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Design and Synthesis of Dual-Responsive Hydrogels Based on *N*,*N*-Dimethylaminoethyl methacrylate by Copolymerization with *N*-Isopropylacrylamide

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Abstract: Copolymeric hydrogels of *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) and *N*-isopropylacrylamide (NIPA) of various monomer ratios were evaluated as thermo-responsive and pH-responsive systems for the development of controlled-release and targeted-delivery devices. The swelling properties were investigated with different temperature, pH, and monomer feed ratios. The results show that the temperature-dependent and pH-dependent phase transition of poly(*N*,*N*-dimethylaminoethyl methacrylate-*N*-isopropylacrylamide) (P(DMAEMA-NIPA)) copolymeric hydrogels can be controlled by changing the amount of NIPA units in the network chains. In experiments to determine the temperature-dependent swelling of copolymeric hydrogels in water, it was found that the swelling ratio rapidly decreases as the temperature increases between 35 and 70 °C. To characterize the network structure of the copolymeric hydrogels corresponding to effective cross-linking density and average network chain length, uniaxial compressive mechanical testing was carried both after the preparation of hydrogels and after their equilibrium swelling in water. The data obtained demonstrates that the resulting copolymeric hydrogels are promising as materials with tunable hydrophilicity-hydrophobicity and swelling behavior responsive to temperature and pH.

Keywords: *N*,*N*-dimethylaminoethyl methacrylate, *N*-isopropylacrylamide, crosslinking, hydrogels, stimuli-sensitive polymers.

Introduction

Dual temperature- and pH-responsive hydrogels that are insoluble crosslinked polymers with ability to hold large amount of water within their three-dimensional network structures contain ionizable weakly acidic or basic moieties attached to the main chains and have a delicate hydrophobic-hydrophilic balance in their structures. The investigations concerning dual-responsive crosslinked hydrogels have received considerable attention with various usages such as microencapsulation, biosensor, and drug delivery.[1-3] In most of these applications, it would be favorable if the resulting hydrogel could response to multiple environmental stimuli with particular emphasis on pH and temperature. Up to now, most dual temperature- and pH-sensitive hydrogels are prepared by incorporating pH-responsive components into the temperature-responsive poly(*N*-isopropylacrylamide) (PNIPA)-based networks. PNIPA is the most known thermosensitive polymer which is highly water soluble at low temperatures but precipitates when the temperature is raised above its lower critical solution temperature (LCST) at 32-33 °C.[4,5] Due to the presence of both hydrophilic amide groups and hydrophobic isopropyl groups in its side chains, PNIPA forms swollen hydrogels. Because of the breakdown of the delicate hydrophilic/hydrophobic balance in the network structure, the hydrogel is in swollen hydrated and hydrophilic state below its LCST, whereas it shrinks and forms a collapsed, dehyrated and hydrophobic state above its LCST.

To date, many studies have been reported on dual-responsive hydrogels based on *N*-isopropylacrylamide (NIPA) and its copolymers with the most widely studied comonomers such as 2-acrylamido-2-methylpropane sulfonic acid sodium salt, acrylic acid, methacrylic acid, sodium acrylate and sodium methacrylate.[6,7] It is well known that the incorporation of a hydrophilic monomer into the network structure of thermo-responsive hydrogels leads to an increase in the LCST behavior while incorporation of a hydrophobic monomer leads to a decrease in LCST and/or the volume phase transition temperature of the hydrogel system.[8,9] NIPA-based hydrogels are also rendered as pH-responsive by copolymerizing with acidic or basic comonomers. In recent years, more attention has been directed to cationic poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) hydrogels which have been shown to be both temperature- and pH-responsive. It was

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reported that PDMAEMA has a lower critical solution temperature in water and PDMAEMA hydrogels may undergo a controllable volume change in response to small variation of pH and temperature changes in solution conditions. The phase transition temperature of PDMAEMA hydrogels in aqueous solutions falls in the wide range of 38-50 ºC.[10,11] Cho *et al.* prepared copolymers of DMAEMA and acrylamide (AAm) to demonstrate the temperature-induced phase transition and observed that LCST shifts to the lower temperature due to the formation of hydrogen bonds between amide and *N*,*N*-dimethylamino groups.[12] Very recently, Lugo-Medina and coworkers prepared a series of NIPA-based hydrogels containing pH-sensitive basic and acidic monomeric units *via* by chemical crosslinking and also, by e-beam irradiation methods.[13] Zhang *et al*. fabricated a series of dual temperature- and pH-sensitive comb-type grafted cationic hydrogels by grafting polymeric chains with freely mobile ends, which are composed of both NIPA segments and DMAEMA segments, onto the backbone of crosslinked poly (NIPA-DMAEMA) networks and showed that these comb-type grafted hydrogels exhibit fast response to pH/temperature change.[14]

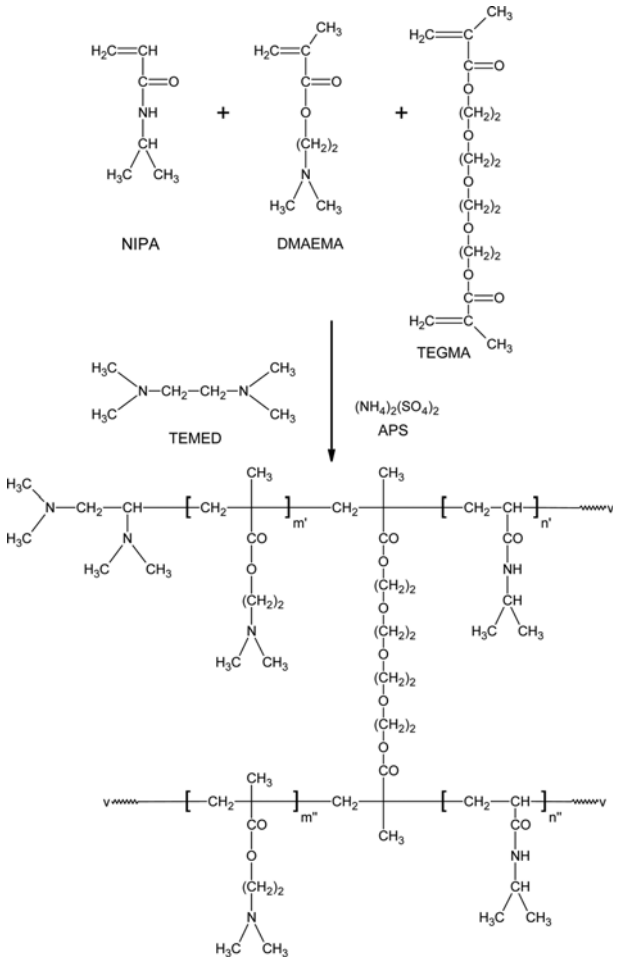
Since the swelling and thermodynamic properties of stimuli-responsive hydrogels are vital to their applications, a major limitation of hydrogels lies in their tendency to fracture at small strains which arises from spatial inhomogeneities during the formation of the network structure. To tackle this limitation in the mechanical robustness of hydrogels, one possibility is to introduce slipping crosslinks into the network structure. Feil *et al*. synthesized terpolymer hydrogels with NIPA as a temperature-sensitive component, diethylaminoethyl methacrylate (DEAEMA) as a pH-sensitive component, and butyl methacrylate (BMA) as a hydrophobic component to increase the mechanical stability of the resulting hydrogels.[15] In another work, poly(*N*,*N*-dimethylaminoethyl methacrylate-butyl methacrylate) (P(DMAEMA-BMA)) copolymeric hydrogels were synthesized by the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent and found that the equilibrium degree of swelling of P(DMAEMA-BMA) hydrogels with changing pH values at different temperatures strongly depends on the concentration of crosslinking agent present in the network structure. Increase in the EGDMA content in the network reduced the swelling degree dramatically at all pH values and hence, the water content of hydrogels is strongly dependent on both pH and temperature.[16] Qian *et al*. showed that pH-sensitive hydrogels and nanohydrogels can be used in the design of smart drug delivery systems. They prepared pH-sensitive poly(caprolactone-methacrylic acid-methoxyl ethylene glycol) hydrogels coated with alginate-Ca^{2+} layer and investigated the swelling, and *in vitro* release behavior of the Bovine serum albumin (BSA). Their results indicated that (BSA) was released slowly in acidic environment while it was released quickly in neutral medium. The resulting composite hydrogels showed great pH-sensitivity and might be a candidate for protein drugs *via* oral administration.[17,18]

Although there have been reports on pH- and temperature-dependent swelling of acrylate-based hydrogels, there has not been any comprehensive report on the elasticity of dual-responsive P(DMAEMA-NIPA) copolymeric hydrogels. The aim of the present work was to investigate the elasticity and the temperature response of pH-sensitive copolymer hydrogels based on DMAEMA and NIPA having potential swelling capacity to be used as stimuli-responsive materials in biotechnology. It is expected that changing DMAEMA/NIPA ratio in the copolymer structure will affect the resulting mechanical properties, pH sensitive swelling behavior and also pH- and temperature-dependent phase transition of hydrogels in the belief that this will increase their versatility for sensor or device applications. The effect of the monomer composition on the thermodynamic properties of resulting dual-responsive P(DMAEMA-NIPA) hydrogels were also investigated. The swelling properties and the mechanical behavior of the copolymeric hydrogels were explored and their robustness to large mechanical deformations were also demonstrated by uniaxial mechanical testing.

Experimental

Materials and Methods. *N*,*N*-Dimethylaminoethyl methacrylate (DMAEMA) and tetraethylene glycol dimethacrylate (TEGMA) were obtained from Fluka Chemical Co. *N*-Isopropylacrylamide (NIPA) were purchased from Aldrich. The redox-initiator system ammonium persulfate (APS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were obtained from Merck Chemical. Hydrochloric acid (Merck), potassium dihydrogen phosphate (Riedel-de Haen), potassium phosphate (J.T. Baker), disodium hydrogen phosphate (Merck) and sodium chloride (Merck) were used for the swelling experiments in buffer solutions. All solvents and starting reagents were of analytical grade and used as received. Double distilled water was used throughout the experiments.

Synthesis of P(DMAEMA-NIPA) Copolymeric Hydrogels. Dual temperature- and pH-responsive copolymeric hydrogels were successfully synthesized by free-radical solution copolymerization of monomers DMAEMA, NIPA and the crosslinking agent TEGMA in water in different ratios. The feed compositions of the monomers and other reactants were listed in Table I. The initial molar concentration of the monomers C_0 was fixed at 16 w/v% whereas NIPA content of the monomer mixture was varied from 0 to 80 mol%. The crosslinker ratio X (the mole ratio of the crosslinker to the monomers DMAEMA and NIPA) was fixed at 1/80. To synthesize P(DMAEMA-NIPA) copolymer hydrogels; DMAEMA and NIPA monomers and the crosslinker TEGMA were mixed in a graduated flask and nitrogen gas was bubbled for 20 min in order to eliminate oxygen from the pre-gel solution. When the homogeneous solution was obtained, the aqueous solution of the redox-initiator system APS (3.51 mM) and



Scheme I. The structures of the monomers and crosslinker and the synthetic procedure for P(DMAEMA-NIPA) hydrogels.

TEMED (24.9 mM) were added and then, the reaction solution was completed with distilled water to give a total volume of 10 mL. After shaking the flask, the solution was poured into several polypropylene syringes with the inner diameters of 5.0 mm and length of 15.0 cm and then, the syringes were sealed and the copolymerization reaction was conducted at 50 °C for 24 h. To make comparison, homologous series of copolymer hydrogels were also prepared at room temperature in the same way. The chemical structures and the preparation procedures of the copolymeric hydrogels were schematically illustrated in Scheme I.

After polymerization, the crosslinked copolymers were removed from the syringes and the hydrogels obtained in long cylindrical shapes were cut into samples of about 10 mm in length. Water was chosen as the extraction solvent and the hydrogel samples were immersed in an excess of distilled water at room temperature for one week to remove the uncrosslinked polymer and/or residual monomer. After that, the gel samples were dried in vacuum at 30 °C to constant weight and then stored in a vacuum desicator.

Measurements of Equilibrium Swelling Ratio of Hydrogels. The swelling behavior of P(DMAEMA-NIPA) hydrogels was investigated in water, in buffer solutions at different pH-values as well as in aqueous salt solutions. In order to reach the swelling equilibrium, the hydrogels in the form of rods of 4 mm in diameter were immersed in water at 24±0.5 °C for at least 10 days replacing the water every other day. After equilibrium swelling was reached, the hydrogels were removed and the excess surface water was lightly dried with filter paper. The swelling equilibrium was tested by measuring the diameter of the hydrogel samples after equilibrium swelling in water D and after preparation D_0 by a calibrated digital compass (Mitutoyo Digimatic Caliper, Series 500, resolution: 0.01 mm). To achieve good precision, four measurements were carried out on samples of different length taken from the same hydrogel, the results indicated that the hydrogel is stable and the response is repeatable. Once equilibrium swelling was attained the equilibrium volume swelling ratio of hydrogels V_{eq} (volume of equilibrium swollen hydrogel/volume of the hydrogel just after preparation) was calculated as:

$$V_{eq} = (D/D_0)^3 \tag{1}$$

Then, the volume fraction of crosslinked polymer in the equilibrium swollen hydrogel ν_2 was calculated using the following equation:

$$\nu_2 = \frac{\nu_2^0}{V_{eq}} \tag{2}$$

where ν_2^0 is the volume fraction of crosslinked polymer network after the gel preparation. By assuming the monomer conversion is complete after the crosslinking, the theoretical value of ν_2^0 was calculated from the initial molar concentration of the monomers C_0, using the equation, $\nu_2^0 = 10^{-3} C_0 V_r$, where V_r is the molar volume of P(DMAEMA-NIPA) repeat units (in mL/mol).

During the pH-dependent swelling measurements, the hydrogel diameter was determined as a function of the temperature by using the digital calibrated compass. The hydrogel samples (1 cm in length, 4 mm in diameter) were immersed in vials filled with 100 mL of buffer solutions and then the vials were set in a temperature controlled bath at suitable temperatures. After equilibration at one temperature, the hydrogel diameter was measured and then the sample was re-equilibrated at another temperature. For the swelling studies in aqueous salt (NaCl) solutions, the ionic strength of the salt solutions ranged from 10^{-5} to 1.0 M and the swelling in aqueous NaCl were carried out in direction of increasing salt concentration from water up to 1.0 M NaCl. The equilibrium swelling of P(DMAEMA-NIPA) hydrogels in aqueous salt solutions was monitored gravimetrically and the weight swelling ratio of hydrogels in the salt solutions q_w was calculated as; $q_w = m_{salt}/m_{dry}$ (mass of gel in salt solution/

mass of dried gel). Then, the volume swelling ratio of hydrogels q_v was calculated according to the following equation:

$$q_v = 1 + \frac{(q_w - 1)\rho}{d_1} \quad (3)$$

where ρ and d_1 are the densities of P(DMAEMA-NIPA) copolymer hydrogel and water, respectively. The values ρ and d_1 used in this study were 1.20 and 1.00 g/mL, respectively.

Stress-Strain Measurements. The mechanical properties of P(DMAEMA-NIPA) copolymeric hydrogels were evaluated by using a compression measurement apparatus as described before.[19] The uniaxial compression measurements were conducted on cylindrical hydrogel samples both after their preparation and after their equilibrium swelling in water. Briefly, the hydrogel sample was placed between the flat plate and analytical balance and the force acting on the hydrogel was calculated from the reading of the balance m as $F=mg$, where g is gravitational acceleration. The resulting deformation $\Delta l=l-l_0$ where l_0 and l are the initial undeformed and deformed lengths, respectively. The deformation ratio α (deformed length/initial length) was calculated using the equation, $\alpha=1-\Delta l/l_0$. The force and the resulting deformation were recorded after 20 s of relaxation and the measurements were conducted up to about 20% compression. The results of these experiments were used to calculate the elastic modulus of P(DMAEMA-NIPA) copolymeric hydrogels after preparation and after their equilibrium swelling and the effective crosslinking density, ν_e.

Results and Discussion

In order to obtain copolymeric hydrogels of a fixed crosslink density but differing in polymer composition, free-radical crosslinking copolymerization of DMAEMA, NIPA, and TEGMA was conducted at a fixed crosslinker ratio (1/80) and initial monomer concentration (16 w/v%) but at various NIPA contents. The investigation of the effect of pH, temperature and comonomer NIPA concentration in P(DMAEMA-NIPA) copolymeric hydrogels on the elasticity, swelling behavior and the physical properties was the main purpose.

Network Structure of P(DMAEMA-NIPA) Hydrogels. The typical stress-strain curves of P(DMAEMA-NIPA) copolymeric hydrogels both after preparation and after their equilibrium swelling in water were shown in Figure 1. It was impressive to find that the slope of the stress-strain isoterms varies depending on the mole fraction of the comonomer NIPA used in the preparation while the chemical crosslink density of P(DMAEMA-NIPA) hydrogels is the same. By simply varying the content of NIPA, the mechanical properties of the hydrogels were tunable, while maintaining high flexibility. According to the theory of rubber elasticity, the elastic modulus of resulting copolymer hydrogels G was calculated using the stress-deformation function:[20,21]

$$f = G(\alpha - \alpha^{-2}) \quad (4)$$

where f is the force acting per unit cross-sectional area of the undeformed gel sample. At low strains, the plot of f *vs.* $(\alpha - \alpha^{-2})$ would yield a straightline whose slope is G. For a network of Gaussian chains, the elastic modulus of swollen gels G is given by the following equation: [20,21]

$$G = A\nu_e RT(\nu_2^0)^{2/3}\nu_2^{1/3} \quad (5)$$

where ν_e is the effective crosslink density, the front factor A equals to 1 for an affine network and $1-2/\phi$ for a phantom network, in which f is the functionality of the crosslinks, R and T are in their usual meanings. For the hydrogels just

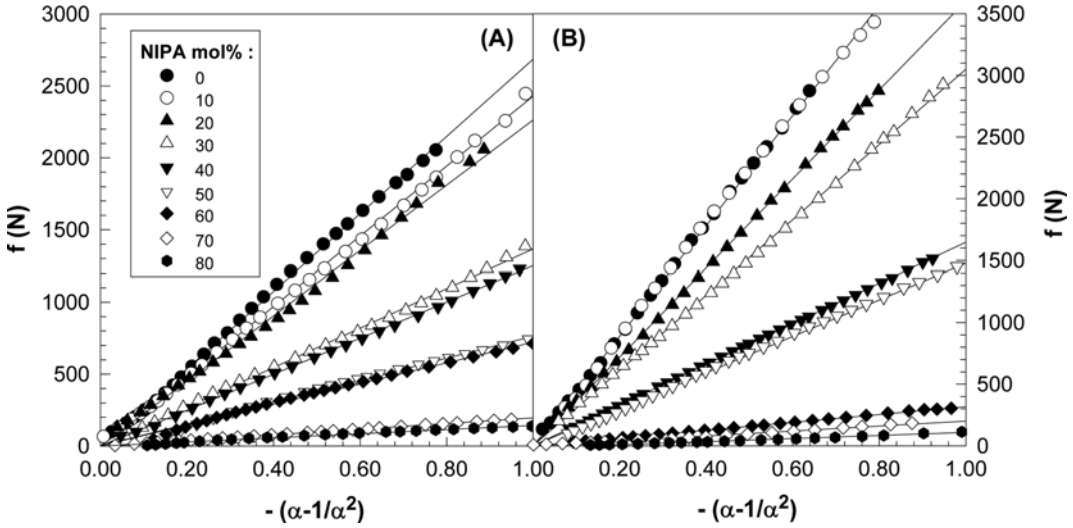


Figure 1. Typical stress-strain data for P(DMAEMA-NIPA) hydrogels both after their preparation at 50 °C (A) and after equilibrium swelling in water (B). The NIPA contents of the hydrogels are already indicated in the figure.

Table I. The Composition and Characteristic Data of P(DMAEMA-NIPA) Copolymeric Hydrogels Prepared at 50 °C[a]

DMAEMA mol%	NIPA mol%	G_0 (Pa)	ν_2	N	ν_e (mol/m^3)
100	0	2,512 (168)	0.0389	4,289	6.506
90	10	2,355 (153)	0.0423	4,622	6.035
80	20	2,094 (217)	0.0480	5,273	5.324
70	30	1,318 (37)	0.0499	8,340	3.333
60	40	1,220 (124)	0.0529	9,129	3.074
50	50	765 (58)	0.0538	14,514	1.925
40	60	505 (41)	0.0546	23,683	1.271
60	70	198 (35)	0.0552	59,923	0.501
20	80	127 (18)	0.0583	88,162	0.321

[a]G_0=the elastic modulus of gels after their preparation, ν_2=the volume fraction of crosslinked polymer after equilibrium swelling calculated using eq. (2) N=the number of segments between two successive crosslinks of the network. ν_e=the effective crosslink density. The numbers in parenthesis are the standard deviations of the separate measurements.

after their preparation, $\nu_2=\nu_2^0$ and hence, the modulus G_0 after preparation is given by:

$$G_0 = A\nu_e RT\nu_2^0 \tag{6}$$

and the effective crosslink densitiy of hydrogels ν_e can be given by the relation as:

$$\nu_e = \frac{1}{NV_1} = \frac{\rho}{\overline{M}_c} \tag{7}$$

where $\overline{M}_c$ is the average molecular weight of the network chains and N is the network chain length related to the effective crosslink density. Since the copolymer hydrogels prepared in this study were highly swollen, the phantom network model (ϕ=4) was used to calculate the network chain length and the other characteristic parameters of P(DMAEMA-NIPA) hydrogels (Table I). Each elastic modulus data reported in this study was an average of four separate elasticity measurements performed in parallel.

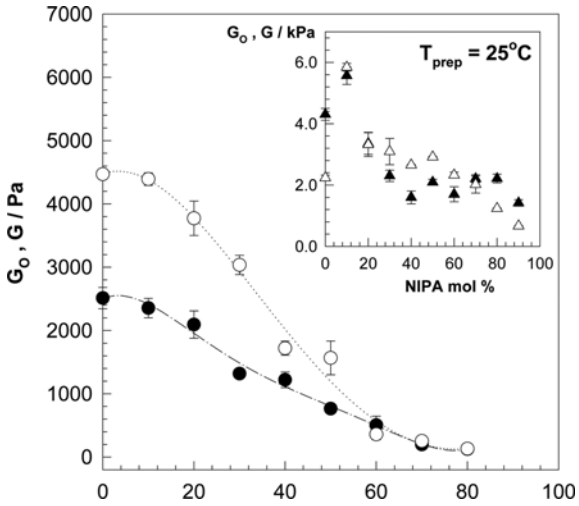


Figure 2. Compression moduli after preparation G_0 (●) and after equilibrium swelling in water G (○) of P(DMAEMA-NIPA) copolymeric hydrogels prepared at 50 °C shown as a function of the comonomer NIPA content (NIPA mol%). Triangles represent the data of P(DMAEMA-NIPA) copolymer hydrogels prepared at 25 °C.

In Figure 2, the elastic moduli of P(DMAEMA-NIPA) copolymeric hydrogels both after preparation G_0 (solid symbols) and after equilibrium swelling in water G (open symbols) are shown as a function of the comonomer NIPA content (NIPA mol%). The circles and triangles represent the data for P(DMAEMA-NIPA) copolymer hydrogels prepared at 50 °C and at room temperature, respectively. The elastic modulus of P(DMAEMA-NIPA) hydrogels both after preparation and after equilibrium swelling in water change depending on the comonomer NIPA content used in the preparation. It is observed that the modulus of copolymer hydrogels, both G_0 and G, decrease continuously as the comonomer NIPA content increased from 0 to 80 mol%, and this result is attributed to the effective crosslink density distribution within the polymer matrix and the role of crosslinks. For P(DMAEMA-NIPA) hydrogels, using the G_0 and ν_2^0 values together with eq. (6), the effective crosslink density ν_e of copolymer hydrogels were calculated and the results were collected in Table I. The addition of a small fraction of NIPA led to a significant decrease in the effective crosslink density of P(DMAEMA-NIPA) hydrogels, ν_e. For PDMAEMA hydrogels, ν_e is about 6.50 mol/m^3 while it is 0.321 mol/m^3 for copolymer hydrogels containing 80 mol% of NIPA. This is in accord with previous findings which shows the incorporation of a hydrophilic comonomer in the structure of copolymeric hydrogels decreases the mechanical strength. Lee and Yeh reported a similar dependency of the elasticity of a series of thermoreversible copolymeric hydrogels with various molar ratios of NIPA and hydrophobic monomers. Their results

showed that the equilibrium swelling ratio decreased with an increase of the content of hydrophobic monomer, but the gel strength increased with an increase of the content of hydrophobic monomer.[22]

One can note from the results of strain-stress curves given in Figure 1, the mechanical properties of P(DMAEMA-NIPA) copolymer hydrogels is also improved by the swelling process in water. As it is seen from Figure 2 that the swelling process increases the elastic modulus of P(DMAEMA-NIPA) copolymer hydrogels. During the swelling process, the polymer chains in the network structure are forced to attain more elongated and less probable configurations. The absorption of water by the hydrogel causes the network to expand and its chains to stretch. Since, the network chains making up the network are assumed in a stretched conformation with respect to dry state, the increase of the elastic modulus of P(DMAEMA-NIPA) copolymer hydrogels is also connected with the high stretching of the network chains. Although P(DMAEMA-NIPA) copolymeric hydrogels prepared at 50 °C exhibit a low modulus of elasticity when compared with those prepared at room temperature (Figure 2), they were tough and can be compressed up to about 90% strain without any crack development. However, the hydrogels prepared at room temperature break at a strain of about 80%. The photographs in Figure 3 demonstrate how P(DMAEMA-NIPA) copolymeric hydrogels prepared at 50 °C sustain a high compression. As shown in the left panel of Figure 3, the swollen P(DMAEMA-NIPA) copolymeric hydrogels prepared at room temperature fractured under low deformation suggesting that cracks develop easily in the hydrogel structure. However, those obtained at 50 °C remain mechanically stable up to about larger compression (right panel of Figure 3). After the release of the load, it was observed that the hydrogel sample immediately recovers its original shape, which definitely contributes to the excellent mechanical properties.

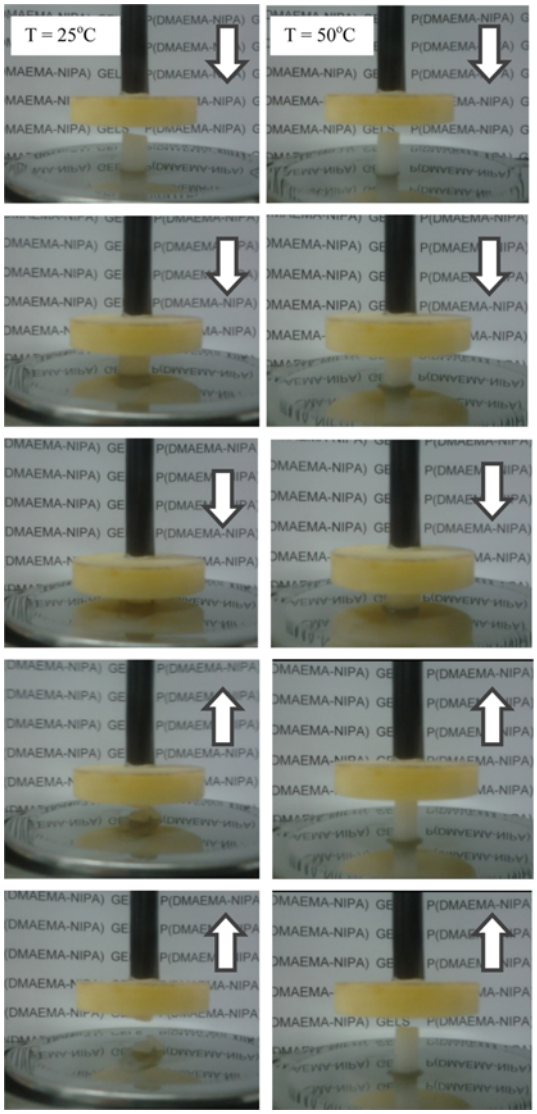


Figure 3. Photographs of P(DMAEMA-NIPA) copolymeric hydrogels formed at T_{prep}=25 °C (left panel) and at 50 °C (right panel) during the compression tests.

Equilibrium Swelling Ratio in Water and Aqueous Salt Solutions. In order to obtain the variation of the equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels by changing the comonomer NIPA concentration in the feed composition, the swelling studies were carried out in water as a function of the temperature. The effect of the temperature on the equilibrium swelling behavior of P(DMAEMA-NIPA) hydrogels is given in Figure 4. As seen, the equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels in water significantly decreased with increasing the comonomer NIPA content, especially in the range of temperature above 35 °C. The copolymeric hydrogels containing higher DMAEMA concentrations exhibited larger equilibrium swelling ratio at

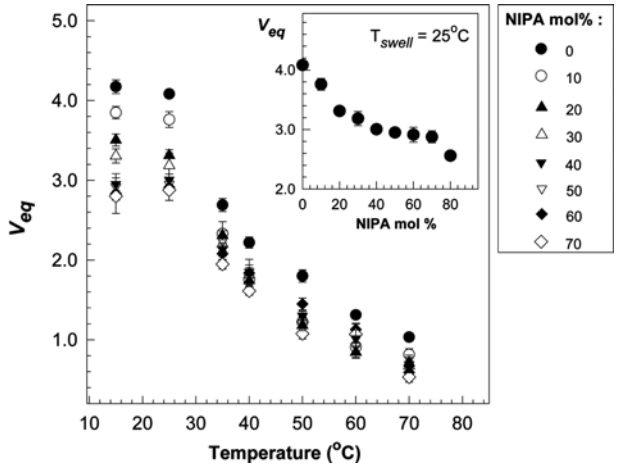


Figure 4. The equilibrium volume swelling ratio of P(DMAEMA-NIPA) copolymeric hydrogels V_{eq} in water shown as a function of the temperature. The NIPA contents of the hydrogels (NIPA mol%) are indicated in the figure. The preparation temperature of the hydrogels is 50 °C.

low temperatures. Since amino groups of NIPA and DMAEMA in the network structure form intermolecular hydrogen bond with surrounding water at low temperature, the hydrogels extend and obtain large swelling ratio; while hydrogen bonds are overwhelmed by hydrophobic interactions among hydrophobic groups over the LCST, which cause phase separation and shrinkage of the hydrogel structure.[23-25]

As can be seen from Figure 4 that the transition temperature between the swollen and shrunken state was also shifted to the lower temperatures. Since the dimethylamino groups in DMAEMA is known to be a powerful hydrogen bond acceptor, these swelling results strongly suggest efficient hydrogen bonding between amide and dimethylamino groups and the LCST shifts to the relatively lower temperature due to the formation of hydrogen bonds, which protects dimethylamino groups from exposure to water and results in a hydrophobic contribution to the LCST. Inomato *et al*. proposed that the gel bearing hydrophobic group has a larger surface area undergoes a discontinuous volume phase transition in water at lower temperatures due to the strength of the hydrophobic interactions.[23] Feil *et al*. investigated the effect of comonomer hydrophilicity and ionization on the LCST of NIPA by copolymerization with butyl methacrylate, acrylamide, acrylic acid, and diethylaminoethyl methacrylate. They found that the changes in LCST caused by the incorporation of comonomers are due to changes in overall hydrophilicity of the polymer and are not due to a direct influence of comonomer hydrophilicity or charge on the structuring of water around hydrophobic groups.[26] Moreover, in their another work related with LCST behavior of copolymers based on DMAEMA and AAm, Cho *et al*.[27] observed that the LCST of poly(DMAEMA-AAm) gel decreased with addition of AAm due to the hydrophobic contribution of hydrogen bonds between amide and *N*,*N*-dimethylamino groups. Yuk and coworkers[28] also showed that LCST of poly (*N*,*N*-dimethylaminoethyl methacrylate-ethylacrylamide) (P(DMAEMA-EAAm)) shifts to the lower temperature due to the formation of hydrogen bonds. The decrease in the LCST of PDMAEMA with the increase in EAAm content was attributed to the increase in hydrophobicity of the polymer.

Figure 4 also illustrates that the temperature increment leads to lower swelling values indicating that the temperature decrease favors the uptake of water into the hydrogel structure. It means that increasing electrostatic repulsion between charged sites on DMAEMA disrupts the hydrogen bonds between NIPA and DMAEMA. Thus, the resulting P(DMAEMA-NIPA) hydrogels become relatively hydrophobic and expel water molecules resulting in a reduced volume swelling ratio at temperatures higher than 25 °C. It was also observed that the copolymer of DMAEMA and NIPA containing both hydrophilic and hydrophobic groups exhibit strong thermosensitivity owing to the strengthening of the hydrophobic interactions with increasing temperature. In Figure 4, the swelling results of P(DMAEMA-NIPA) hydrogels carried out in water at room temperature is also shown as a function of the comonomer NIPA content as inner figure. The swelling studies showed that the incorporation of NIPA into the structure of DMAEMA changes the swelling behavior of the resulting hydrogels drastically. As can be seen from Figure 4, at a certain temperature, increasing the NIPA content of the copolymer caused a gradual decrease in the swelling ratio of the hydrogels.

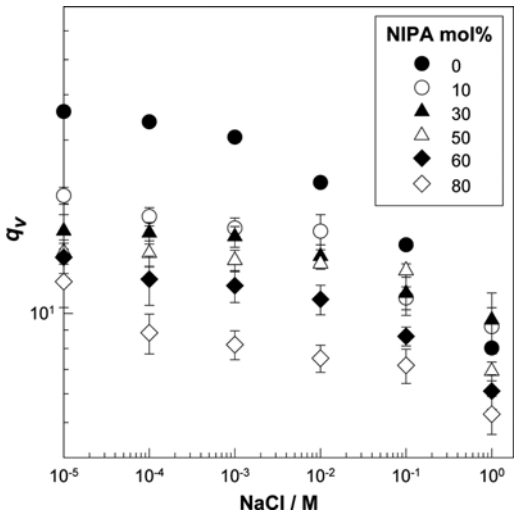


Figure 5. Variation of the volume swelling ratio q_v of P(DMAEMA-NIPA) copolymeric hydrogels in aqueous NaCl solutions with the mole fraction of NIPA used in the gel preparation.

Figure 5 shows the volume swelling ratio q_v of P(DMAEMA-NIPA) copolymeric hydrogels in aqueous NaCl solutions plotted as a function of the mole fraction of NIPA. P(DMAEMA-NIPA) hydrogels exhibit strong salt sensitive swelling behavior over the entire range of the NIPA content. The volume swelling ratio of hydrogels gradually decreased with increasing the salt concentration in the external solution. This is mainly because of the presence of strong interactions between DMAEMA and NIPA units in the copolymer stucture and the mobile ions. Due to the decrease in the difference of osmotic pressure between the network structure of the copolymer hydrogel and the external solution, that is, the water molecule is hard to infiltrate into the hydrogel structure and hence, the copolymer hydrogels tend to deswell by increasing the NaCl concentration in the external solution.

Effects of pH and Temperature on the Equilibrium Swelling Ratio. To investigate the effect of pH on the equilibrium swelling ratio, P(DMAEMA-NIPA) hydrogels are equilibrated in buffer solutions at pH ranged from 2.1 to 11.4 at room temperature. Figure 6 illustrates the equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels prepared with different NIPA concentrations. All P(DMAEMA-NIPA) hydrogels in these series showed a pH-dependent swelling transition. The hydrogels produced with higher DMAEMA concentrations exhibited larger equilibrium swelling ratio in the acidic

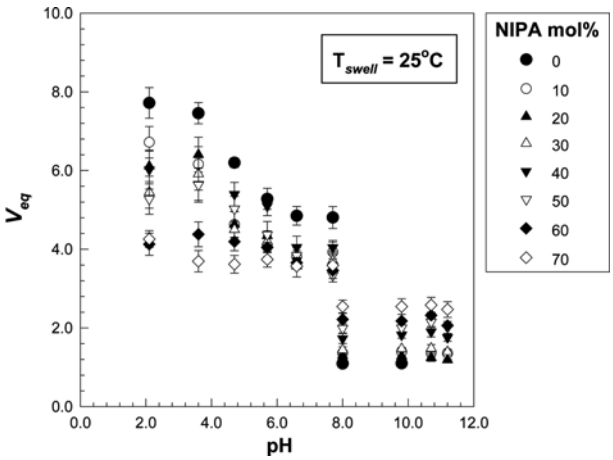


Figure 6. The effect of pH on the equilibrium swelling behavior of P(DMAEMA-NIPA) hydrogels with different NIPA concentrations. The swelling measurements were carried at room temperature. The NIPA contents of the hydrogels are already indicated in the figure.

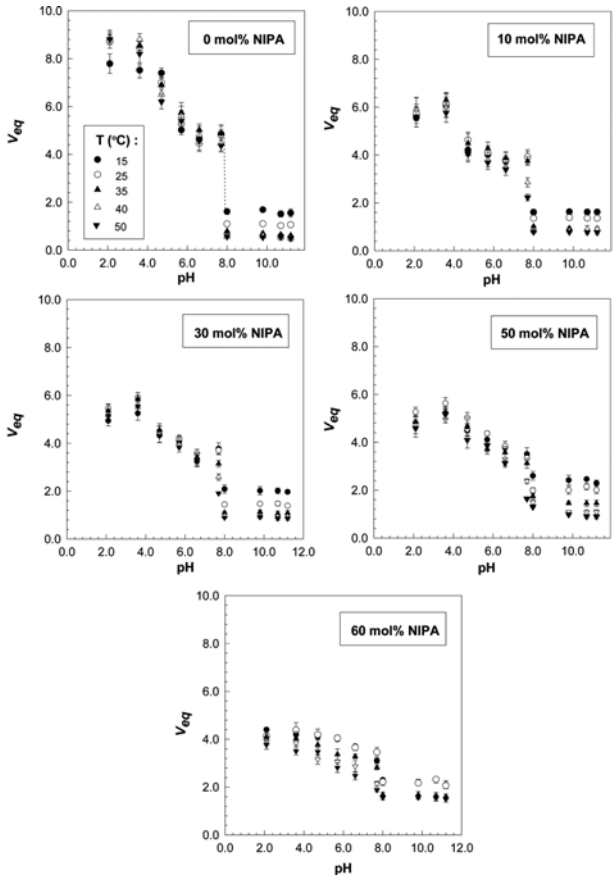


Figure 7. The equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels as a function of pH at different temperatures. The NIPA contents of the hydrogels (NIPA mol%) are already indicated in the figure.

pH region. As seen from Figure 6 that the equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels significantly decreased with increasing pH of the solution, especially in the range of pH between 8.0 and 11.4. It was also observed that P(DMAEMA-NIPA) copolymer hydrogels undergo a smooth pH-sensitive phase transition at pH between 7.7 and 8.0. The copolymer composition impacts significantly on the equilibrium swelling ratio of the hydrogels and hence, the extent of the transition changes with the NIPA content of the copolymer structure. Also, the transition for the hydrogels containing 70 mol% NIPA appears to be discontinuous while the transitions for other comonomer NIPA concentrations are continuous. Siegel and Firestone[10] investigated pH-dependent equilibrium swelling properties of hydrophobic polyelectrolyte copolymer gels and showed that the extent of the transition and the pH at which it occurs are affected by the comonomer composition.

The results in Figure 6 indicated that P(DMAEMA-NIPA) copolymer hydrogels have trends to swell faster and to higher degree at an acidic solution than at an alkaline solution. The origin of pH-dependent swelling behavior of copolymer hydrogels is attributed to the protonation of the copolymer network structure. Since the amine side groups of DMEAMA chains in the network structure are protonated under acidic conditions (pH between 2.1 and 7.7), then a higher degree of protonation in the acidic pH region provides larger swelling ratios of the hydrogels. By contrast, the most of the nitrogen atoms of DMEAMA chains in the network structure are not protonated under alkaline conditions (pH between 8.0 and 11.4). Thus, the electrostatic repulsion in the hydrogels at pH below 7.7 increases compared with that of at pH 8.0. This increase in electrostatic repulsion is a dominant driving force of the swelling of copolymeric hydrogels upon a change in pH. Figure 6 also illustrates that the increase in DMAEMA content of the copolymer provides higher degree of protonation in a certain acidic pH value, which in turn also causes an increase in the equilibrium swelling ratio.

In order to explain the temperature-dependent swelling of P(DMAEMA-NIPA) hydrogels, the pH-dependent swelling experiments were also performed in buffer solutions as a function of the temperature and the comonomer NIPA content. Figure 7 shows the effect of the temperature on the equilibrium swelling ratio of P(DMAEMA-NIPA) hydrogels in the solutions of different pH values. The NIPA contents of the hydrogels are already indicated in the figure. It was observed that the water content of the hydrogels is strongly dependent on both pH and temperature. As can be seen, it is possible to achieve a very broad range of phase transition behavior by changing the chemical composition of the hydrogels as a function of temperature. In the dual thermo- and pH-responsive P(DMAEMA-NIPA) copolymer hydrogels, DMAEMA segments respond to pH and NIPA segments respond to temperature. It can be concluded from Figure 7 that pH-induced swelling transition can be controlled by the temper-

ature due to the influence of NIPA on the ionization of DMAEMA. P(DMAEMA-NIPA) copolymer hydrogels are swollen at lower temperatures and acidic pH (lower than 7.7), and become shrunken at higher temperatures and alkaline pH (higher than 7.7).

According to the above-mentioned results in Figures 6 and 7, an appropriate balance of the hydrophilicity and hydrophobicity in the molecular structure of the polymer network is the key factor in the phase transition behavior of the resulting hydrogels. As can be seen from Figure 7, for PDMAEMA hydrogels (with 0 mol% of NIPA), a sharp pH-dependent phase transition was observed at a pH of 7.7. In their previous work, Siegel and Firestone also reported the relatively sharper volume transitions at pH of 7.0 for alkylmethacrylate-DMAEMA copolymer gels.[10] However, the phase transition of P(DMAEMA-NIPA) copolymer hydrogels completely disappears with increasing the NIPA content of the copolymer structure. As seen from the Figure 7, the pH-dependent phase transition in the hydrogels containing 60 mol% NIPA was not as sharp as those obtained with 10 mol% NIPA. Increasing the NIPA content in the copolymer structure decreased the swelling capacity of the hydrogels and the extent of the pH-sensitive phase transition. The effect of increasing temperature or NIPA content can be explained by the role of hydrophobicity in the phase transition behavior of hydrogels. At a constant pH, incorporation of the hydrophilic comonomer increases the gel hydrophilicity which in turn lowers the amount of amine side groups of DMEAMA chains in the network structure and the degree of protonation which also causes a gradual decrease in the swelling ratio of the hydrogels. It can be concluded that the concentration of DMAEMA, temperature, pH and the copolymer composition are the important factors affected on the characteristic features of the swelling and the phase transition behavior of P(DMAEMA-NIPA) copolymeric hydrogels.

Conclusions

The focus of this study is the synthesis of pH- and temperature-responsive cationic hydrogels with dual stimuli-sensitive from various molar ratios of *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) and *N*-isopropylacrylamide (NIPA). The role of the pH of solution, temperature and comonomer content in the swelling behavior and the mechanical properties of P(DMAEMA-NIPA) copolymeric hydrogels were investigated. The experiments to determine the temperature-dependent swelling of copolymeric hydrogels were performed in water at different temperatures. The rapid deswelling was observed as the temperature increased between 35 and 70 ºC and found that the equilibrium swelling ratio of copolymer hydrogels in water significantly decreased with increasing NIPA content, especially in the range of temperature above 25 ºC. pH-Dependent swelling studies of P(DMAEMA-NIPA) hydrogels investigated in buffer solutions at various temperatures as a function of the comonomer NIPA content showed that the extent of the transition from the swollen hydrophilic state to the hydrophobic state strongly depends on the comonomer composition. The resulting P(DMAEMA-NIPA) copolymer hydrogels obtained in this work showed good mechanical properties, high swelling capacities in water and also displayed strong temperature- and pH-sensitivity. Since the amino side groups of network chains in P(DMAEMA-NIPA) hydrogels are protonated at acidic pH, and on becoming hydrophilic, the copolymer hydrogels start to absorb water. However, at alkaline pH, reversed behavior is observed; the polymer becomes hydrophobic and begins to exclude water. The results provide some useful information for the preparation of dual pH- and temperature-responsive copolymeric hydrogels with tunable hydrophilicity-hydrophobicity which have the potential to be used in the controlled drug delivery systems and tissue culture substrates.

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