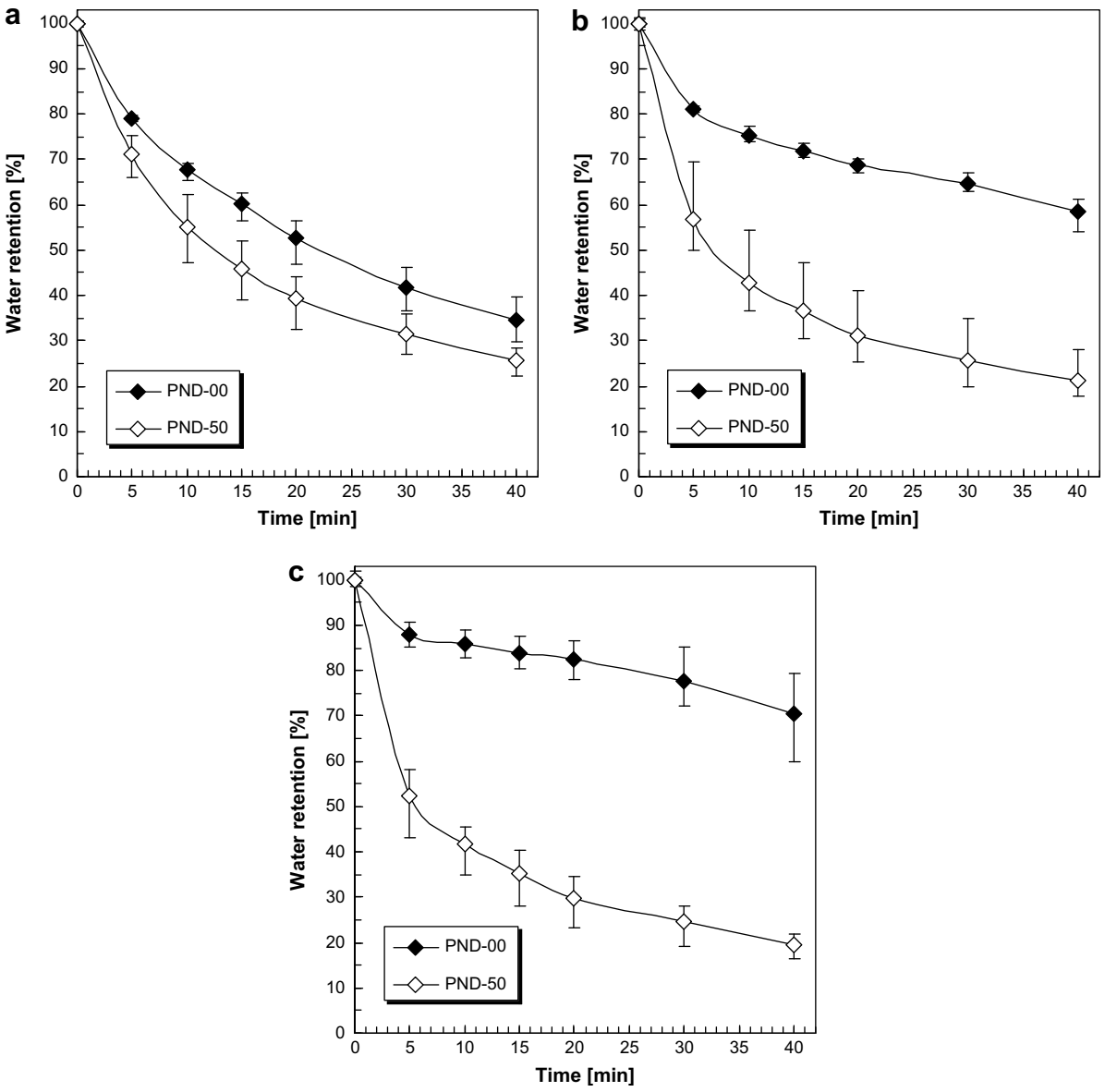

Fig. 8. Dynamic deswelling behaviors of hydrogels in buffer solutions triggered by simultaneous temperature and pH sudden-stimuli. The original conditions of hydrogels (in the equilibrium state) before testing are: (a) pH 2.0, $T = 18\ ^{\circ}C$; (b) pH 6.0, $T = 18\ ^{\circ}C$; and (c) pH 7.4, $T = 18\ ^{\circ}C$. The changed temperature and pH for the observation are 44 °C and pH 11.0 respectively.

In Table 1, the crosslinker BIS used is the same for PND-00 and PND-50, but for PND-50 half of NIPAM and DMAEMA go to the side chain. Therefore, the crosslinking density of the backbone of PND-00 should be around half that of PND-50. As a result, the mesh size of the comb-type hydrogel is much smaller than that of the normal-type one in the original state after the polymerization. Even so, the introduction of side chains with freely mobile ends in PND-50 hydrogel makes the mobility of the networks increase.

3.5. Dynamic deswelling behaviors in fixed pH buffer solutions with temperature stimuli

Fig. 7 exhibits dynamic deswelling behaviors of hydrogels in different pH buffer solutions with a sudden temperature increase. The hydrogels before the test are immersed in the same buffer solutions to the equilibrium state at 18 °C. It is obvious that PND-50 hydrogels deswell more rapidly than PND-00 hydrogels in each pH buffer solution (from acidic pH to basic pH). Especially, the PND-50 hydrogel approaches to the smallest volume state within 5 min at pH 11.0, but the PND-00 hydrogel shrinks much slowly. Moreover, the higher pH value the buffer solution has, the larger difference between the shrinking rates the two types of hydrogels show. When the crosslinked normal-type hydrogel meets abrupt environment stimuli, the polymer networks composed of two types of thermo-sensitive segments near the surface of the hydrogel shrink firstly and form dense skin layer, which blocks further dehydrating of the hydrogel matrixes. Along with the process, the aqueous solution near the surface is vented quickly that brings anticlimactic deswellings of all hydrogels in the beginning (with surface effect). However, the swelling effect that occurs at an acidic solution resists the shrinking force caused by the temperature increase; on the contrary, the shrinking effect that occurs at a basic solution assists the shrinking force. For the PND-00 hydrogel, the aqueous solution is expulsed easily from the interior of hydrogel at pH 2.0, but is enwrapped by the dense skin layer at pH 11.0. Therefore, the response rate of PND-00 hydrogel increases with decreasing the pH value, which is mainly governed by the integrality of the dense skin layer. On the other hand, immediate dehydration of freely mobile

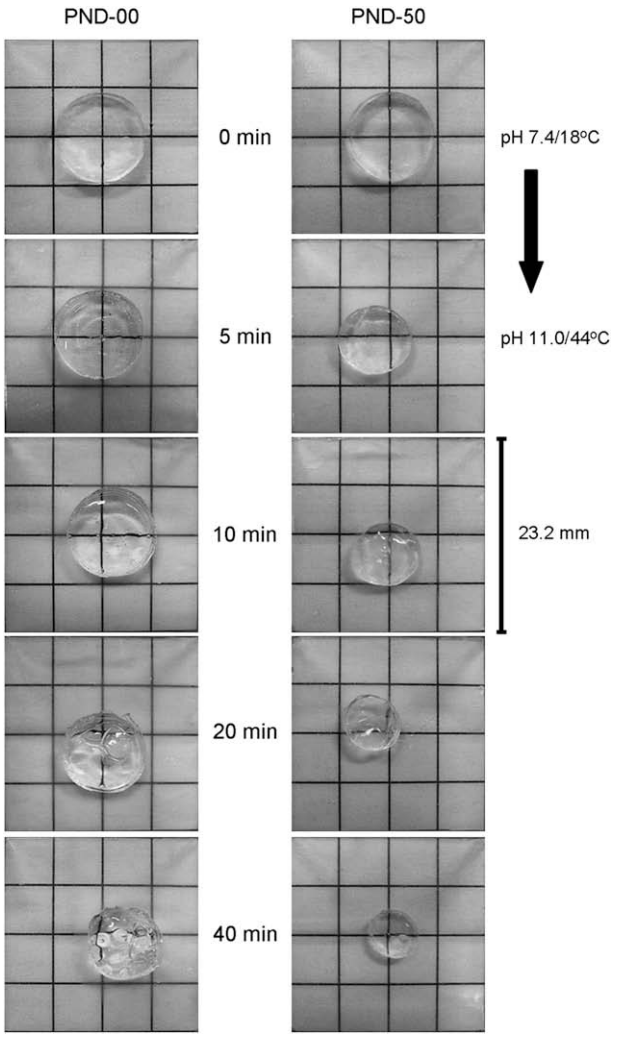

Fig. 9. Photographs of the deswelling process of disk-shaped normal-type hydrogel (PND-00) and comb-type grafted hydrogel (PND-50) that triggered by simultaneous temperature and pH sudden-stimuli. The pH and temperature are changed from pH 7.4 and 18 °C to pH 11.0 and 44 °C suddenly.

grafted chains in the PND-50 hydrogel matrixes and the subsequent hydrophobic interactions between dehydrated grafted chains accelerate the shrinkage of the whole network [12,50]. Moreover, there is no integrated dense skin layer formed on the surface of comb-type grafted hydrogel, therefore the aqueous solution could not be enwrapped tightly inside the hydrogel. As a result of the above-mentioned two reasons, the comb-type grafted hydrogel shrinks much more rapidly than the normal-type hydrogel. The pH-sensitive DMAEMA units in the flexible grafted chains would counteract with the shrinking force to a certain extent because of their expanding effect in acidic solution, but enhance the shrinking force in alkaline solution contrarily. Therefore, in reverse with the order of that of PND-00 hydrogels, the response rates of PND-50 hydrogels increase to a certain extent with the increase of surrounding pH.

3.6. Dynamic deswelling behaviors in buffer solutions with both pH and temperature stimuli

Fig. 8 shows the dynamic deswelling behaviors of hydrogels in buffer solutions triggered by simultaneous temperature and pH sudden-stimuli. The shrinking trends of two types of hydrogels are similar to those in Fig. 7. Similarly, the comb-type grafted hydrogel shrinks more rapidly than normal-type hydrogel when both temperature and pH are increased suddenly.

Fig. 9 shows the deswelling process of disk-shaped normal-type hydrogel (PND-00) and comb-type grafted hydrogel (PND-50) that triggered by simultaneous temperature and pH sudden-stimuli. The pH and temperature are changed from pH 7.4 and 18 °C to pH 11.0 and 44 °C suddenly. Transparent blister formation is immediately observed on the surface of PND-00 hydrogel after an abrupt environmental change [44,50], and the blister breaks after a period of time. However, the PND-50 hydrogel shrinks continuously with no obvious blister. The phenomena verify the above-mentioned dense skin layer formation on the hydrogel surface.

During the shrinking process, the polymer networks near the surface of crosslinked normal-type hydrogel form the temporal dense skin layer, which is probably attributed mainly to the firstly occurred hydrophobic aggregation forces [58]. There are also anti-climactic deswellings of all hydrogels in the beginning because of the drainage near the surface (*i.e.*, the surface effect). For the hydrogels pre-equilibrated at pH 2.0, the neutralization between the buffer solution maintained in hydrogels and the environmental buffer solution (pH 11.0 in Fig. 8a) occurs. The actual pH surrounding is low, so the response to pH resists the shrinking force caused by the temperature increases, and then makes the dense skin layer not-well-compacted. As a result, the well-proportioned expulsion of solution from interior of hydrogels is observed. As for the hydrogels pre-equilibrated at pH 6.0 or pH 7.4, the pH surrounding in them is closer to the exterior pH, the resistance to the hydrophobic aggregation would vanish and is replaced by the cooperation. Thereupon, the dense skin layer forms on the surface of the normal-type hydrogels, as a result the solution in them is enwrapped and hardly effuses. However, the PND-50 hydrogel exhibits much faster deswelling due to the absence of dense skin layer on the surface and the acute aggregation of the dual sensitive grafted chains.

3.7. Drug release from the hydrogels

One of the current interests in stimuli-sensitive hydrogels for both biomedical and non biomedical uses is the possibility that

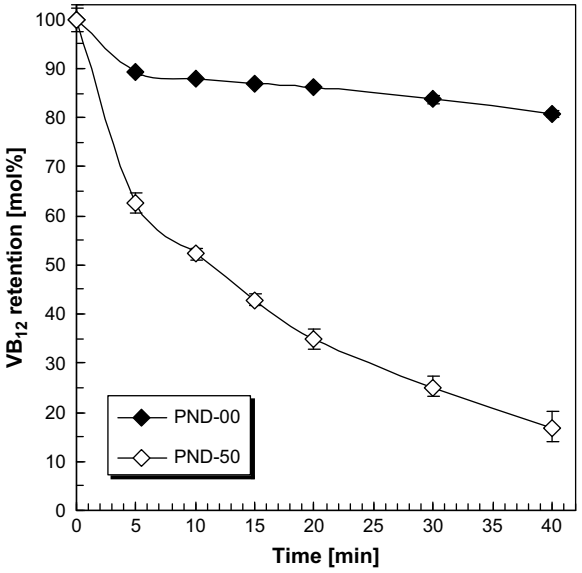

Fig. 10. Release of VB_{12} from the disk-shaped normal-type hydrogel (PND-00) and comb-type grafted hydrogel (PND-50) that triggered by simultaneous temperature and pH sudden-stimuli. The pH and temperature are changed from pH 7.4 and 18 °C to pH 11.0 and 44 °C suddenly.

Table 2
Values of parameters of the kinetic model for the release rate (Eq. (4)).

Sample	Including surface effect[a]			Excluding surface effect[b]		
	A	*B*	R^2	*A*	*B*	R^2
PND-00	94.185	0.0041	0.7739	90.657	0.0027	0.9845
PND-50	84.027	0.0415	0.9759	75.206	0.0374	0.9990

Note: *R* is the correlation coefficient. The closer the R^2 value approaches to 1, the better the kinetic model fits in with the experimental data.

[a] Experimental data from 0 min are used for fitting the kinetic model, *i.e.*, the surface effect during the release is included.

[b] Experimental data from 5 min are used for fitting the kinetic model, *i.e.*, the surface effect during the release is excluded.

the release of small molecules from the gel can be controlled by environmental temperature and pH stimuli. VB_{12} is selected as a model drug in this study because it is a neutral macromolecule and then there is no specific interaction between the drug and hydrogel. The release of VB_{12} from the normal-type and comb-type grafted P(NIPAM-*co*-DMAEMA) hydrogels that triggered by simultaneous temperature and pH sudden-stimuli is shown in Fig. 10. The pH and temperature are changed from pH 7.4 and 18 °C to pH 11.0 and 44 °C suddenly. The model drug molecules are mainly squeezed out from the hydrogels together with the solution when the hydrogels meet environmental stimuli. The results show that only a small fraction of VB_{12} is released from the normal-type PND-00 hydrogel even after 40 min; on the other hand, the release rate of VB_{12} from the comb-type PND-50 hydrogel is significantly fast due to the rapid deswelling behavior of comb-type hydrogels. The release rate data are fitted to an exponential model as the following equation:

$$y = Ae^{-Bx} \tag{4}$$

where *y* is the VB_{12} retention in the hydrogel, *A* and *B* are two constants, and *x* is the time. The values of these parameters are listed in Table 2. It shows that the exponential model is accordant with the rate of release from hydrogels, especially in the condition that the surface effect is excluded. The *A* values for PND-00 and PND-50 hydrogels are pretty much the same thing, but the *B* value for the PND-50 hydrogel is over decuple larger than that for the PND-00 hydrogel. According to the characters of exponential function, the larger the constant *B* is, the larger the decrease degree of *y* along with the increase of *x*. That is, comparing with that of the normal-type PND-00 hydrogel, the release rate of the model drug VB_{12} from the comb-type PND-50 hydrogel is significantly faster.

4. Conclusions

In this study, rapid pH/temperature-responsive cationic hydrogels with dual stimuli-sensitive poly(NIPAM-*co*-DMAEMA) backbone networks and grafted poly(NIPAM-*co*-DMAEMA) side chains are successfully fabricated. Due to the introduction of freely mobile grafted side chains into the polymer backbone networks, the mobility of polymers in the comb-type grafted hydrogels is improved. The grafted poly(NIPAM-*co*-DMAEMA) chains inside the comb-type hydrogels could easily swell and shrink as environmental pH and/or temperature changes. The grafted poly(NIPAM-*co*-DMAEMA) chains prevent from forming dense skin layer on the surface of comb-type hydrogels; as a result, the comb-type poly(NIPAM-*co*-DMAEMA) hydrogels show acute response to temperature/pH stimuli. Fast release of model drug from the comb-type grafted hydrogels is also observed with simultaneous temperature and pH stimuli. Such rapid pH/temperature-responsive cationic hydrogels are promising new material candidates for various applications, such as for fabricating novel sensors, actuators and chemical/drug carriers. Based on the strategy presented in this study, it is possible to develop new dual stimuli-sensitive polymeric materials with improved response to environment stimuli.

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Appendix. Supporting information

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.polymer.2009.03.044.

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