# Thermoreversible Hydrogels. XVIII. Synthesis, Swelling Characteristics, and Diffusion Behaviors of Porous, Ionic, Thermosensitive Hydrogels

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**ABSTRACT:** Porous, ionic, thermosensitive hydrogels were prepared from *N*-isopropylacrylamide, a cationic monomer [trimethyl (acrylamido propyl) ammonium iodide (TMAAI)], an anionic monomer [acrylic acid (AA)], a zwitterionic monomer [*N*′,*N*′-dimethyl (acrylamido propyl) ammonium propane sulfonate], or a nonionic monomer [poly(ethylene glycol) methyl ether acrylate], and a pore-forming agent [poly(ethylene glycol) (PEG)] of different molecular weights. Some fundamental properties and dynamic swelling kinetic parameters and solute permeation for these porous gels were investigated. The results showed that the gel containing the cationic monomer TMAAI had a higher equilibrium swelling ratio. The diffusion coefficients showed that the swelling rates for the gels with the anionic monomer AA and PEG with a higher molecular weight (20,000) were faster. The results showed that the fast swelling–deswelling behavior for the porous structure gels was due to them being more available than the gels with long hydrophilic side chains. In addition, the interactive force between the solutes and gels and the solute permeation through the porous gels were investigated. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 90: 2214–2223, 2003

**Key words:** ionic hydrogels; drug release; thermosensitive

## INTRODUCTION

Stimuli-sensitive hydrogels change their structures and physical properties in response to their surrounding environment, including the pH,[1] temperature,[2] and electrical potential.[3–5] Because of these characteristics, they can be widely applied in biomaterials such as controlled drug-release and delivery systems,[6–10] on–off switching materials,[11] artificial muscles,[12] biosensors, separation, and adsorptive materials.[13–15]

A poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel in an aqueous solution exhibits a rapid and reversible hydration–dehydration change in response to small temperature changes around its lower critical solution temperature (LCST).[2] Because the isopropyl group in the PNIPAAm side chain forms a hydrophobic aggregate in water, there is phase separation above the LCST. When a swollen PNIPAAm hydrogel is immersed in water above the LCST, deswelling immediately starts at the gel surface. Then, the gel forms a dense polymer skin layer at the surface.[16] This retards the permeability of water or a solute through the gel. To promote the applications of hydrogels in drug-release or fast-response materials such as artificial muscles, reducing the formation of a dense skin layer is important. Many researchers have shown that incorporating a hydrophilic monomer[8] such as acrylic acid (AA) or a hydrophilic long-chain monomer such as poly(ethylene oxide)[17] into a PNIPAAm hydrogel can reduce the dense skin layer. In addition, using hydrogels with porous structures[18,19] to increase the surface area can also achieve rapid swelling and deswelling.

Polymer networks containing ionic moieties show a sudden or gradual change in their dynamic and equilibrium swelling properties in response to the pH[1] and ionic strength. Because of the charge repulsion in the ionic hydrogels, they can absorb a lot of water. Therefore, ionic hydrogels containing high water contents are very suitable for absorption materials and biotissue. In addition, the polymeric chains of ionic hydrogels carry charges, so they can be used in ion-exchange and separation membranes.

The amount and character of the imbibed water in a hydrogel determine the absorption and diffusion of solutes through the hydrogel. In particular, the average pore size, the pore size distribution, and the pore interconnections are important factors in solute permeation into and out of a hydrogel. These factors, in turn, are most influenced by the composition and crosslinking density of the network. The solute size and shape, its relative hydrophilic and hydrophobic character, and the availability of water molecules for hydrating the solute molecules are also important fac-

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tors governing solute permeation through any particular hydrogel.[20]

The investigation of the influence of the pore size and different charges of the ionic hydrogels on the swelling–deswelling behavior, the interactive force between the solute and gels, and the drug diffusion behavior was the main purpose of this study.

## EXPERIMENTAL

### Materials

*N*-Isopropylacrylamide (NIPAAm; Wako Pure Chemical Co., Osaka, Japan) was recrystallized in *n*-hexane before use. *N,N*-(3-Dimethyl aminopropyl) acrylamide (DMAA), propane sultone (PS), and phenol red were purchased from Tokyo Kasei Chemical Industry (Tokyo, Japan). Methyl iodide, AA, acryloyl chloride, poly(ethylene glycol) monomethyl ether (PEGME), *N,N,N′,N″*-tetramethylethylenediamine (TEMED) as an accelerator, caffeine, and crystal violet (CV) were obtained from Fluka Chemical Co. (St. Gallen, Switzerland). *N,N′*-Methylenebisacrylamide (NMBA) as a crosslinking agent and vitamin $B_{12}$ were obtained from Sigma Chemical Co. (St. Louis, MO). Ammonium persulfate (APS) as an initiator was purchased from Wako Pure Chemical. Poly(ethylene glycol) (PEG) as pore-forming agent of different molecular weights was purchased from Aldrich Chemical Co. All solvents and other chemicals were analytical-grade.

### Synthesis of the monomers

The cationic monomer trimethyl (acrylamido propyl) ammonium iodide (TMAAI), synthesized from DMAA, methyl iodide, and butanone as a solvent in a 0°C ice bath, was reported in a previous study.[3] The zwitterionic monomer *N′,N′*-dimethyl (acrylamido propyl) ammonium propane sulfonate (DMAAPS), synthesized from DMAA, PS, and acetone as a solvent in a 0°C ice bath, was also reported in a previous study.[21] The nonionic monomer poly(ethylene glycol) methyl ether acrylate (PEGMEA) was synthesized from PEGME (molecular weight = 350), acryloyl chloride, and benzene as a solvent in 0°C ice bath, as previously reported.[11]

### Preparation of the hydrogels

The hydrogels were prepared by free-radical polymerization in deionized water. Cationic and anionic hydrogels were synthesized from NIPAAm (93 mol %) with TMAAI (7 mol %) and neutralized 50 mol % AA (7 mol %), respectively. Zwitterionic and nonionic hydrogels were synthesized from NIPAAm (93 mol %) with DMAAPS (7 mol %) and PEGMEA (7 mol %). NMBA, APS, TEMED, and PEG were used as a crosslinker, an initiator, a coinitiator, and a pore-forming agent, respectively. The reaction was processed in a space with a silicon spacer between two glass plates. The polymerization was carried out for 1 day at 0°C. After the gelation was completed, the gel membrane was cut into disks (8 mm in diameter) and immersed in an excess amount of deionized water for 3 days for

**TABLE I**
**Fundamental Properties and Compositions of the Hydrogels**

| Sample code | NIPAAm (mol %) | TMAAI (mol %) | Neutralized 50% AA (mol %) | DMAAPS (mol %) | PEGMEA (mol %) | Swelling ratio (g/g) | $D \times 10^7$ ($cm^2/s$) | $n$ | Pore volume (cc/g) | Surface area ($m^2/g$) |
|---|---|---|---|---|---|---|---|---|---|---|
| N | 100 | 0 | 0 | 0 | 0 | 4.54 | 0.71 | 0.28 | — | — |
| NT | 93 | 7 | 0 | 0 | 0 | 13.00 | 1.77 | 0.53 | 1.96 | 3.51 |
| NA | 93 | 0 | 7 | 0 | 0 | 11.02 | 1.91 | 0.59 | 1.75 | 2.24 |
| ND | 93 | 0 | 0 | 7 | 0 | 5.52 | 0.92 | 0.38 | 1.38 | 1.02 |
| NP | 93 | 0 | 0 | 0 | 7 | 5.03 | 0.78 | 0.36 | 1.59 | 0.93 |
| N 2K | 100 | 0 | 0 | 0 | 0 | 4.99 | 0.74 | 0.29 | — | — |
| NT 2K | 93 | 7 | 0 | 0 | 0 | 14.66 | 2.15 | 0.53 | 2.13 | 4.68 |
| NA 2K | 93 | 0 | 7 | 0 | 0 | 13.99 | 2.34 | 0.59 | 1.97 | 3.41 |
| ND 2K | 93 | 0 | 0 | 7 | 0 | 6.38 | 1.04 | 0.34 | 1.56 | 1.79 |
| NP 2K | 93 | 0 | 0 | 0 | 7 | 6.28 | 0.84 | 0.35 | 1.89 | 1.37 |
| N 8K | 100 | 0 | 0 | 0 | 0 | 5.56 | 0.74 | 0.29 | — | — |
| NT 8K | 93 | 7 | 0 | 0 | 0 | 17.00 | 2.24 | 0.65 | 2.87 | 5.96 |
| NA 8K | 93 | 0 | 7 | 0 | 0 | 14.92 | 2.38 | 0.61 | 2.52 | 4.37 |
| ND 8K | 93 | 0 | 0 | 7 | 0 | 7.21 | 1.18 | 0.39 | 1.78 | 2.66 |
| NP 8K | 93 | 0 | 0 | 0 | 7 | 6.78 | 0.90 | 0.37 | 2.36 | 2.03 |
| N 20K | 100 | 0 | 0 | 0 | 0 | 5.61 | 0.77 | 0.30 | — | — |
| NT 20K | 93 | 7 | 0 | 0 | 0 | 18.36 | 2.29 | 0.61 | 3.87 | 9.22 |
| NA 20K | 93 | 0 | 7 | 0 | 0 | 16.92 | 2.43 | 0.63 | 3.61 | 6.24 |
| ND 20K | 93 | 0 | 0 | 7 | 0 | 7.32 | 1.30 | 0.40 | 2.30 | 4.97 |
| NP 20K | 93 | 0 | 0 | 0 | 7 | 7.15 | 0.93 | 0.39 | 3.04 | 3.77 |

the removal of the residual unreacted monomer. Swollen gels were dried at 25°C for 1 day and then were further dried in a vacuum oven for 2 days. The sample codes, compositions, and fundamental properties of the gels are listed in Table I.

### Determination of the equilibrium swelling ratio ($SR_e$)

For insight into $SR_e$ of the different ionic, thermosensitive hydrogels, the dried gels were immersed in an excess amount of deionized water at different temperatures (25–70°C) until swelling equilibrium was attained. The weight of the equilibrium wet sample ($W_\infty$) was determined after the surface water was removed via blotting with filter paper. The dry weight ($W_0$) was determined after the gel was dried in a vacuum oven for 2 days. $SR_e$ and the swelling ratio at time $t$ ($SR_t$) were calculated with the following equations:

$$SR_e = \left(\frac{W_\infty - W_0}{W_0}\right) \quad (1)$$

$$SR_t = \left(\frac{W_t - W_0}{W_0}\right) \quad (2)$$

where $W_t$ is the weight of the hydrogel at time $t$.

### Swelling and deswelling kinetics

The dried gels were immersed in excess deionized water. The swelling ratio was obtained by the weighing of the initial and swollen samples at various time intervals. The amount of water sorbed ($W_t$) was reported as a function of time, and the equilibrium sorption at infinitely long time was designated $W_\infty$. The following equation was used to calculate the diffusion coefficient ($D$) for $W_t/W_\infty \leqq 0.8$:[22]

$$\frac{W_t}{W_\infty} = \left(\frac{4}{\pi^{0.5}}\right)\left(\frac{Dt}{L^2}\right)^{0.5} \quad (3)$$

where $t$ is the time and $L$ is the initial thickness of the dried gel. To investigate the diffusion model of the gel, we fitted the initial swelling data to the exponential heuristic equation for $W_t/W_\infty \leqq 0.6$:[23,24]

$$\frac{W_t}{W_\infty} = Kt^n \quad (4)$$

where $K$ is a characteristic constant of the gel and $n$ is a characteristic exponent of the mode transport of the penetrant.

In addition, to investigate the deswelling kinetics of the hydrogels, we immersed the dried gels in excess deionized water at 25°C and then placed them in deionized water at different temperatures until the shrinkage equilibrium was attained:

$$\text{Shrinking ratio (\%)} = \frac{SR_e - SR_t}{SR_e} \times 100 \quad (5)$$

### Permeation and partition studies

The following solutes were used in permeation and partition studies: caffeine (molecular weight = 194), phenol red (molecular weight = 354), CV (molecular weight = 408), and vitamin B12 (molecular weight = 1355). Permeation studies through gel membranes were performed with a side-by-side cell that consisted of donor and receptor reservoirs. The temperature was maintained at 25°C by the circulation of a constant-temperature fluid through the water jackets. For continuous agitation, each half-cell also contained a magnetic stirrer.

Gel membranes preswollen in deionized water were placed between the two half-cells. Then, 25 mL of deionized water was poured into the receptor cell, and 25 mL of a freshly prepared drug solution (50 ppm) was poured into the donor cell. Periodically, the solution in the receptor cell was analyzed as a function of time with an ultraviolet spectrophotometer (V530, Jasco, Tokyo, Japan) at 273 nm for caffeine, at 430 nm for phenol red, at 589 nm for CV, and at 360 nm for vitamin B12. The permeability coefficients ($P$'s) of the hydrogels were determined as follows:

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = \frac{2A}{V}Pt \quad (6)$$

where $C_t$ is the concentration in the receptor cell at time $t$, $C_0$ is the initial concentration in the donor cell,

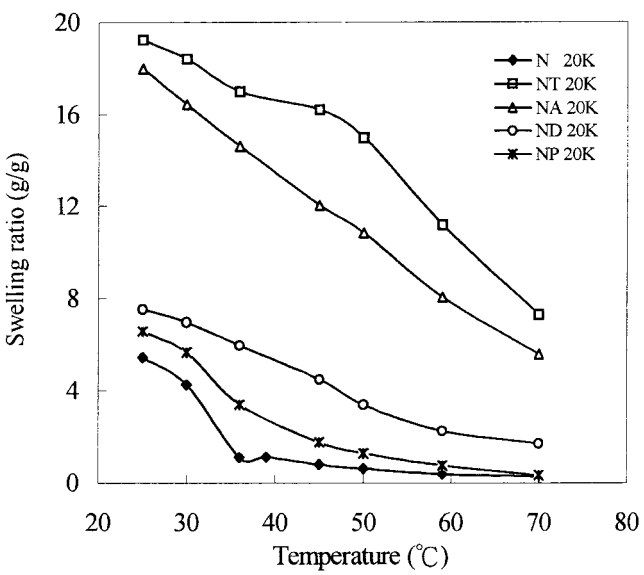


**Figure 1** Effect of temperature on $SR_e$ for the different ionic hydrogels with PEG 20K in deionized water.

$V$ is the volume of each half-cell, and $A$ is the effective area of permeation.

Partition coefficients ($K_d$'s) were determined by the solution depletion technique with an ultraviolet spectrophotometer for the measurement of the solution concentration. The hydrogels preswollen in deionized water were at equilibrium in a drug solution at 25°C. $K_d$ was calculated from a decrease in the solute concentration of the external solution:

$$K_d = \frac{(C_0 - C_S)\ V_S}{C_s V_m} \tag{7}$$

where $C_0$ and $C_s$ are the initial and final solute concentrations in solution; $V_s$ is the solution volume; and $V_m$ is the hydrogel volume.

The diffusion coefficients of the solutes ($D_s$'s) were calculated as follows:

$$D_S = \frac{P\delta}{K_d} \tag{8}$$

where $\delta$ is the gel membrane thickness. $\delta$ was measured with a micrometer at the end of the diffusion experiment.

### Morphology

Samples were equilibrated in deionized water for 2 days; the swollen gels were frozen at −80°C, fractured, and freeze-dried. The fractured specimens were examined for morphological details with scanning electron microscopy (SEM; JXA8600, JEOL, Tokyo, Japan) at an acceleration voltage of 15 kV. The specimens were coated with a layer of gold for proper surface conduction.

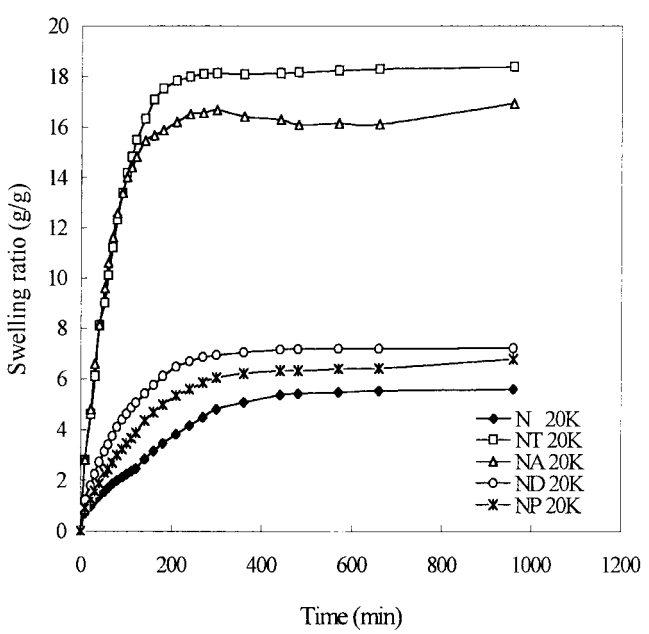


**Figure 2** Swelling ratio as a function of time for the different ionic hydrogels with PEG 20K in deionized water at 25°C.

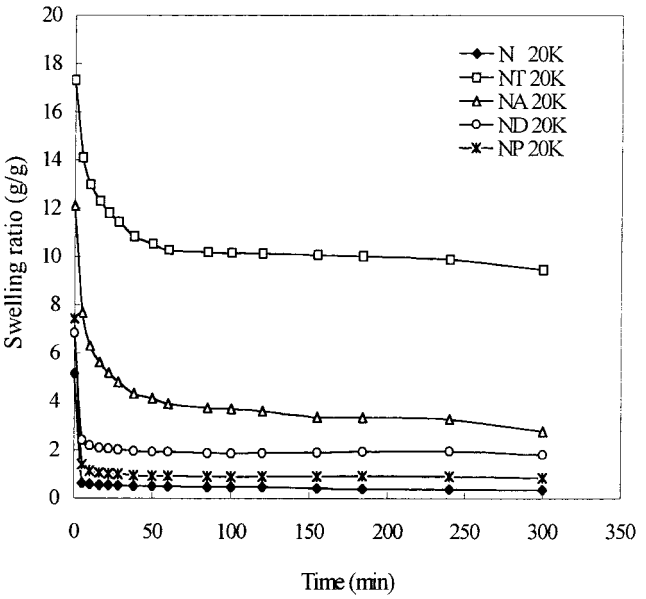


**Figure 3** Deswelling ratio as a function of time for the different ionic hydrogels with PEG 20K in deionized water at 55°C.

### Surface area and pore structure

The equipment used for the surface area and pore structure characterization was an accelerated surface area and porosimetry system (ASAP2000, Micromeritics, Georgia). It was a fully automatic and computerized system that performed the $N_2$ adsorption and processed the data simultaneously. The surface area was calculated with the Brunnauer–Emmett–Taylor (BET) equation, and the pore volume was calculated according to the Barrett–Joyner–Halenda (BJH) theory. The results are listed in Table I.[25]

## RESULTS AND DISCUSSION

### Equilibrium swelling

The effect of the temperature on $SR_e$ for these copolymeric hydrogels is shown in Figure 1. According to Flory's swelling theory for ionic gels,[26]

$$Q^{5/3} = \left[\frac{(i/2V_\mu S^{0.5})^2 + (1/2 - \chi_1)}{V_1}\right] / (\nu_e / V_0) \tag{9}$$

where $Q$ is the swelling ratio of the hydrogel, $i/V_\mu$ is the fixed charge density in the hydrogel, $S$ is the ionic strength of the external solution, $\chi_1$ is the interaction energy per solvent molecule, $V_1$ is the molar volume of the solvent, $(1/2 - \chi_1)/V_1$ is the affinity of the hydrogel, and $\nu_e/V_0$ is the crosslinking density of the

**TABLE II**
**Shrinking Ratio of Hydrogels at Various Temperatures**

| Temperature (°C) | Sample code | Shrinking ratio (%) 0–10 (min) | 10–60 (min) | 60–100 (min) | 0–100 (min) |
|---|---|---|---|---|---|
| 35 | N 2K | 20.29 | 21.65 | 8.36 | 50.30 |
| | NT 2K | 3.16 | 1.97 | 0.50 | 5.62 |
| | NA 2K | 4.29 | 5.10 | 2.36 | 11.74 |
| | ND 2K | 6.28 | 6.23 | 2.45 | 14.97 |
| | NP 2K | 10.41 | 12.16 | 4.78 | 27.35 |
| | N 8K | 42.11 | 27.70 | 4.06 | 73.87 |
| | NT 8K | 3.34 | 2.70 | 0.23 | 6.27 |
| | NA 8K | 6.05 | 4.73 | 1.18 | 11.95 |
| | ND 8K | 5.76 | 7.68 | 2.29 | 15.73 |
| | NP 8K | 9.95 | 12.59 | 4.29 | 26.83 |
| | N 20K | 53.19 | 15.65 | 2.82 | 71.67 |
| | NT 20K | 3.11 | 3.74 | 0.50 | 7.34 |
| | NA 20K | 5.71 | 5.03 | 1.71 | 12.44 |
| | ND 20K | 7.05 | 6.75 | 1.18 | 14.97 |
| | NP 20K | 10.69 | 11.17 | 3.46 | 25.31 |
| 45 | N 2K | 32.39 | 30.19 | 7.55 | 70.13 |
| | NT 2K | 8.86 | 6.94 | 1.93 | 17.73 |
| | NA 2K | 14.37 | 16.05 | 8.14 | 38.56 |
| | ND 2K | 17.21 | 17.36 | 8.56 | 43.13 |
| | NP 2K | 31.32 | 28.33 | 10.88 | 70.53 |
| | N 8K | 84.02 | 3.04 | 0.51 | 87.57 |
| | NT 8K | 8.41 | 6.42 | 1.53 | 16.36 |
| | NA 8K | 18.43 | 19.60 | 5.64 | 43.67 |
| | ND 8K | 20.80 | 19.44 | 4.82 | 45.06 |
| | NP 8K | 51.16 | 25.37 | 2.95 | 79.49 |
| | N 20K | 85.91 | 3.12 | 0.45 | 89.47 |
| | NT 20K | 9.44 | 6.77 | 0.75 | 16.96 |
| | NA 20K | 17.40 | 18.66 | 4.48 | 40.53 |
| | ND 20K | 28.76 | 15.29 | 2.89 | 46.94 |
| | NP 20K | 51.46 | 18.41 | 3.51 | 73.38 |
| 55 | N 2K | 37.35 | 35.82 | 6.38 | 79.55 |
| | NT 2K | 15.75 | 15.25 | 3.74 | 34.75 |
| | NA 2K | 48.83 | 25.67 | 3.98 | 78.48 |
| | ND 2K | 26.16 | 29.68 | 8.30 | 64.14 |
| | NP 2K | 46.20 | 37.06 | 3.19 | 86.45 |
| | N 8K | 87.25 | 1.34 | 0.20 | 88.79 |
| | NT 8K | 16.35 | 12.96 | 3.46 | 32.77 |
| | NA 8K | 33.42 | 28.02 | 5.21 | 66.66 |
| | ND 8K | 41.26 | 25.06 | 2.72 | 69.04 |
| | NP 8K | 74.40 | 13.16 | 1.59 | 89.15 |
| | N 20K | 88.60 | 1.67 | 0.56 | 90.83 |
| | NT 20K | 25.10 | 15.72 | 0.61 | 41.43 |
| | NA 20K | 47.78 | 19.83 | 1.72 | 69.33 |
| | ND 20K | 68.14 | 3.87 | 0.87 | 72.88 |
| | NP 20K | 84.78 | 2.81 | 0.28 | 87.87 |

hydrogel. Therefore, the swelling ratio is related to the charge density of the hydrogel, the crosslinking density, and the affinity of the gel for water from eq. (9). The crosslinking density and ionic strength of the external solution in these hydrogel systems are fixed; therefore, the swelling ratio is only affected by the charge density and affinity of the hydrogels. When a dry hydrogel begins to absorb water, the water molecules first hydrate the most polar, hydrophilic groups, which are the ionic and hydrogen-bonding groups. This kind of water is sometimes called *primary bound water*. After those group are hydrated, the chains begin to expand, and as the hydrophobic groups are exposed to water molecules, they interact via hydrophobic interactions, leading to a kind of bound water coating the surroundings of those groups. This kind of water is often called *secondary bound water*. These two types of water are often combined and simply called *bound water*.[20] NT and NA are hydrophilic, ionic hydrogels. Besides hydrogen bonding, ionic bonding exists between them and the water molecules. Therefore, the hydrophilicity of NT and NA gels is very strong, and they can combine with a lot of bound water. Consequently, the swelling ratios of the ionic hydrogels are large. The swelling ratio for the ND gel is not affected by the net charge in the gel because the net charge of DMAAPS is zero. Therefore, the swelling ratio is related to the affinity of the ND gel toward water. Similarly, the swelling ratio for the NP gel is also related to the affinity of the gel toward water because the PEGMEA component is a nonionic monomer. The results shown in Figure 1 indicate that the swelling ratios and hydrophilicity for these gels in deionized water are in the order of NT > NA > ND > NP > N.

The LCST of a PNIPAAm gel in an aqueous solution is around 34°C. That is, when the temperature is 34°C, the outside aqueous solution can supply enough thermal energy to the hydrogel to break up the hydrogen bonding between the PNIPAAm gel and water molecules, and the hydrogel changes its hydrophilic state into a hydrophobic state. Therefore, incorporating a hydrophilic monomer into the PNIPAAm hydrogel can make the hydrogen bonding stronger between the hydrogel and water molecules. To break up the hydrogen bond-

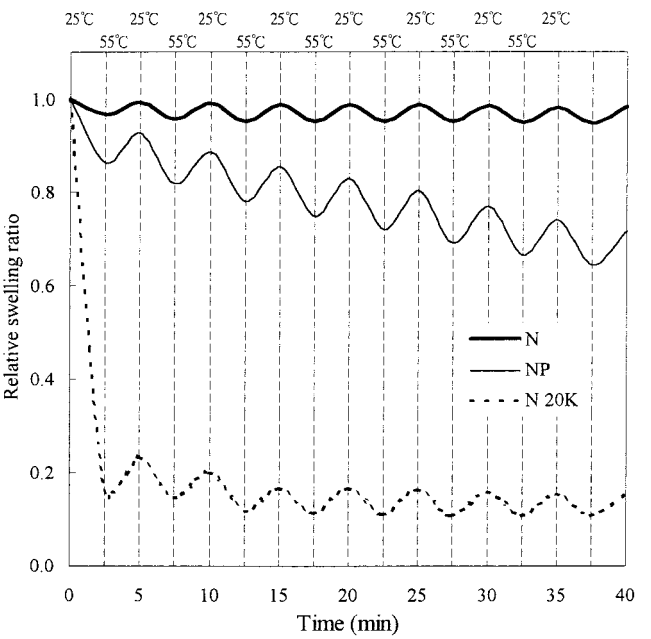


**Figure 4** Fast swelling–deswelling kinetics for the PNIPAAm gel, nonionic hydrogel, and PNIPAAm gel with PEG 20K by temperature modulation from 25 to 55°C.

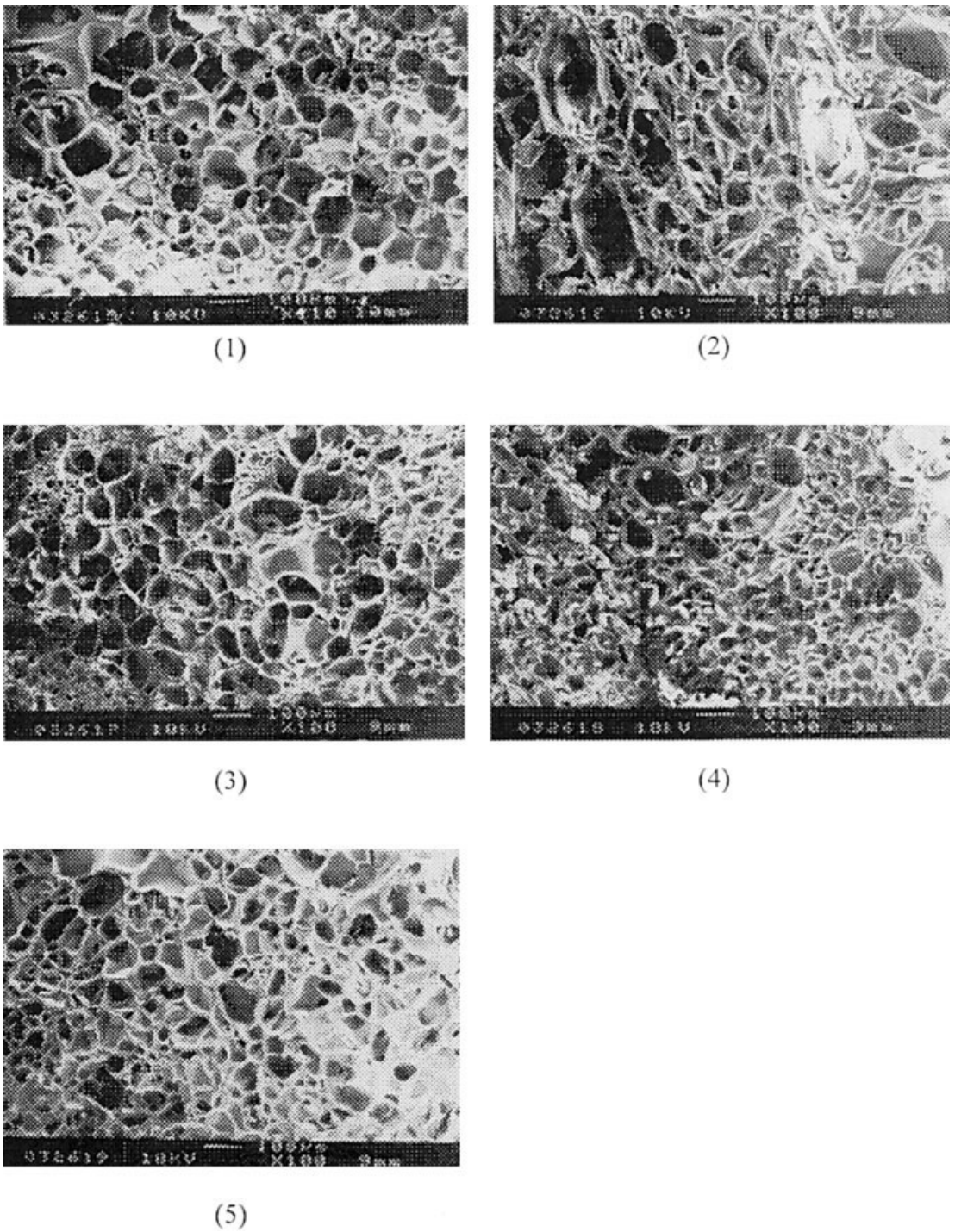


**Figure 5** SEM micrographs of cross sections of the gels (100× magnification): (1) N 8K, (2) NT 8K, (3) NA 8K, (4) ND 8K, and (5) NP 8K.

ing, it needs more thermal energy, and the LCST of the hydrogel would become higher. When the thermal energy of the outside aqueous solution is not enough, the hydration–dehydration change of the hydrogel is not obvious. Therefore, the differences in the LCSTs for copolymeric gels will appear with different hydrophilic degrees of the incorporating monomer. Figure 1 shows that the LCSTs for other hydrogels are higher than that for the PNIPAAm hydrogel, and the LCSTs of the ionic hydrogels, NT and NA, are not obvious below 70°C. Moreover, NIPAAm is the main component in these copolymeric gels, and so the swelling ratio decreases with an increase in the temperature.

### Swelling and deswelling kinetics

The swelling ratios as a function of time for the copolymeric gels in deionized water are shown in Figure

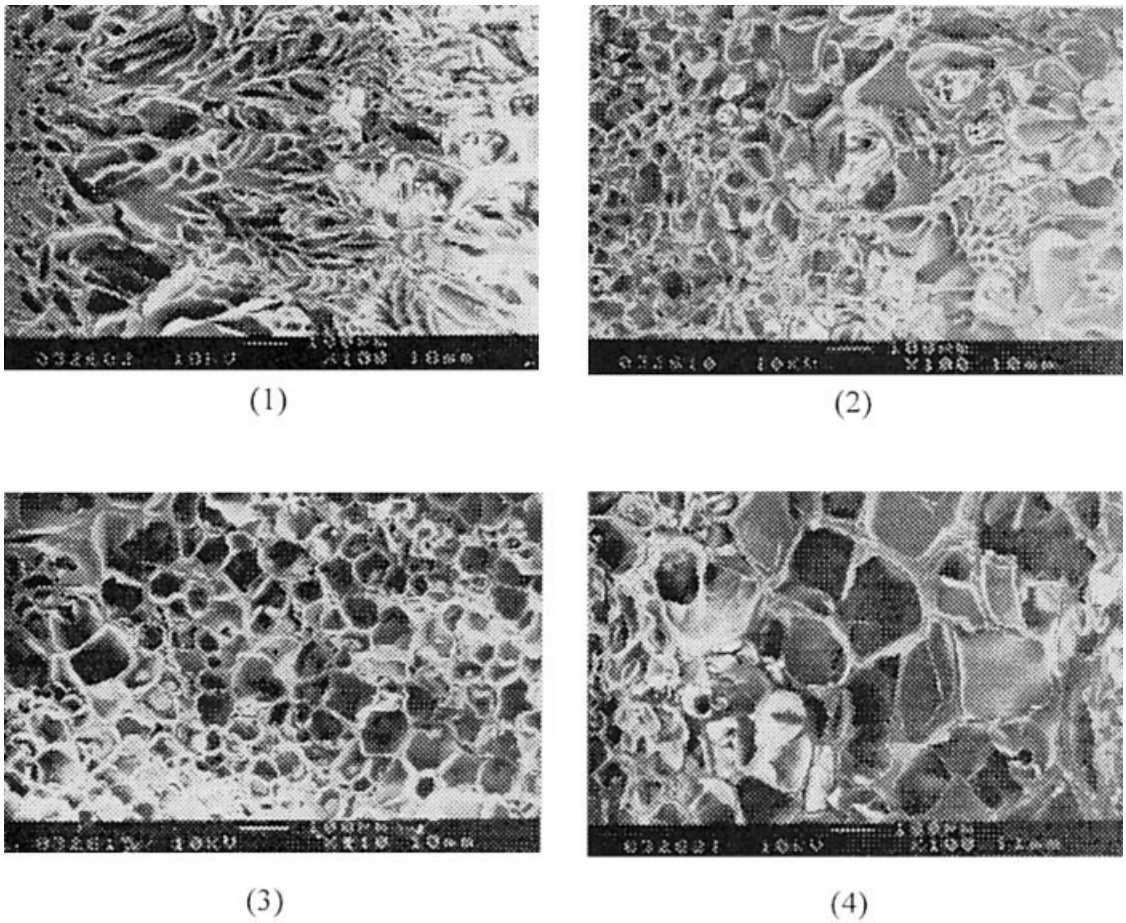


**Figure 6** SEM micrographs of cross sections of the gels (100× magnification): (1) N, (2) N 2K, (3) N 8K, and (4) N 20K.

2. The $n$, $K$, and $D$ values calculated from eqs. (2) and (3) are listed in Table I. The results show that the $D$ values for the copolymeric gels in deionized water are in the order of NA > NT > ND > NP > N. This shows that the swelling ratio of the cationic hydrogel (NT) is the highest, but the rate of water penetrating into a gel is highest for the anionic hydrogel (NA) during the swelling process. The swelling rate also increases with an increase in the pore sizes of the gels. Alfrey et al.[27] distinguished three classes of diffusion according to the relative rates of diffusion and polymer relaxation. First, there is Fickian diffusion ($n$ = 0.5), in which the rate of diffusion is much smaller than that of relaxation. In this case, the system is controlled by a diffusion phenomenon. Second, there is case II diffusion ($n$ = 1.0), the other extreme, in which the diffusion process is very fast in comparison with the relaxation process. The controlling step is the velocity of an advancing front, which forms the boundary between a swollen gel and a glassy core. Finally, non-Fickian diffusion ($n$ = 0.5–1.0) describes those cases in which the diffusion and relaxation rates are comparable. Therefore, the results shown in Table I indicate that the transport mechanism of PNIPAAm, zwitterionic, and nonionic hydrogels with low swelling ratios belong to Fickian transport. Cationic and anionic hydrogels belong to non-Fickian diffusion. The results also indicate that the $n$ values increase with an increase in the pore size of the gels.

**TABLE III**
**$K_d$ of Various Solutes in the Ionic Hydrogels**

| Sample code | $K_d$ | | | |
|---|---|---|---|---|
| | Caffeine | Vitamin $B^{12}$ | CV | Phenol red |
| N 2K | 2.81 | 2.30 | 3.39 | 1.39 |
| NT 2K | 1.68 | 1.95 | 0.16 | 28.98 |
| NA 2K | 2.08 | 1.93 | 758.19 | 0.51 |
| ND 2K | 2.56 | 2.22 | 2.15 | 1.45 |
| NP 2K | 2.78 | 2.53 | 21.83 | 1.65 |
| N 8K | 2.56 | 2.52 | 3.16 | 1.47 |
| NT 8K | 1.67 | 1.72 | 0.30 | 30.54 |
| NA 8K | 1.92 | 1.94 | 767.63 | 0.66 |
| ND 8K | 2.33 | 2.29 | 2.64 | 1.46 |
| NP 8K | 2.44 | 2.46 | 21.05 | 1.79 |
| N 20K | 2.70 | 2.85 | 3.23 | 1.43 |
| NT 20K | 1.58 | 1.55 | 0.29 | 32.14 |
| NA 20K | 1.71 | 1.77 | 772.39 | 0.97 |
| ND 20K | 2.40 | 2.28 | 2.17 | 1.73 |
| NP 20K | 2.41 | 2.48 | 15.13 | 1.80 |

The results given in Figure 3 and Table II show that the shrinkage ratios of the hydrogels at high temperatures are affected by their hydrophilicity. The hydro-

**TABLE IV**
**$K_d$ of Various Solutes in the Ionic Hydrogels at Different Temperatures**

| Temperature (°C) | Sample code | $K_d$ | | |
|---|---|---|---|---|
| | | Caffeine | CV | Phenol red |
| 25 | N 20K | 2.70 | 3.23 | 1.43 |
| | NT 20K | 1.58 | 0.29 | 32.14 |
| | NA 20K | 1.71 | 772.39 | 0.97 |
| | ND 20K | 2.37 | 2.17 | 1.80 |
| | NP 20K | 2.41 | 15.13 | 1.73 |
| 35 | N 20K | 1.32 | 13.70 | 2.64 |
| | NT 20K | 0.70 | 0.39 | 33.61 |
| | NA 20K | 0.72 | 2381.06 | 0.96 |
| | ND 20K | 0.94 | 3.01 | 2.03 |
| | NP 20K | 0.96 | 27.93 | 2.35 |
| 45 | N 20K | 1.05 | 14.26 | 2.89 |
| | NT 20K | 0.45 | 0.63 | 57.85 |
| | NA 20K | 0.48 | 2663.13 | 1.22 |
| | ND 20K | 0.62 | 7.63 | 2.60 |
| | NP 20K | 0.83 | 58.06 | 3.40 |

philicity of the gels is lower and the shrinkage ratio of the gels is larger when they are immersed at the same high temperature. Therefore, the shrinkage ratios for the copolymeric gels in deionized water are in the order of N > NP > ND > NA > NT. The results in Table II also show that the shrinkage ratios for the hydrogels are higher when PEG 20K is incorporated. In addition, NIPAAm is the main component of the hydrogels. Therefore, all the hydrogels still possess thermoreversibility. Figure 4 shows the fast swelling–deswelling kinetics for the N gel, N 20K gel, and nonionic NP gel by temperature modulation from 25 to 55°C. The results show a small swelling–deswelling range of the N gel and a small shrinkage ratio range. As the LCST of the PNIPAAm gel (N gel) is around 34°C, when the swollen hydrogel us immersed in the 55°C water, the surface of the hydrogel immediately dehydrates to form the hydrophobic skin layer, which blocks the inner water flow out of the hydrogel. When the hydrogel is immersed in 25°C water again, the water molecules also first hydrate with the surface of the hydrogel. Therefore, the hydration–dehydration change occurs on the surface of the hydrogel in a brief time, and it causes the small swelling and deswelling, small shrinkage ratio range, and constant relative swelling ratio of the N gel. Kaneko and coworkers[17,28] reported that incorporating a hydrophilic monomer or a hydrophilic long-chain monomer into a PNIPAAm hydrogel could lead to a weaker hydrophobic skin layer on the surface of the hydrogel. The water can easily flow out of the hydrogel along the hydrophilic side chains. The NP gel incorporates a hydrophilic long-chain monomer, PEGMEA, into the PNIPAAm hydrogel. Therefore, a higher shrinkage ratio and a larger swelling–deswelling range are observed, and the relative swelling ratio of the NP gel decreases with increasing time. Adding a pore-forming agent, PEG 20K, to the PNIPAAm hydrogel can lead to the N 20K gel with a porous structure and increase the surface area of the hydrogel. Therefore, when the N 20K gel is immersed in 55°C water, more water molecules in the hydrogel can obtain thermal energy to break up the hydrogen bonding between the hydrogel and water molecules, and more water can flow out of the gel. Therefore, the shrinkage ratio of N 20K is the highest of the three gels, and the swelling–deswelling change in a short time for the N 20K gel is more obvious than for the N gel.

### SEM observations

To prove that hydrogels with high swelling ratios and hydrogels prepared with PEG of higher molecular weights have larger pore sizes, we took SEM images of the morphologies of swollen and freeze-dried gels. Figures 5 and 6 show that porous hydrogels with high swelling ratios have larger pore sizes, and the pore sizes in porous gels increase with an increase in the molecular weight of PEG added during the gel preparation. The pore volume and surface area of the gels are shown in Table I.

### Effect of the interactive force between the solute and gel on $K_d$ of the solute in the ionic gels

One of the changing factors of solute diffusion behaviors in gels is the interactive force. Kim et al.[29] found a stronger interactive force between drugs and gels for $K_d > 1$ with an experiment involving a hydrophilic

**TABLE V**
**$P$, $K_d$, and $D_s$ Values of Various Solutes Permeating Through Hydrogels with Different Charges**

| | | Caffeine | CV | Phenol red | Vitamin B12 |
|---|---|---|---|---|---|
| $P \times 10^7$ (cm s$^{-1}$) | NT 20K | 150 | 3 | 315 | 63 |
| | NA 20K | 147 | 10 | 30 | 35 |
| | ND 20K | 121 | 54 | 432 | 33 |
| $K_d$ | NT 20K | 1.58 | 0.29 | 32.14 | 1.55 |
| | NA 20K | 1.71 | 772.39 | 0.97 | 1.77 |
| | ND 20K | 2.40 | 2.17 | 1.73 | 2.28 |
| $D_S \times 10^7$ (cm$^2$ s$^{-1}$) | NT 20K | 10.73 | 1.21 | 1.13 | 4.95 |
| | NA 20K | 9.89 | 0.002 | 3.49 | 2.61 |
| | ND 20K | 5.24 | 2.21 | 25.22 | 1.57 |

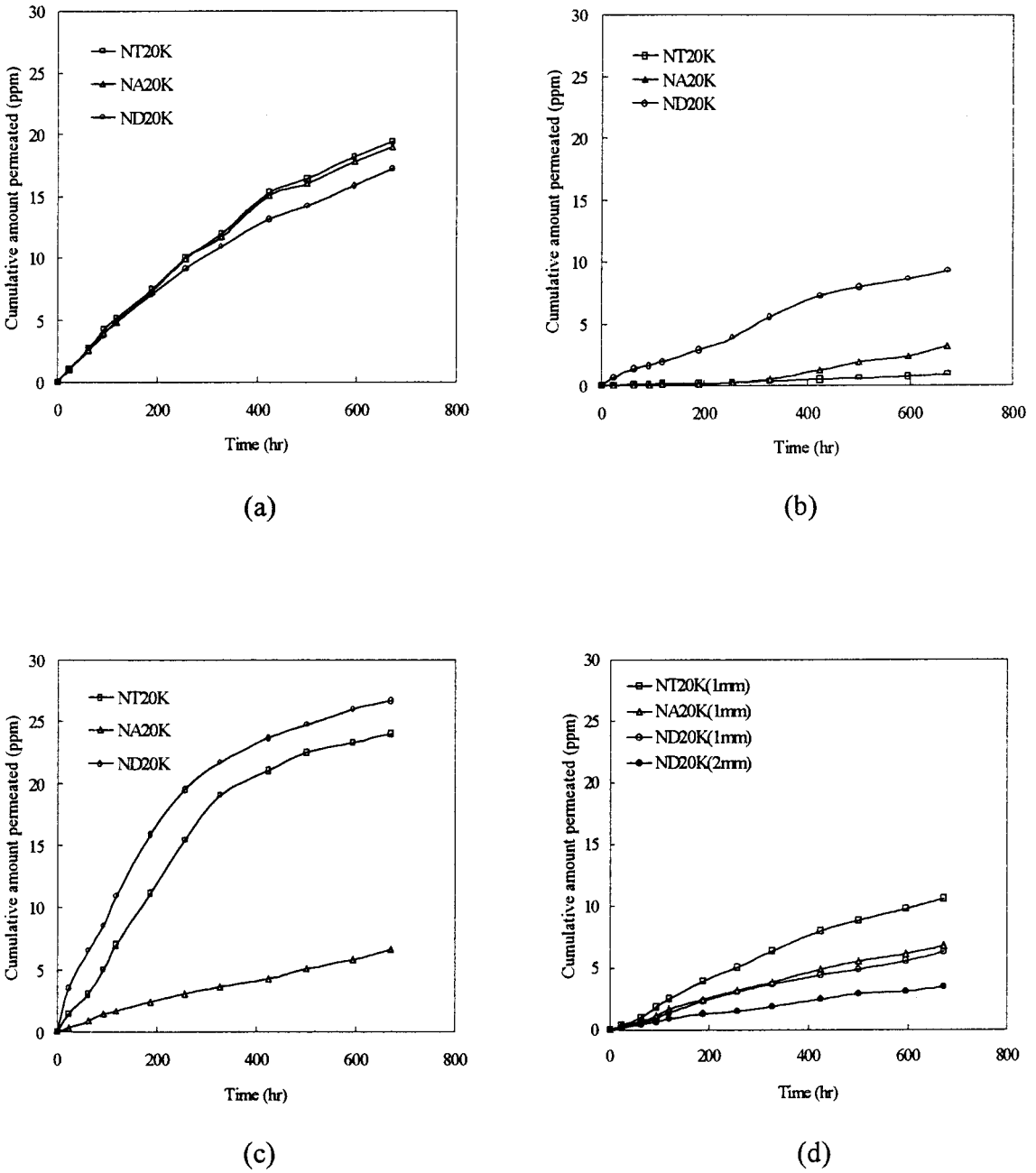


**Figure 7** Amounts of the different kinds of solutes permeating through the hydrogels with different charges as a function of time in (a) caffeine, (b) CV, (c) phenol red, and (d) vitamin B12.

carbohydrate solute and a hydrophobic steroid solute. For the chemical potential energy, solutes tend to stay in the solution phase because $K_d$ is less than 1. The results of the interactive force between the solute and gels on $K_d$ of the solute in the gels are given in Table III. For caffeine and vitamin B12 (molecular weight = 1355) solutions, the $K_d$ values in the gels are in the order of N > NP > ND > NA > NT. This indicates that the interactive force between the hydrogels and nonionic drugs such as caffeine and vitamin B12 is in the order of N > NP > ND > NA > NT. This also shows that the interactive force decreases with the increasing affinity of the hydrogel. However, the caffeine release profile is not significantly affected by the charges in the gels. For ionic drugs such as CV and phenol red, the interactive force between the drug solute and the hydrogel with a different electric charge is affected by the electrostatic attraction. For example, CV easily combines with the NA gels. Therefore, $K_d$ of CV in the NA gels is very large (e.g., 758.2, 767.6, and 772.3 for NA 2K, NA 8K, and NA 20K, respectively). When the drug solutes and the hydrogel have the same electric charge, the solute is not easily loaded into the hydrogel. Therefore, $K_d$ of the solutes in the gels is very small. For example, $K_d$ of phenol red in the NA gels is 0.51, 0.66, and 0.97 for NA 2K, NA 8K, and

NA 20K, respectively. Therefore, the ionicity of the solutes profoundly affects the release behavior of the solutes in the gels. Table IV shows $K_d$ at different temperatures. For the nonionic solute caffeine, $K_d$ decreases with increasing temperature. This is due to the fact that caffeine and hydrogel combine with hydrogen bonding. The hydrogen bonding between them is easily broken when the temperature increases; then, the interactive force between the solute and gel becomes smaller. However, for ionic solutes such as CV and phenol red, $K_d$ increases with increasing temperature. Prausnitz et al.[30] reported that a rising temperature increased $K_d$ between a polyelectrolyte hydrogel and an ionic solute.

### Solute permeation through the hydrogels

Table V shows $K_d$, $P$, and $D$ for the NT, NA, and ND gels, and Figure 7 shows diffusion experiments for the solutes caffeine, CV, phenol red, and vitamin B12 through gel membranes at 25°C. Figure 7(a,d) shows the diffusion of the nonionic drug solutes caffeine and vitamin B12. When the hydrogels have a larger swelling ratio, more solute can pass through the gel membranes. Therefore, the permeation for the gels is in the order of NT > NA > ND. The larger solute, vitamin B12, does not easily pass through the gel membranes. Figure 7(d) indicates that vitamin B12 can more easily pass through a 1-mm gel membrane than through a 2-mm gel membrane.

For ionic solutes such as CV and phenol red, an electrostatic force exists between the drug solute and the hydrogel. When the solute and the hydrogel have different electric charges, there is an electrostatic attraction between them. Therefore, the charges in the gels are neutralized by ionic solutes during the diffusion process. After neutralization, ionic gels become nonionic gels, and solutes can pass through the gel membranes without being affected by electrostatic attraction. For example, the permeation of CV passing through the NA gel and of phenol red passing through the NT gel is lower than that of CV and phenol red passing through the ND gel. When the drug solutes and the hydrogels have the same electric charge, such as NT and phenol red and NA and CV, the solute does not easily pass through the gel because of the charge repulsion. Therefore, its permeation is lowest.

## CONCLUSIONS

Gels with the cationic monomer TMAAI have higher values of $SR_e$. The results for $D$ show that the swelling rates of the gels with the anionic monomer AA and PEG of larger molecular weights are faster. Incorporating a hydrophilic monomer such as PEGMEA into the PNIPAAm hydrogel leads to a higher shrinkage ratio and a larger swelling–deswelling range. However, the fast swelling–deswelling behavior for the porous structure gels is due to them being more readily available than the gels with long hydrophilic side chains. The interactive force between ionic drug solutes and hydrogels with different electric charges is affected by electrostatic attraction. The results of solute diffusion experiments indicate that gels with larger pores can enable macromolecules such as vitamin B12 to pass through gel membranes.

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