

# Preparation and Swelling Characterization of Poly(*n*-isopropylacrylamide)-Based Porous Hydrogels

Jia-Ming Chern, Wen-Fu Lee, Meng-Yow Hsieh

Department of Chemical Engineering, Tatung University, 40 Chungshan North Road, 3rd Section, Taipei 10452, Taiwan

Received 13 November 2003; accepted 14 January 2004

**ABSTRACT:** Nine different poly(*n*-isopropylacrylamide)-based hydrogels, including nonionic, cationic, and anionic hydrogels, were synthesized in with and without the addition of pore-forming agents. The synthesized hydrogels were characterized with dry gel density measurements, scanning electron microscopy observations, and the determination of the swelling ratio swelling kinetics. All the results showed that the cationic hydrogels had faster swelling kinetics than the anionic and nonionic hydrogels. The

addition of pore-forming agents (NaHCO<sub>3</sub> and carboxymethylcellulose) during the synthesis process led to porous hydrogels with lower dry densities, swelling ratios, and swelling kinetic parameter values. An empirical equation was developed to successfully correlate the swelling kinetic parameter with the hydrogel swelling ratio. © 2004 Wiley Periodicals, Inc. *J Appl Polym Sci* 92: 3651–3658, 2004

**Key words:** hydrogels; swelling; synthesis; density; kinetics

## INTRODUCTION

A hydrogel is a type of hydrophilic polymer with a three-dimensional structure. If a hydrogel is put in water, it will not dissolve; instead, it will swell and absorb a lot of water. The swollen volume and swelling ratio of a hydrogel depend on the hydrogel itself and the surrounding environment, including the solution temperature, pH, ionic strength, types of ions, and even the existence of an electric field.<sup>1–5</sup> For this reason, hydrogels can be used in drug release systems to obtain a desired release rate through the control of the surrounding environment.<sup>6–11</sup> Furthermore, hydrogels have been used as an artificial tissue because they can absorb and hold water, allowing oxygen and other small-molecule nutrients to pass through.<sup>12</sup>

Poly(*n*-isopropylacrylamide) (NIPAAm) is a typical thermosensitive hydrogel, possessing a lower critical solution temperature. NIPAAm hydrogels suddenly change their shape from a swollen form to a shrunken form at the transition temperature ( $\approx 32^\circ\text{C}$ ) through an increase in the incubation temperature in water. NIPAAm hydrogels, therefore, are useful in thermosensitive drug delivery systems<sup>13</sup> and separation processes.<sup>14</sup> In these systems, the substrates in NIPAAm hydrogels are squeezed out at the target tissue in a body by the shrinking of the gels in response to the temperature.<sup>15</sup>

The swelling properties of hydrogels are mainly related to the elasticity of the network, the presence of hydrophilic functional groups (e.g., —OH, —COOH, —CONH<sub>2</sub>, and —SO<sub>3</sub>H) in the polymer chains, the extent of crosslinking, and the porosity of the polymer. The physical characteristics of hydrogels, including their swelling ratio, also depend on the balance between attractive and repulsive ionic interactions and solvent-mediated effects.<sup>16</sup> Because of their rigid crystalline structure and low elasticity in polymer chains, conventional hydrogels swell very slowly, and so the time for absorbing water is long, ranging from a few hours to even days. Although such slow swelling is beneficial for many applications, there are many situations in which fast polymer swelling is more desirable. Therefore, a new generation of hydrogels, superporous hydrogels (SPHs) and SPH composites, which swell and absorb water very rapidly, has been developed.<sup>17</sup> This study was aimed at synthesizing NIPAAm-based porous hydrogels through the addition of pore-forming agents and comparing the swelling characteristics of the porous hydrogels with nonionic and ionic NIPAAm-based hydrogels.

## EXPERIMENTAL

The experimental work of this study included the synthesis of thermosensitive copolymeric hydrogels, the characterization of the synthesized hydrogels, and the measurement of the swelling kinetics of the hydrogels.

### Materials

The main monomer, *N*-isopropylacrylamide (NIPAAm), was purchased from Wako Pure Chemical Co. (Osaka,

Correspondence to: J.-M. Chern (jmchern@ttu.edu.tw).

Contract grant sponsor: Tatung University.

Contract grant sponsor: National Science Council of Taiwan.

Japan). *N,N*-(3-Dimethyl aminopropyl) acrylamide (DMAA), dimethyl amino ethyl methacrylate (DMAEMA), and propane sulfone (PS) were purchased from Tokyo Kasei Chemical Industry (Tokyo, Japan). Methyl iodide and *N,N,N',N'*-tetramethylethylenediamine (TEMED), an accelerator, were obtained from Fluka Chemical Co. (St. Gallen, Switzerland). *N,N'*-Methylenebisacrylamide (NMBA), used as a crosslinking agent, was obtained from Sigma Chemical Co. (St. Louis, MO). Ammonium persulfate (APS), used as an initiator, was also purchased from Wako Pure Chemical. The purchased NIPAAm was recrystallized in *n*-hexane before it was used. All the solvents and other chemicals were analytical-grade.

### Synthesis of the monomers

In addition to the aforementioned monomers, which were commercially available, the cationic monomer trimethyl (acrylamido propyl) ammonium iodide (TMAAI) was synthesized with DMAA, methyl iodide, and butanone (used as a solvent) in a 0°C ice bath.<sup>2</sup> The zwitterionic monomer, 3-dimethyl(methacryloxyethyl) ammonium propane sulfonate (DMAPS), was synthesized from DMAEMA, PS, and acetone (used as a solvent) in a 0°C ice bath.<sup>18</sup>

### Preparation of the nonionic copolymeric hydrogels<sup>2,3,5</sup>

The nonionic copolymeric hydrogels used in this study were prepared by free-radical polymerization in deionized water with a conductivity of 18.3 MΩ cm. NMBA (5 mol %; crosslinker), 1 mol % APS (initiator), and 1 mol % TEMED (coinitiator), with respect to the total amount of the monomer, were added to 10 mL of a 1M NIPAAm solution. The mixture was uniformly mixed in a 0°C ice bath. Then, the mixed solution was injected into the free space between two glass plates separated by a silicon spacer. The glass-plate set was put in a 25°C water bath for 24 h to form nonionic copolymeric hydrogels. The synthesized hydrogel thickness was controlled by the silicon spacer thickness. After the formation of the hydrogels, the gel membrane was cut into disks 8 mm in diameter, and they were immersed in an excess amount of deionized water for 7 days to remove the residual unreacted monomer. The swollen gel membranes were first air-dried at 25°C for 24 h and then were further dried in a vacuum oven for 48 h.

### Preparation of the ionic copolymeric hydrogels<sup>19</sup>

The ionic copolymeric hydrogels were prepared with the same procedure, except that 5 mol % NMBA, 1 mol % APS, 1 mol % TEMED, 5 mol % TMAAI, and 5 mol % DMAPS were used for the preparation of the cationic copolymeric hydrogels and 5 mol % NMBA, 1

mol % APS, 1 mol % TEMED, 5 mol % acrylic acid (AA), and 5 mol % DMAPS were used for the preparation of the anionic copolymeric hydrogels.

### Preparation of the nonionic copolymeric porous hydrogels

A 1M NIPAAm solution (10 mL) was first prepared, and 5 mol % NMBA, 1 mol % APS, 1 mol % TEMED, and 0.5 g of NaHCO<sub>3</sub> were added. The mixture was uniformly mixed in a 0°C ice bath. Then, the mixed solution was injected into the free space between two glass plates separated by a silicon spacer. The glass-plate set was put in a 25°C water bath for 24 h to form nonionic copolymeric hydrogels. The synthesized hydrogel thickness was controlled by the silicon spacer thickness. After the formation of the hydrogels, the gel membrane was cut into disks 8 mm in diameter, and they were immersed in a 6N HCl solution for 3 days for the removal of the residual unreacted monomer and for the formation of pores. The swollen gel membranes were first air-dried at 25°C for 24 h and then were further dried in a vacuum oven for 48 h. Carboxymethylcellulose (CMC; 0.05 g) was added to the polymerization mixture to further improve the water-absorbing capability.

### Preparation of the ionic copolymeric porous hydrogels

The ionic copolymeric porous hydrogels were prepared by the same procedure, except that 5 mol % NMBA, 1 mol % APS, 1 mol % TEMED, 5 mol % TMAAI, 5 mol % DMAPS, and 0.5 g of NaHCO<sub>3</sub> were used for the preparation of the cationic copolymeric porous hydrogels and 5 mol % NMBA, 1 mol % APS, 1 mol % TEMED, 5 mol % AA, 5 mol % DMAPS, and 0.5 g of NaHCO<sub>3</sub> were used for the preparation of the anionic copolymeric hydrogels. The synthesis recipes for these different hydrogels are summarized in Table I.

### Determination of the dry gel density

The dry gel densities were measured in weighing bottles with the nonpolar solvent *n*-hexane. The procedure was as follows:

1. The empty bottle weight ( $m_0$ ) was measured.
2. The weight of the bottle filled with the solvent ( $m_1$ ) was measured.
3. The weighing bottle was filled about half-way with dry gel ( $m_s$ ), the solvent was slowly added to remove the air, and the weight of the bottle filled with the solvent ( $m_2$ ) was measured.
4. The dry gel density was calculated with the following equation:

TABLE I  
Compositions of NIPAAm-Based Hydrogels

Gel code	Monomer				Crosslinking agent: NMBA (mol %) <sup>a</sup>	Initiator: APS (mol %) <sup>a</sup>	Coinitiator: TEMED (mol %) <sup>a</sup>	Pore-forming agent	
	NIPAAm (mol %)	TMAAI (mol %)	DMAPS (mol %)	AA (mol %)				CMC (g)	NaHCO <sub>3</sub> (g)
N	100	0	0	0	5	1	1	0	0
T	90	5	5	0	5	1	1	0	0
A	90	0	5	5	5	1	1	0	0
SN	100	0	0	0	5	1	1	0	0.5
ST	90	5	5	0	5	1	1	0	0.5
SA	90	0	5	5	5	1	1	0	0.5
SNC	100	0	0	0	5	1	1	0.05	0.5
STC	90	5	5	0	5	1	1	0.05	0.5
SAC	90	0	5	5	5	1	1	0.05	0.5

<sup>a</sup> Based on total monomer amounts.

$$\rho_s = \frac{m_s}{m_1 - m_2 + m_s} \rho_L \quad (1)$$

where  $\rho_s$  and  $\rho_L$  are the dry gel density and the solvent density, respectively.

### Scanning electron microscopy (SEM)

The hydrogel samples were equilibrated in deionized water for 3 days to allow the gels to reach the equilibrium swollen state. Then, the swollen gels were frozen at  $-80^\circ\text{C}$ , and this was followed by fracturing and drying. The fractured and dried specimens were coated with a gold-metal layer to improve the surface conduction, and they were examined for morphological details with a JEOL JXA 8600 SEM instrument with an acceleration voltage of 15 kV (Tokyo, Japan).

### Measurement of the swelling kinetics

The weight of the dry gel ( $W_0$ ) was determined after the gel was dried in a vacuum oven for 48 h. The dried gel was immersed in an excess amount of deionized water at  $25^\circ\text{C}$  until the swelling equilibrium was attained. The weight of the wet gel ( $W_t$ ) was determined after the removal of the surface water through blotting with filter paper. The swelling ratio (SR) was calculated with the following equation:

$$SR = \frac{W_t - W_0}{W_0} \quad (2)$$

The swelling kinetic curves of all the prepared hydrogels were measured and compared.

## RESULTS AND DISCUSSION

### Hydrogel density

Because hydrogels are capable of absorbing water, water cannot be used to measure the dry hydrogel

density. Instead, *n*-hexane was used because the hydrogels did not dissolve in it. The densities of the synthesized dry hydrogels are summarized in Table II. The density sequences of the dry hydrogels are as follows:

Hydrogel without pore-forming agents: T > A > N.  
Hydrogel with NaHCO<sub>3</sub>: ST > SA > SN.

Hydrogel with NaHCO<sub>3</sub> and CMC: STC > SAC > SNC.

These results show that the cationic hydrogels have less free volume and are more compact than the anionic and nonionic hydrogels.

The density values listed in Table II also show the following sequences:

Nonionic hydrogel: N > SN > SNC.

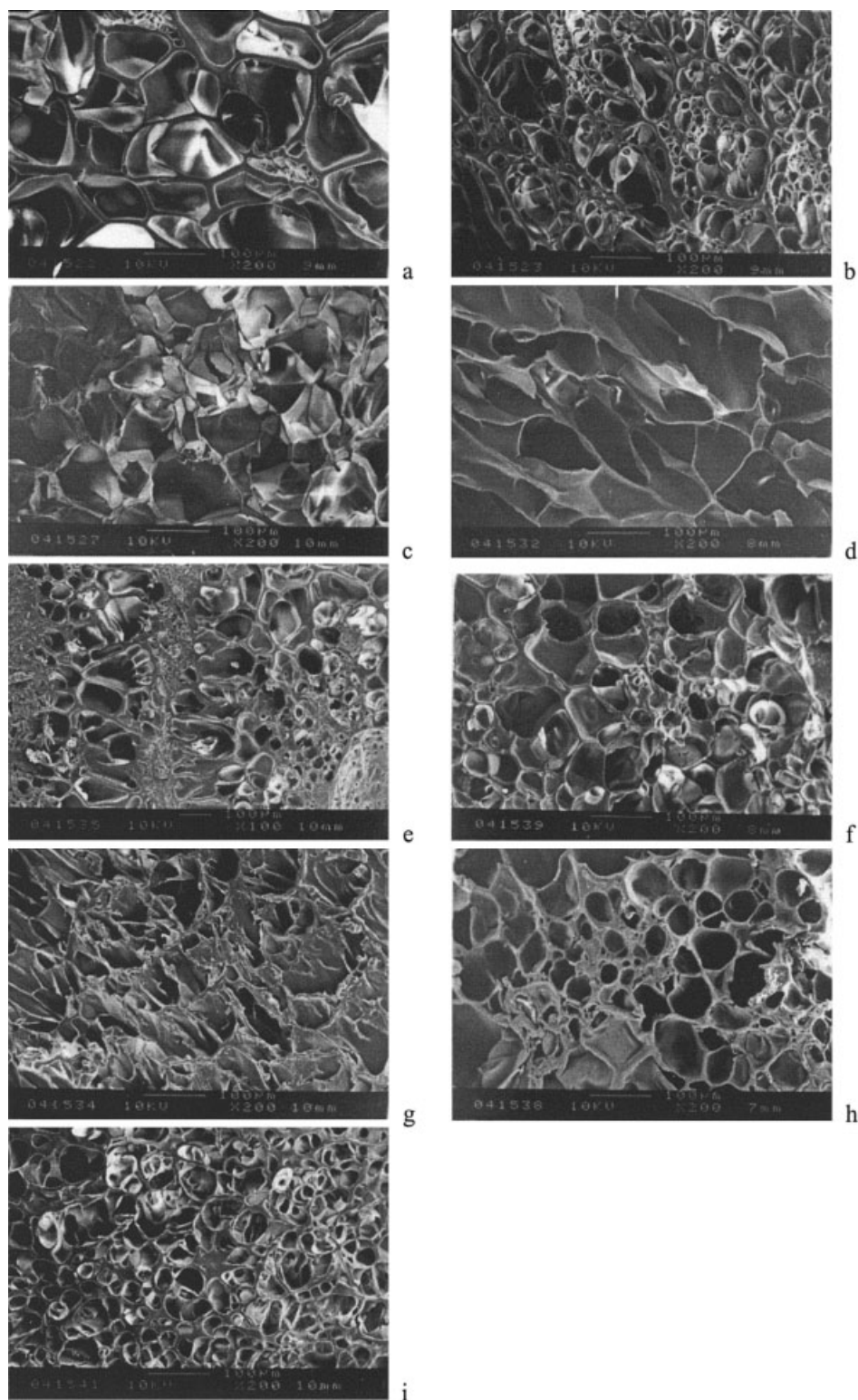
Cationic hydrogel: T > ST > STC.

Anionic hydrogel: A > SA > SAC.

These results show that the densities of the hydrogels with the addition of NaHCO<sub>3</sub> are less than those of the hydrogels without the pore-forming agents, probably because more pores are formed by the release of CO<sub>2</sub>

TABLE II  
Characteristic Parameters of the Various Hydrogels

Gel code	Dry gel density (g/cm <sup>3</sup> )	Wet gel density (g/cm <sup>3</sup> )	Swelling ratio (g/g)	<i>n</i>	<i>k</i> × 10 <sup>3</sup>
T	1.847	1.032	22.67	0.64	4.4
A	1.626	1.036	14.81	0.59	5.3
N	1.430	1.050	7.88	0.46	6.6
ST	1.603	1.019	26.57	0.65	3.6
SA	1.494	1.023	17.66	0.62	3.9
SN	1.375	1.029	10.81	0.52	3.5
STC	1.593	1.015	32.13	0.66	3.8
SAC	1.359	1.014	20.43	0.63	4.0
SNC	1.022	0.999	12.19	0.57	4.2

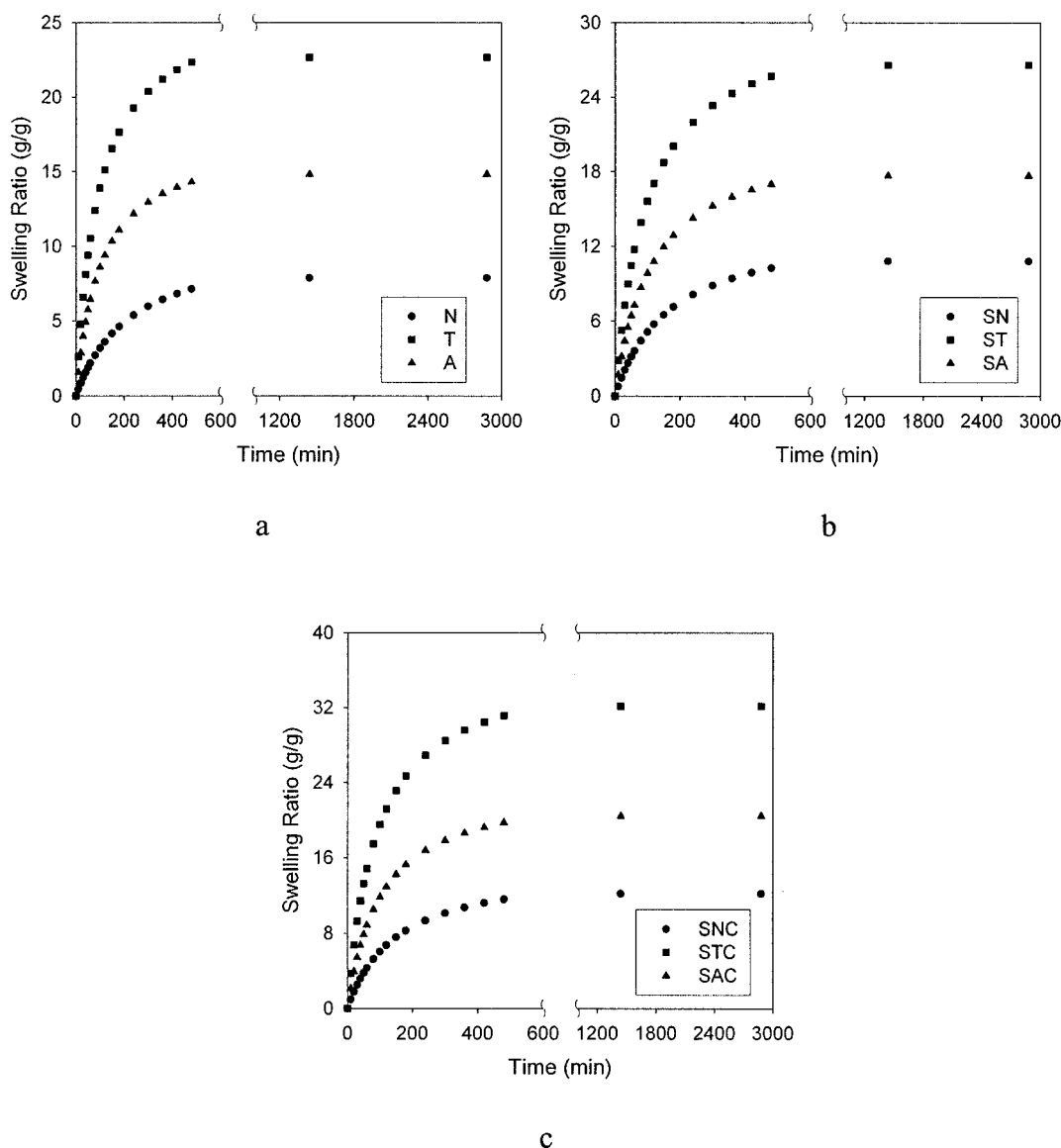


**Figure 1** SEM micrographs of gel cross sections of the hydrogels: (a) N, (b) T, (c) A, (d) SN, (e) ST, (f) SA, (g) SNC, (h) STC, and (i) SAC.

from  $\text{NaHCO}_3$  during the preparation of the porous hydrogels. The addition of the pore-forming agent, CMC, further increases the void volume fraction and, therefore, reduces the dry gel densities.

The densities of the swollen hydrogels were measured in water, and the results are listed in Table II.

The density sequence of the swollen hydrogels is slightly different from that of the dry hydrogels. However, the differences between the various hydrogels is not significant. Because all the synthesized hydrogels are capable of absorbing a lot of water, all the densities are very close to that of water.



**Figure 2** Swelling kinetic curves of the synthesized hydrogels at 25°C: (a) the hydrogels without pore-forming agents, (b) the hydrogels with NaHCO<sub>3</sub> added, and (c) the hydrogels with both NaHCO<sub>3</sub> and CMC added.

### SEM observations

As shown in Figure 1(a), the pore size of the nonionic N-type hydrogel is about 100  $\mu\text{m}$ . This size is much greater than those of the ionic T-type [Fig. 1(b)] and A-type [Fig. 1(c)] hydrogels. Because the number of hydrophilic groups in the ionic hydrogels is greater than that of the nonionic hydrogels, the network structures are denser. We can conclude that a hydrogel with a larger pore size has a lower density because a greater void volume fraction results in a lower density. Similar trends for the pore sizes of porous hydrogels can be observed in Figure 1(d–i).

Comparing the SEM micrographs of the nonionic hydrogels shown in Figure 1(a,d), we find that the added NaHCO<sub>3</sub> reacts with HCl to release CO<sub>2</sub> bubbles, which serve as pore formers. More fine pores appear in the SN-type hydrogel than in the N-type

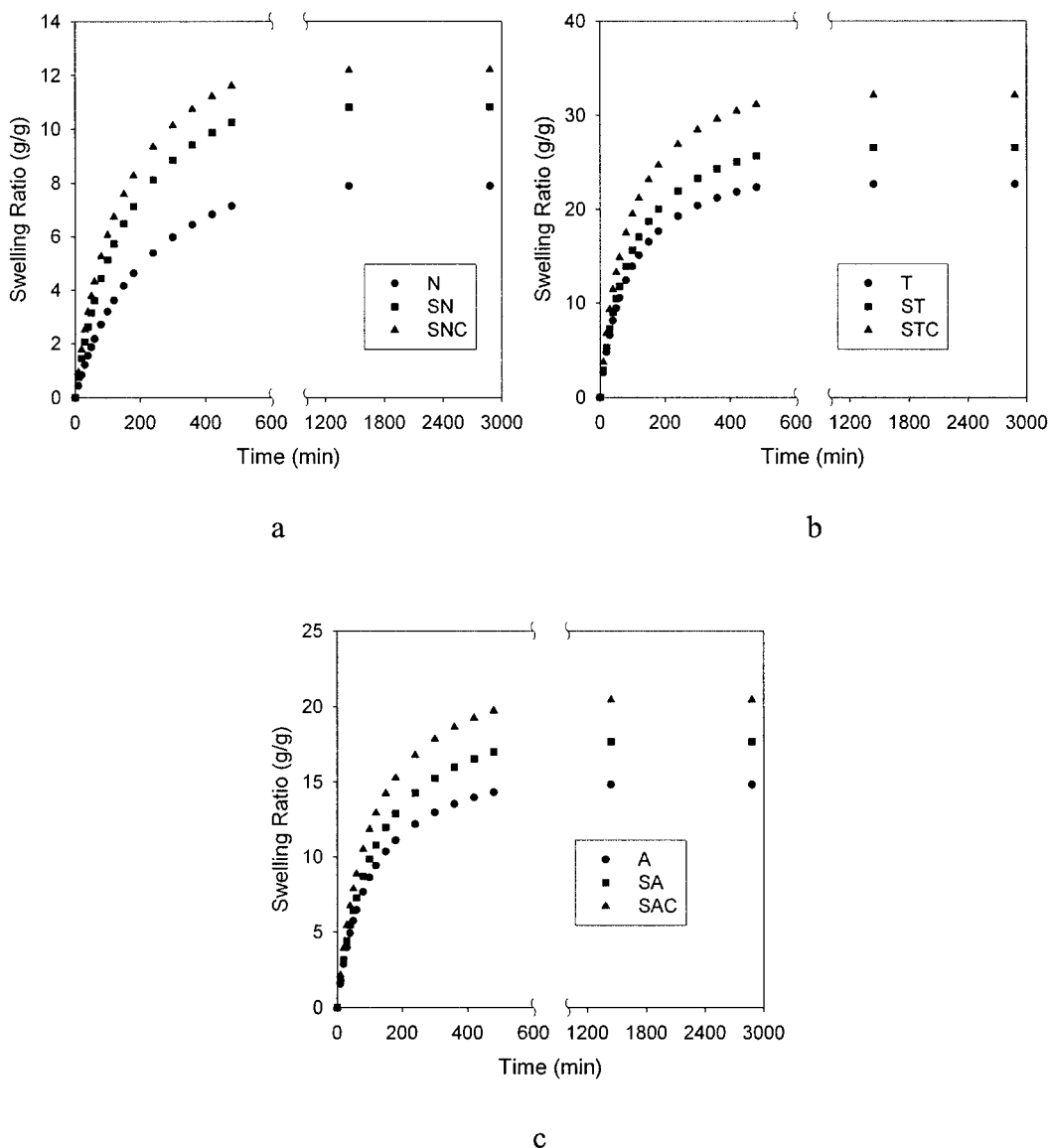
hydrogel. Added CMC produces more fine pores in the SNC-type hydrogel, as shown in Figure 1(g).

Comparing the SEM micrographs of the cationic hydrogels shown in Figure 1(b,e), we find that the added NaHCO<sub>3</sub> does not produce more fine pores, probably because too many CO<sub>2</sub> bubbles form and aggregate to form very large pores. Figure 1(h) shows that the addition of CMC seems to produce a more uniform pore size.

Comparing the SEM micrographs of the anionic hydrogels shown in Figure 1(c,f), we find that the added NaHCO<sub>3</sub> indeed results in more fine pores. The addition of CMC produces even more fine pores, as shown in Figure 1(i).

### Swelling ratios

The equilibrium swelling ratios of various hydrogels are shown in Table II. Figure 2 shows the swelling



**Figure 3** Comparison of the swelling kinetic curves of the hydrogels with and without pore-forming agents at 25°C: (a) the nonionic hydrogels, (b) the cationic hydrogels, and (c) the anionic hydrogels.

kinetic curves of the hydrogels with and without pore-forming agents. The cationic monomer produces more fine pores, which help to absorb more water than the anionic and nonionic hydrogels absorb. This result agrees with the density measurements and SEM observations. Larger swelling ratios of the ionic hydrogels can also be explained by Flory's swelling theory.<sup>20</sup>

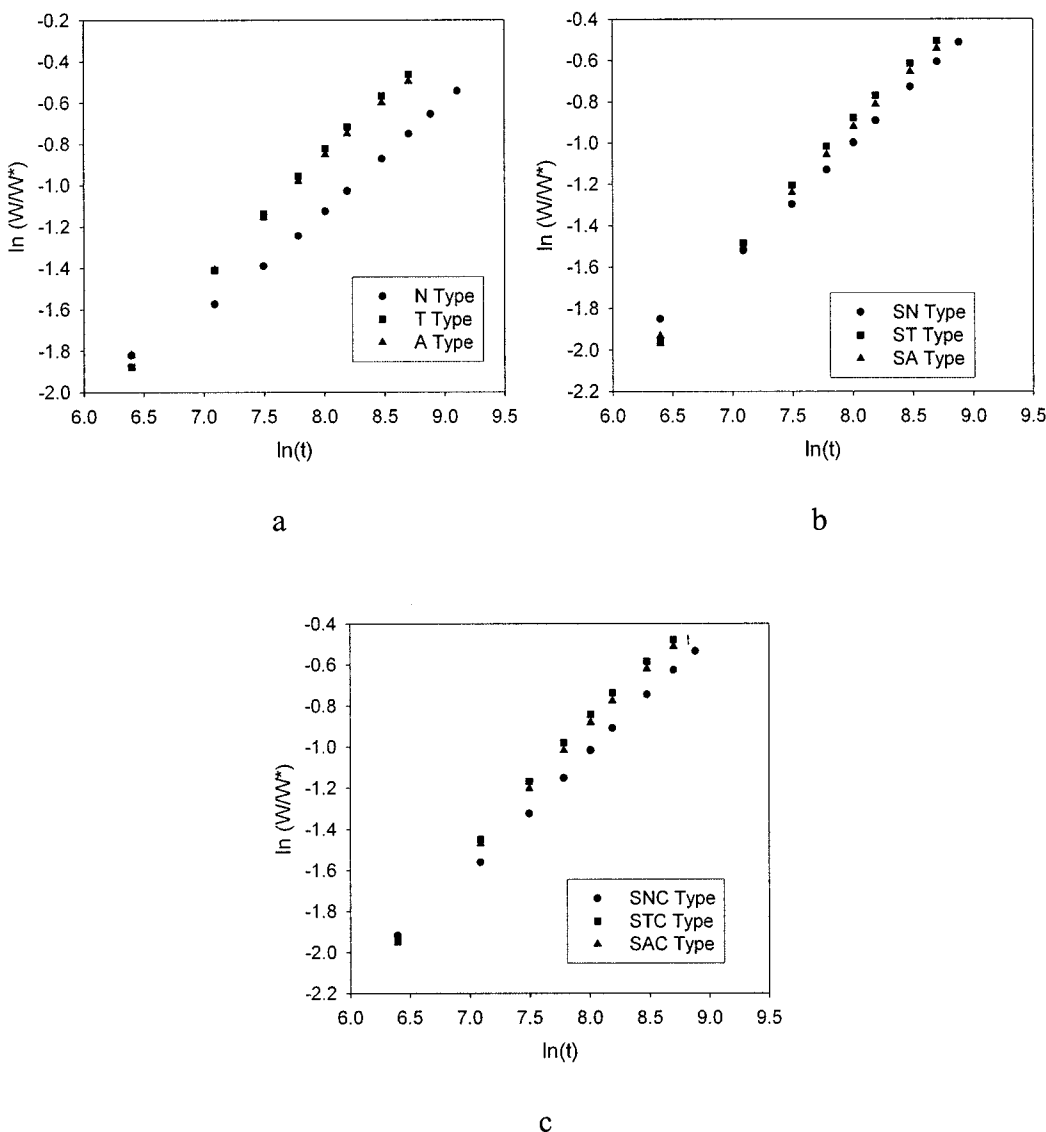
Figure 3(a,b) shows that the formation of more fine pores by CO<sub>2</sub> bubbles indeed helps with the absorption of more water. Some NaHCO<sub>3</sub> could be consumed, and this produces CO<sub>2</sub> gas before polymerization and gelation. Although we mixed the monomer solution and NaHCO<sub>3</sub> in a 0°C ice bath, we could not guarantee that no CO<sub>2</sub> was produced during this stage. Actually, we tried to add smaller amounts of NaHCO<sub>3</sub> to the monomer solution, and this resulted in hydrogels with not significantly different swelling

ratios and swelling kinetic curves. This indicated that some NaHCO<sub>3</sub> was consumed to produce CO<sub>2</sub> gas. Therefore, we added more NaHCO<sub>3</sub> to compensate for its loss. In the future, probably more NaHCO<sub>3</sub> should be added to the monomer solution to increase the porosity of the hydrogels for higher swelling ratios and quicker swelling kinetics.

### Swelling kinetics

Swelling kinetics are a complicated phenomenon. If a hydrogel is very porous and its size does not change during the swelling process, water will be absorbed into the gel by convection, and this results in a linear weight increase with time:

$$\frac{W}{W^*} = kt \quad (3)$$



**Figure 4** Linearized swelling kinetic plots of the hydrogels with and without pore-forming agents at 25°C: (a) the hydrogels without pore-forming agents, (b) the hydrogels with NaHCO<sub>3</sub> added, and (c) the hydrogels with both NaHCO<sub>3</sub> and CMC added.

where  $k$  is the rate constant and  $W$  and  $W^*$  are the amounts of water sorbed at time  $t$  and at equilibrium, respectively.

If the hydrogel swelling kinetics can be described by the Fickian diffusion of water inside the gel, the following equation can be used to fit the swelling kinetic data:<sup>21</sup>

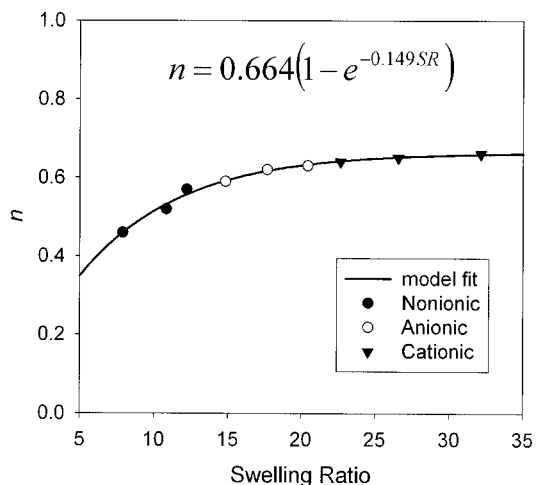
$$\frac{W}{W^*} = 4 \sqrt{\frac{Dt}{\pi L^2}} \propto t^{0.5} \text{ for } W/W^* < 0.8 \quad (4)$$

where  $D$  is the effective water diffusion coefficient in the hydrogel and  $L$  is the hydrogel thickness. If there is no convection transport and the water sorption is a pure diffusion phenomenon, then the weight of the water absorbed is proportional to the square root of time, as shown by eq. (4).

Equations (3) and (4) were first used to fit all swelling kinetics data, but they fail for some cases. Therefore, a more empirical equation was used to correlate the swelling data:<sup>22,23</sup>

$$\frac{W}{W^*} = kt^n \quad (5)$$

According to eq. (5), a plot of  $\ln(W/W^*)$  versus  $\ln(t)$  should be a straight line from which the parameters  $k$  and  $n$  can be obtained. Figure 4 shows such linear plots, and the resultant parameters are also listed in Table II. Table II shows that the  $n$  value for nonionic hydrogels is close to 0.5; this means that Fickian diffusion is the major transport mechanism in the nonionic hydrogels. That the  $n$  value is greater than 0.5 but less than 1 suggests that non-Fickian diffusion may be the primary mechanism in



**Figure 5** Effect of the hydrogel swelling ratio on the swelling kinetic parameter  $n$ .

the cationic and anionic hydrogels. The sequences of the  $n$  value shown in Table II are as follows:

Hydrogel without pore-forming agents:  $T > A > N$ .

Hydrogel with  $\text{NaHCO}_3$ :  $ST > SA > SN$ .

Hydrogel with  $\text{NaHCO}_3$  and CMC:  $STC > SAC > SNC$ .

Nonionic hydrogel:  $SNC > SN > N$ .

Cationic hydrogel:  $STC > ST > T$ .

Anionic hydrogel:  $SAC > SA > A$ .

Obviously, the cationic hydrogels with larger swelling ratios have larger  $n$  values, as also shown in Table II and Figure 5. The porous hydrogels will absorb water faster because the  $n$  values of the hydrogels with  $\text{NaHCO}_3$  are greater than those of the hydrogels without pore-forming agents. The addition of CMC results in larger  $n$  values and thus further improves the swelling kinetics. According to the correlation equation shown in Figure 5, the ultimate  $n$  value is 0.664 for an infinite swelling ratio. This suggests that non-Fickian diffusion plays an important role in the swelling kinetics. A better model of the swelling kinetics should be developed in the future to determine the water-transport mechanism in hydrogels.

## CONCLUSIONS

Various hydrogels, including nonionic, cationic, and anionic hydrogels, were prepared with NIPAAm as the main monomer. For the preparation of porous hydrogels,  $\text{NaHCO}_3$  and HCl were used to form  $\text{CO}_2$  bubbles, which helped to form more fine pores and thus enhance the water-absorbing capability of the hydrogels. The results of the swelling ratios, density measurements, and SEM observations consistently showed that the cationic hydrogels had faster swelling kinetics than the anionic and nonionic hydrogels. The addition of  $\text{NaHCO}_3$  and CMC during the synthesis process indeed helped in obtaining porous hydrogels with larger dry densities, swelling ratios, and  $n$  values.

## References

1. Peppas, L. B.; Peppas, N. A. *Biomaterials* 1990, 11, 635.
2. Lee, W. F.; Hsu, C. H. *Polymer* 1998, 39, 5393.
3. Lee, W. F.; Shieh, C. H. *J Polym Res* 1999, 6, 41.
4. Makino, K.; Hiyoshi, J.; Ohshima, H. *Colloids Surf B* 2000, 19, 197.
5. Lee, W. F.; Yuan, W. Y. *J Appl Polym Sci* 2000, 77, 1760.
6. Am Ende, M. T.; Hariharan, D.; Peppas, N. A. *React Polym* 1995, 25, 127.
7. Bell, C. L.; Peppas, N. A. *J Controlled Release* 1996, 39, 201.
8. Gutowska, A.; Bark, J. S.; Kwon, I. C.; Bae, Y. H.; Cha, Y.; Kim, S. W. *J Controlled Release* 1997, 48, 141.
9. Makino, K.; Hiyoshi, J.; Ohshima, H. *Colloids Surf B* 2001, 20, 341.
10. Lee, W. F.; Yuan, W. Y. *J Polym Res* 2000, 7, 29.
11. Lee, W. F.; Lin, Y. H. *J Appl Polym Sci* 2003, 90, 1683.
12. Li, Y.; Hu, Z.; Chen, Y. *J Appl Polym Sci* 1997, 63, 1173.
13. Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. *Advanced Drug Delivery Reviews* 1993, 11, 85.
14. Seida, Y.; Nakano, Y. *J Chem Eng Jpn* 1996, 29, 767.
15. Chiu, R. J. Master Thesis, Tatung University, 2001.
16. Barbieri, R.; Quaglia, M.; Delfini, M.; Brosio, E. *Polymer* 1998, 39, 1059.
17. Chen, J.; Park, K. *J Controlled Release* 2000, 65, 73.
18. Lee, W. F.; Tsai, C. C. *Polymer* 1994, 35, 2210.
19. Lee, W. F.; Chiu, R. J. *Mater Sci Eng* 2002, 20, 161.
20. Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: New York, 1953; Chapter 13.
21. Kabra, B. G.; Gehrke, S. H.; Hwang, S. T.; Ritschel, W. A. *J Appl Polym Sci* 1991, 42, 2409.
22. Franson, N. M.; Peppas, N. A. *J Appl Polym Sci* 1983, 28, 1299.
23. Korsmeyer, R. W.; Von Meerwall, E.; Peppas, N. A. *J Polym Sci Part B: Polym Phys* 1986, 24, 409.