pH-Reversible Hydrogels. IV. Swelling Behavior of the 2-Hydroxyethyl Methacrylate-*co*-Acrylic Acid-*co*-Sodium Acrylate Copolymeric Hydrogels

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ABSTRACT: A series of 2-hydroxyethyl methacrylate (HEMA) and sodium acrylate (SA50) copolymeric gels were prepared from HEMA and the anionic monomer SA50 with various molar ratios. The influence of SA50 on the copolymeric gels on their swelling behavior in deionized water at different temperatures and various pH buffer solutions was investigated. Results indicated that the poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels exhibited an overshooting phenomenon in their dynamic swelling behavior. The maximum overshooting value decreased with increasing of the temperature. The same results were also found in the HEMA/SA50 copolymeric gels with a lower SA50 content. On the contrary, the overshooting phenomenon for HEMA/SA50 copolymeric gels with a higher content of SA50 was exhibited only under higher temperature (over 35°C). These copolymer gels were used to assess drug release and drug delivery in this article. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 81: 1360–1371, 2001

Key words: hydrogel, overshooting, 2-hydroxyethyl methacrylate-*co*-sodium acrylate copolymeric gel

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymeric networks that swell but do not dissolve when brought into contact with water. There are some hydrogels which sometimes undergo a volume change in response to a change in the surrounding conditions such as temperature,[1,2] pH,[3,4] solvent composition,[5–7] salt concentration,[8] chemistry,[9] photoirradiation,[10] and electric field.[11]

The dynamic swelling behavior of poly(2-hydroxyethyl methacrylate) (PHEMA) was reported by Peppas et al.[12–14] For example, Shieh and Peppas[12] reported the swelling behaviors of copolymers prepared from the copolymerization of 2-hydroxyethyl methacrylate (HEMA) with ethylene glycol dimethacrylate (EGDMA), triethylene glycol dimethacrylate (TrEGDMA), tetraethylene glycol dimethacrylate (TeEGDMA), hexaethylene glycol dimethacrylate (HeEGDMA), and dodecaethylene glycol dimethacrylate (DoEGDMA). The swelling dynamics of poly(HEMA-*co*-TeEGDMA) with 55 mol % HEMA exhibited light water uptake over the equilibrium value, a result similar to the one obtained by Franson and Peppas.[13] They described the swelling behaviors of copolymers prepared from the copolymerization of HEMA with methyl methacrylate (MMA) or *N*-vinyl-2-pyrrolidone (NVP).

Huglin and Rego[15–17] reported on the swelling behavior of copolymeric gels which were prepared

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from the copolymerization of HEMA and a zwitterionic monomer, *N,N*-dimethyl-*N*-methacryloyloxyethyl-*n*-(3-sulfopropyl)ammonium betaine (SPE).[15–17] In our previous studies, the swelling behavior of a copolymer prepared from *N*-isopropyl acrylamide (NIPAAm) and acrylic acid (AA), which was neutralized with sodium hydroxide to 50 mol % and various degrees of neutralization,[18,19] was investigated. The results showed that the gels exhibited an overshooting phenomenon at higher temperatures and this phenomenon was more significant as the degree of neutralization was lower. However, the copolymerization of HEMA and AA, which was neutralized with sodium hydroxide to 50 mol %, was not found in the literature.

The overshooting phenomenon of HEMA disappears with increasing temperature, but that of AA appears with increasing temperature.[18] Hence, a series of HEMA/SA50 copolymeric gels were prepared in attempt to investigate the overshooting behavior for these copolymeric gels in deionized water at various temperatures. At the same time, the swelling behavior of the present copolymeric hydrogel in various pH buffer solutions and the availability of the copolymer gels used for drug release were also investigated.

EXPERIMENTAL

Materials

HEMA (TCI Chemical Co., Tokyo, Japan) was purified by vacuum-distillation at 68°C/5 mmHg. *N,N′*-Methylenebisacrylamide (NMBA; SIGMA Chemical Co., St. Louis, MO) as a crosslinker was used as received. Materials purchased from Tokyo Kasei Industries Ltd. (Tokyo, Japan) included AA and sodium hydroxide (NaOH). *N,N,N′,N′* Tetramethylethylenediamine (TEMED; Fluka Chemical Co., Buchs, Switzerland), as an accelerator, was used as received. Ammonium persulfate (APS; Wako Pure Chemical Co., Osaka, Japan), as an initiator, was further purified by recrystallization.

Preparation of AA-Neutralized 50 mol % Monomer Solution

AA was carefully added to a predetermined amount of an aqueous caustic solution to obtain a complete degree of neutralization theoretically (sodium hydroxide and AA in equal 0.05-mol amounts). Then, the neutralized 50 mol % AA was obtained from adding 0.05 mol AA to the sodium acrylate solution. This solution is referred to here as SA50. The method was described in a previous report.[18]

Preparation of Hydrogels

HEMA and SA50 with various molar ratios and 3 mol % NMBA, based on the total monomer, were dissolved in 10 mL of deionized water. To this solution, 1 mol % APS and 1 mol % TEMED, as redox initiators, were added, and the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was adjusted with a silicone spacer between the two glass plates. Polymerization was carried out at room temperature for 1 day. After gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and immersed in an excess of deionized water for 4 days to remove the residual unreacted monomer. Swollen polymer gels were dried at 70°C for 1 day, and these samples were further dried in a vacuum oven for 2 days at 50°C.

Measurement of Swelling Ratio

The preweighed (W_d) dried gels were immersed in an excess of deionized water at different temperatures until swelling equilibrium was attained. The weight of the wet sample (W_w) was determined after removing the surface water by blotting with filter paper. The swelling ratio (SR) was calculated from the following equation:

$$SR = \frac{Ww - Wd}{Wd} \tag{1}$$

Dynamic Swelling

The dried gels were immersed in an excess of various pH buffer solutions or deionized water at different temperatures. The swelling ratio was obtained by weighing the initial and swollen samples at various time intervals. The amount of the water sorbed, M_t, was reported as a function of time, and the equilibrium sorption at a infinitely long time was designated M_∞. The following equation can be used to calculate the diffusion coefficient, D, for $M_t/M_\infty \leq 0.8$[20]:

$$\frac{M_t}{M_\infty} = \frac{4}{\sqrt{\pi}} \times \left(\frac{Dt}{L^2}\right)^{1/2} \tag{2}$$

where t is the time, and L, the initial thickness of the dried sample.

Measurement of Swelling Ratios in Various pH Solutions and pH-reversibility

The measurement procedure for the swelling ratios, for the copolymeric gels under various pH buffer solutions, was the same as that in deionized water. The pH of various solutions were measured with a pH meter (Radiometer PHM95) calibrated by a standard buffer solution. The pH reversible experiments were carried out at pH 4.03 and 10.02 for a 0.01*M* buffer solution. Buffer solutions were prepared by aqueous solutions of HCl, KCl, $KHC_8H_4O_4$, NaOH, KH_2PO_4, and H_3BO_3.

Caffeine-release Experiment

The dry gels were equilibrated in 30 mg/10 mL of a pH 10.02 buffer solution at 25°C for 1 day to load caffeine into the gels. The caffeine-release experiments were carried out by transferring previously incubated drug gels into 10 mL of a pH 4.03 buffer solution at 25°C. The gels were repeatedly removed and transferred into a 10-mL fresh pH 4.03 buffer solution at each fixed time interval. The released caffeine was analyzed at 272 nm by an ultraviolet spectrophotometer (JASCO UV-530).

Phenolphthalein Deswelling Kinetics Experiments

The dry gels were equilibrated in 30 mg phenolphthalein in a 10-mL pH 10.02 buffer solution at 25°C for 1 day for loading phenolphthalein into the gels. The phenolphthalein deswelling kinetic experiments were carried out by transferring previously incubated drug gels into a 10-mL pH 4.03 buffer solution without phenolphthalein at 25° or another pH. The gels were removed and transferred into a 10-mL fresh pH 4.03 buffer solution at each fixed time interval. The released phenolphthalein was analyzed at 299 nm by an UV-spectrophotometer (JASCO UV-530).

Phenolphthalein Delivery Experiment

The dry gels were equilibrated in 30 mg/10 mL of a pH 10.02 buffer solution at 25°C for 1 day for loading phenolphthalein into the gels. The phenolphthalein delivery experiments were carried out by transferring previously incubated drug gels into a 10-mL pH 4.03 buffer solution at 25°C. The gels were repeatedly removed and transferred into a 10-mL pH 4.03 buffer solution at each fixed time interval. When phenolphthalein was no longer released from the gels (about 5 h), the gels were reimmersed into the original phenolphthalein solution for 1 day. Then, the release experiment was repeated. The above steps were repeated to perform the drug-delivery tests. The released phenolphthalein was analyzed at 299 nm by an ultraviolet spectrophotometer (JASCO UV-530).

RESULTS AND DISCUSSION

The swelling behavior of the hydrogels depends on the nature of the polymer and the environmental conditions. The polymer's nature involves the nature of the charge, ionic content, and crosslinking agent content. The environmental conditions include temperature and pH.

The swelling behavior of HEMA hydrogels has been widely studied by many researchers.[12–17,21,22] A series of HEMA/SA50 copolymeric hydrogels was investigated in this article. The effect of the SA50 content and the temperature on the swelling ratio for these copolymeric gels was investigated.

Characterization of HEMA/SA50 Copolymeric Gel

Some characteristics of the HEMA/SA50 copolymeric gels with various feed compositions are shown in Table I. The results observed in Table I indicate that the gel is opaque when the SA50 content is below 10 mol % and then the gels become transparent when the SA50 content is increased. The equilibrium swelling ratios of the copolymeric gels in deionized water are also increased with increasing of the content of SA50. The crosslinking densities of the gels decrease with increase in the SA 50 content or the swelling ratio.

Effect of Temperature on Equilibrium Swelling Ratio for the HEMA/SA50 Copolymeric Gels

The effect of temperature on the equilibrium swelling ratio (SR_{eq}) for a series of the HEMA/SA50 copolymeric gels is shown in Figure 1. The results show that sample M0, PHEMA, exhibits a minimum swelling ratio at 55°C. This behavior conforms to the result reported by Warren and Prins.[23] This phenomenon can be attributed to the hydrogen bond between the water molecule

Table I Characterization of HEMA/SA50 Copolymeric Gels

Sample No.	Feed Composition (%)		Appearance	Equilibrium Swelling Ratio at 25°C (g H_2O/g dry gel)	Crosslinking Density ($\times 10^{-4}$ mol/cm^3)
	HEMA	SA50			
M0	100	0	o	1.52	3.9
M5	95	5	o	1.98	2.7
M10	90	10	t	2.29	1.7
M20	80	20	t	3.23	0.9

t, transparent; o, opaque.

and the polymeric chain when it is below 55°C. The hydrogen bond is reduced with increasing of the temperature. Then, the bound water is transferred to free water that can be moved rapidly out of the polymeric networks. The SR_{eq} of M0 will be decreased to the minimum value at 55°C. However, the entropy of water and the polymeric network will be increased as the temperature increases. When the temperature is over 55°C, the dispersion force of the water molecules is greater than is the attraction force of water and the polymeric network. The free water will be moved from the surrounding medium into the hydrogels. Therefore, the SR_{eq} of M0 will be increased again when the temperature is over 55°C. The result also shows that the minimum swelling ratio disappears with increase in the content of SA50.

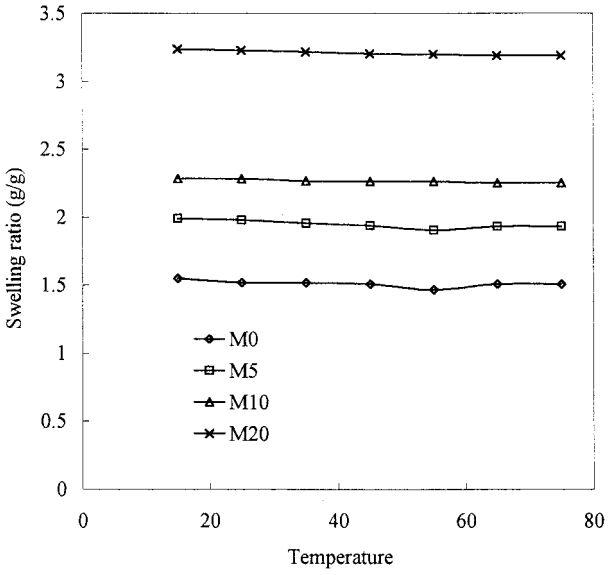

Figure 1 Equilibrium swelling ratios as a function of temperature for HEMA/SA50 copolymeric gels.

Effect of SA50 Content on Swelling Ratio for HEMA/SA50 Copolymeric Gels

The swelling ratios, as a function of time, for HEMA/SA50 copolymeric gels in deionized water at various temperatures are shown in Figure 2(a–g). The results shown in these figures indicate that the more the SA50 content the higher is the swelling ratio. According to Flory's swelling theory,[24] the following equation was given:

$$Q^{5/3} = [(i/2V_uS^{1/2})^2 + (1/2 - \chi_1)/v_1]/(\nu_e/V_0) \quad (3)$$

where i/V_u is the concentration of the fixed charge referred to the unswollen network; S, the ionic concentration in the external solution; $(1/2 - \chi_1)/v_1$, the affinity of the hydrogel for deionized water or a solvent; and ν_e/V_0, the crosslinking density of the hydrogel. Thus, the swelling ratios for these gels depend on the ionic osmotic pressure, crosslinking density, and affinity of the hydrogel for deionized water or a solvent. Because the crosslinking density for the present copolymeric gels was fixed, the swelling ratios of the gel were dependent on the concentration of the fixed charge in the gel and the affinity of the gel for deionized water. When the anionic monomer SA50 was introduced into the copolymeric gel, the sodium ion was dissociated and a carboxylate group (COO^-) with a negative charge was formed. The repulsion of the negative charge of the polymeric network increases and the network expands. Therefore, the swelling ratio of the gel increases as the content of SA50 increases.

Moreover, the results in these figures also indicate that the water uptake of the gel increases over the equilibrium value. This phenomenon is called "overshooting." The overshooting phenomenon is displayed at a higher HEMA content and lower temperature [see Fig. 2(a,b)] and at a

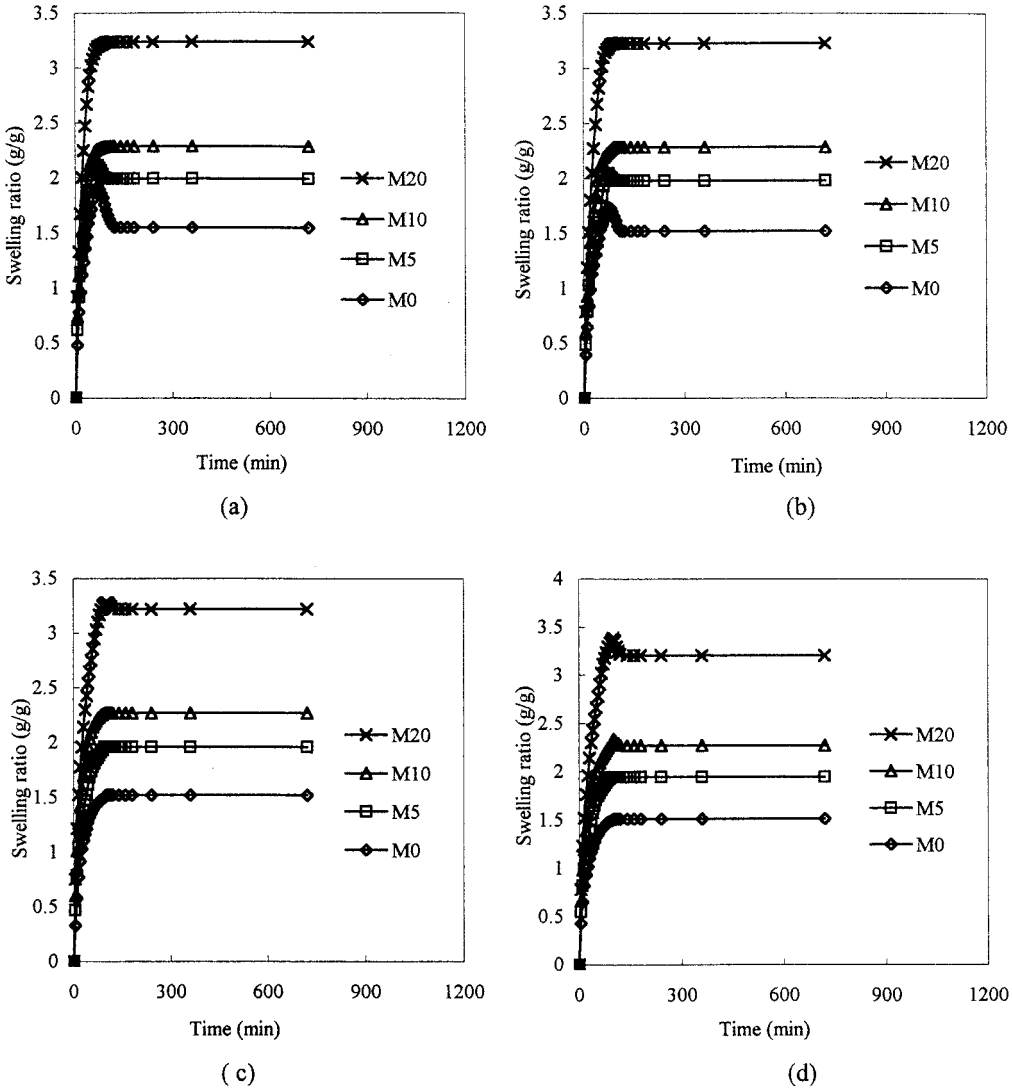

Figure 2 Swelling ratios as a function of time for HEMA/SA50 copolymeric gels at various temperatures: (a) 15°C; (b) 25°C; (c) 35°C; (d) 45°C; (e) 55°C; (f) 65°C; (g) 75°C.

higher SA50 content and higher temperature [see Fig. 2(c–g)]. Hence, the overshooting phenomenon is related to the temperature. The influence of the temperature on the overshooting phenomenon is discussed in the next paragraph.

Effect of Temperature on Overshooting Phenomenon

The fractional swelling ratio, Mt/M_∞, of the M0 hydrogels as a function of the time at various temperatures is shown in Figure 3(a). The dynamic swelling ratio of the M0 hydrogel exhibits an overshooting phenomenon: This result is similar to that reported by Shieh and Peppas[12] and our previous reports.[21,22] This is attributed to molecular chain relaxation. The molecular chains have enough time to relax when water diffuses into the polymeric network, that is, the rate of relaxation of the molecular chain is faster than is the rate of diffusion of water. Therefore, the Mt/M_∞ curve would reach a maximum value (overshooting value). When the final relaxation of the chain is achieved, the water is forced out of the network and the SR reaches its equilibrium value. This overshooting value decreases with an increase in temperature. Moreover, the Mt/M_∞ of the M20 copolymeric gel at various temperatures is also shown in Figure 3(b).

The results of the overshooting and the times for maximum overshooting for the present copoly-

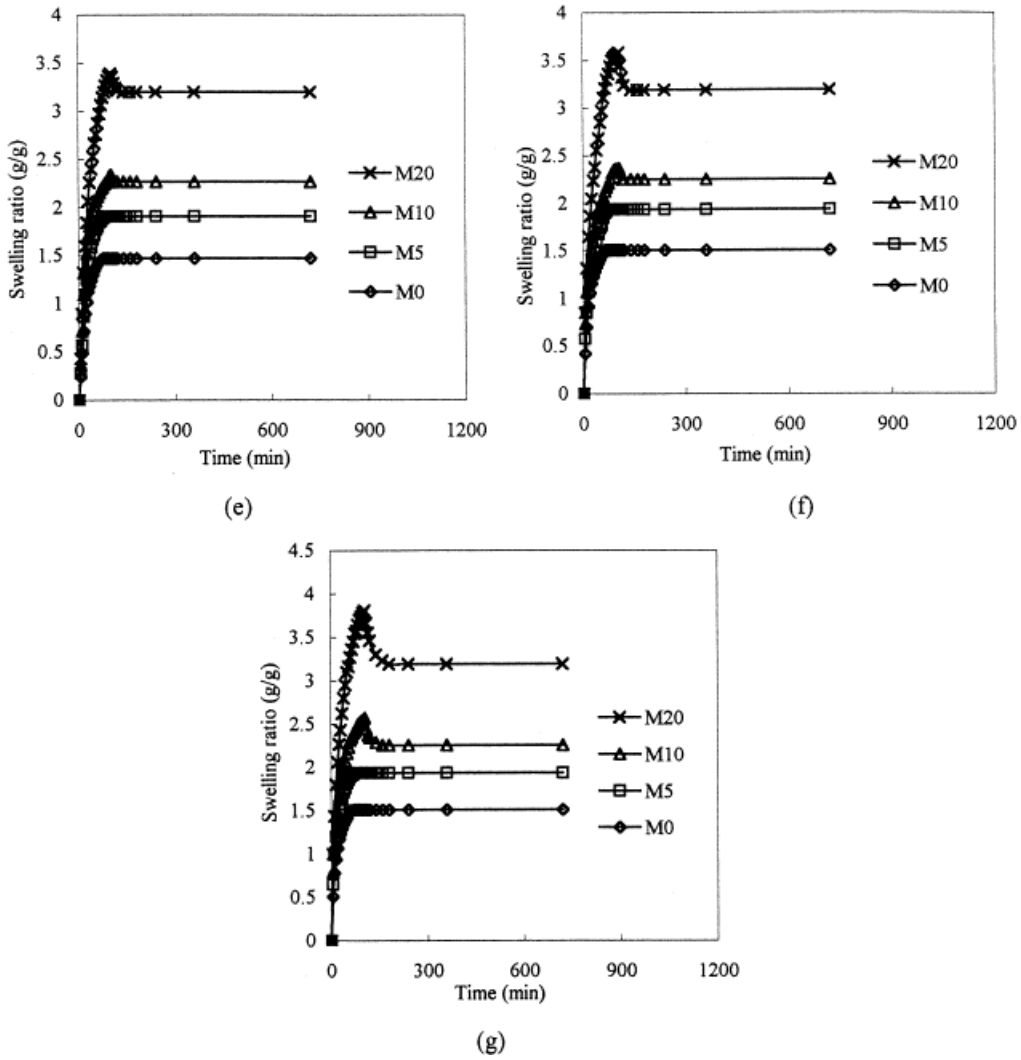

Figure 2 (*Continued from the previous page*)

meric gels are shown in Table II. The results shown in Table II indicate that the overshooting value for the M0 and M5 gels decrease with increase of the temperature and the time of overshooting appeared at 70 min. But for M10 and M20 gels, the overshooting phenomena appeared when the temperature was over 35°C and increased with an increasing of the temperature.

This result indicates that the relaxation phenomenon of the HEMA gel (M0) is more significant at lower temperature, but the relaxation phenomenon of the M20 copolymeric gel is more significant at higher temperature. This phenomenon conforms to our previous results for HEMA/SPE and NIPAAm/SA50 gel systems.[19,21] But the expected double overshooting was not observed in this system.

Investigation of Water Diffusion in Xerogels

To investigate the diffusion model of the gel, the initial swelling data are fitted to the exponential heuristic equation[25,26]:

$$\frac{M_t}{M_\infty} = kt^n \quad \left(\frac{M_t}{M_\infty} \leq 0.6\right) \tag{4}$$

where k is a characteristic constant of the gel, and n, a characteristic exponent of the mode of transport of the penetrate. Values of n and k were calculated from the slopes and intercepts of the plot of log Mt/M_∞ against log t, respectively. From eq. (2), the diffusion coefficient D can be calculated from the slope $4/(\pi D)^{1/2}$ of the plot of Mt/M_∞ against $(t/L^2)^{1/2}$. The diffusion of the gel depends

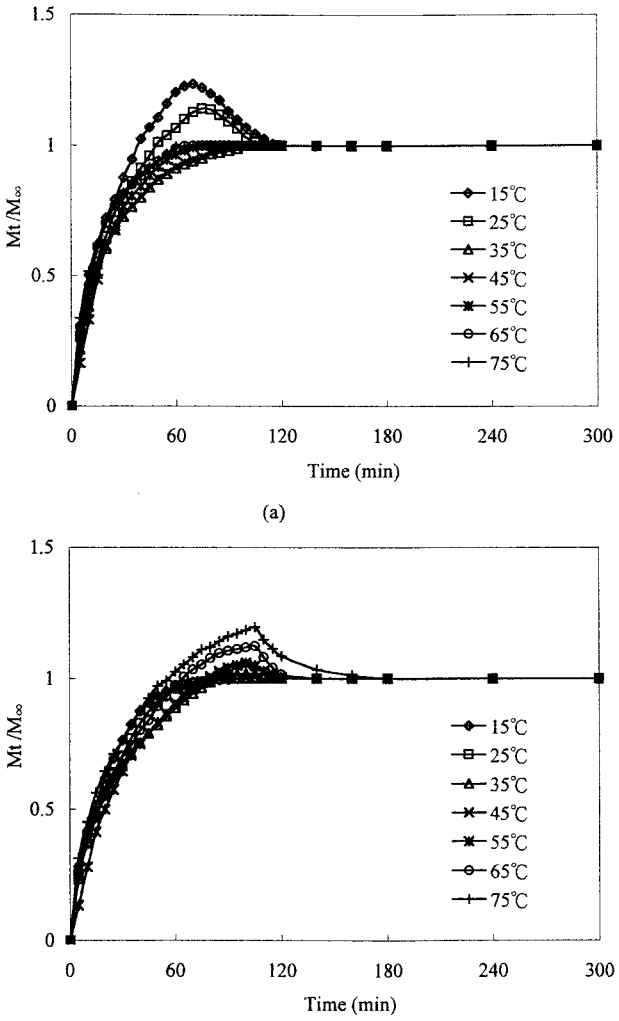

Figure 3 Fractional swelling ratio of the (a) PHEMA (M0) and (b) M20 gels as a function of time at various temperatures.

on the diffusion rate of absorbing solvent into the gel and the relaxation rate of the polymer network. If the value of n is 0.5, the diffusion mechanism is called Case I transport or Fickian diffusion, that is, the rate of diffusion is much less than is the rate of relaxation. When the value of $n = 1.0$, it is called Case II transport, that is, the rate of relaxation is much less than is the rate of diffusion. When the values of n are between 0.5 and 1.0, that is, non-Fickian diffusion—the rate of diffusion is comparable to the rate of relaxation.[27]

The results shown in Table III indicate that the swelling exponents, n, for the PHEMA (M0) gel at various temperatures are between 0.53 and 0.72. This evidence indicates that the swelling transport mechanisms for the M0 gel are non-Fickian transport. Furthermore, the swelling exponents, n, for the M5 copolymeric gel at various temperatures are between 0.61 and 0.81. These phenomena indicate that the swelling transport mechanisms for the M5 gel are non-Fickian transport. On the other hand, the swelling exponents, n, for the M10 and M20 copolymeric gels at various temperatures are also between 0.61 and 0.86. In other words, the swelling transport mechanisms for the M10 and M20 gels also belong to non-Fickian transport. Hence, it can be concluded that the swelling transport mechanisms are non-Fickian for this gel system. At the same time, the values of n and D increase with increase of the temperature and the content of SA50, that is, the rate of diffusion is faster at higher temperature.

Effect of pH on Swelling Kinetics for HEMA/SA50 Copolymeric Gels

The swelling ratios, as a function of time for HEMA/SA50 copolymeric hydrogels in several pH

Table II Analysis of Transport Mechanism of Water Transport in Glassy HEMA/SA50 Copolymeric Gels for Various Temperatures

Temperature (°C)	M0		M5		M10		M20	
	OS	T	OS	T	OS	T	OS	T
15	24.7	70	6.12	70	—	—	—	—
25	14.1	75	3.43	75	—	—	—	—
35	—	—	—	—	0.21	100	1.93	100
45	—	—	—	—	3.09	100	5.55	100
55	—	—	—	—	3.18	100	5.99	100
65	—	—	—	—	5.10	105	12.35	105
75	—	—	—	—	14.01	105	19.43	105

OS, overshooting (%); T, time obtained from maximum overshooting (min).

Table III Initial Diffusion Coefficient, *D*, and Kinetic Exponent, *n*, and Characteristic Constant, *k*, of Water Penetrated Through HEMA/SA50 Copolymeric Gels at Various Temperatures

Sample No.	Temperature (°C)	*n*	*k*	*D* ($\times 10^8$ cm^2/s)
M0	15	0.72	0.02	1.15
	25	0.67	0.02	1.23
	35	0.61	0.02	1.28
	45	0.56	0.03	1.31
	55	0.55	0.04	1.61
	65	0.55	0.05	1.74
	75	0.53	0.05	2.11
M5	15	0.73	0.04	1.53
	25	0.72	0.04	1.67
	35	0.69	0.04	1.83
	45	0.68	0.05	1.94
	55	0.62	0.05	2.34
	65	0.61	0.05	2.97
	75	0.61	0.06	2.98
M10	15	0.73	0.05	1.61
	25	0.73	0.05	1.72
	35	0.71	0.05	1.79
	45	0.70	0.06	1.97
	55	0.64	0.06	2.23
	65	0.63	0.06	2.67
	75	0.63	0.07	2.73
M20	15	0.75	0.05	2.32
	25	0.74	0.05	2.98
	35	0.72	0.05	3.19
	45	0.72	0.05	3.72
	55	0.69	0.06	4.05
	65	0.64	0.07	4.15
	75	0.63	0.07	4.15

buffer solutions, are shown in Figure 4. The results show that, under acidic conditions, anionic carboxylate groups are protonated and the copolymeric network deswelled. As the pH of the aqueous media is increased from low pH, the concentration of anionic carboxylate groups in the polymer network increases. This occurrence makes the swelling ratio of the gels drastically increase with an increase of the SA50 content in the copolymeric gels. The largest swelling ratio occurred at pH 10.02. This may reflect the complete neutralization of carboxylic acid groups. The results also indicate that the hydrophilicity of the gels is obviously influenced by the amount of SA50 and the degree of ionization of the carboxylate groups.

Table IV shows the values of n, k, and D of water penetrated through three HEMA-SA50 gels at various pH buffer solutions. The results in Table IV indicate that the swelling exponents, n, for the gels at various pH media range from 0.72 to 0.86. This evidence shows that the swelling transport mechanism is non-Fickian. The data for the diffusion coefficient D shown in Table IV indicate that the diffusion coefficients for various HEMA/SA50 copolymeric gels are increased with a decrease of pH.

Effect of pH on Swelling Ratio for HEMA/SA50 Copolymeric Gels

We reported earlier that, by incorporating SA50 into poly(NIPAAm) as a comonomer, the LCST variation depends on the external pH. For higher pH solutions, the LCST shifts to higher temperature owing to ionization and electrostatic repulsion between anionic carboxylate groups. For lower pH solutions, however, the LCST shifts to lower temperature owing to polymer interactions enhanced by hydrogen bonding between protonated carboxylic acid groups. As a result, at a certain constant temperature, the gels undergo substantial swelling–deswelling changes in response to external pH changes.

Figure 5 shows the pH dependence of the gel equilibrium swelling ratio for the HEMA/SA50 copolymeric gels at 25°C. The results in Figure 5 indicate that the swelling ratios remain constant from pH 4.03 to 7.02. The gel transition for M20 and M10 gels occurs at pH 7.02, leading both swelling ratios to increase with an increase of the external pH, and the gel transition is later at pH 8.04 for M5. This is because the ionization of polymeric networks containing carboxylic acid groups takes place as the pH of the external medium increases. Basic conditions, however, will accelerate the reaction of carboxylic acid groups and increase the repulsive effect of the charges of (COO^-) on the gels, and both factors would make the swelling ratio higher and make the effect of deswelling insignificant. Therefore, the gel containing the most carboxylate ions (COO^-) will cause the largest ionic repulsion inside the gels and can affect the pH-sensitive character of gels (M20 > M10 > M5).

Effect of Reversibilities on Swelling Ratio for HEMA/SA50 Copolymeric Gels

Figure 6 presents the effect of cycling pH on the swelling behavior of these ionic networks. The pH

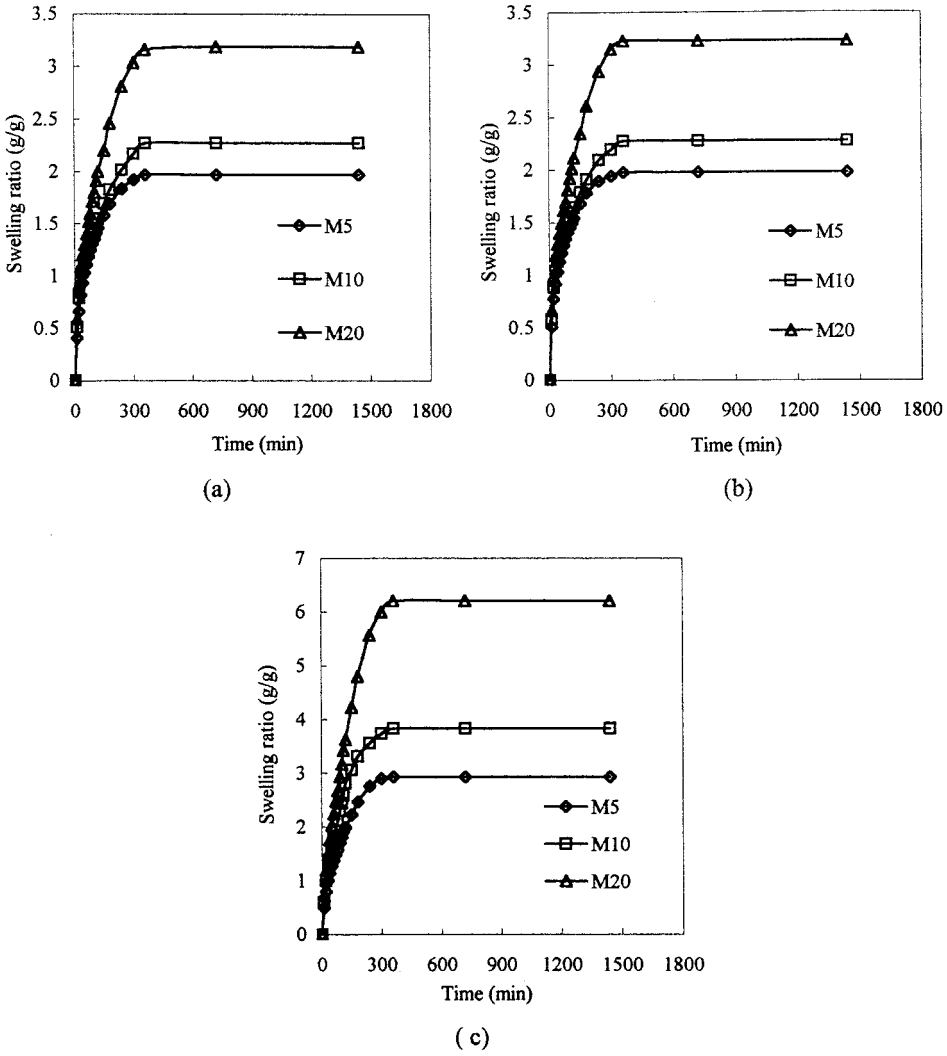

Figure 4 Swelling ratio as a function of time for various copolymeric gels in pH buffer solution at 25°C: (a) pH 4.03; (b) pH 7.02; (c) pH 10.02.

was changed from 10.02 to 4.03 and the same cycle was repeated several times. The first swelling time in pH 10.02 was a period of swelling equilibrium, followed by 4 h in pH 4.03 and then 4 h in pH 10.02 buffer. At the first swelling stage, the carboxylate groups (COO^-) enhance the swelling ratios, but when the gels are transferred to low pH (4.03), the carboxylate groups are protonated to carboxylic acid groups (COOH), which decreases the electrostatic repulsive force between the charge sites on the network and cause the swelling ratios to decrease. This figure also shows that the more the SA50 the larger are the swelling ratios. Hence, the changes of the swelling ratio for the gels are M20 > M10 > M5.

The results shown in Figure 6 explicitly indicate that the pH reversibility for the M5 gel is not

Table IV Initial Diffusion Coefficient, *D*, and Kinetic Exponent, *n*, and Characteristic Constant, *k*, of Water Penetrated Through HEMA/SA50 Copolymeric Gels in Various pHs at 25°C

Sample No.	pH	*n*	*k*	*D* ($\times 10^8$ cm^2/s)
M5	4	0.72	0.12	2.23
	7	0.72	0.11	2.11
	10	0.75	0.08	1.15
M10	4	0.74	0.14	2.22
	7	0.75	0.12	2.15
	10	0.78	0.10	1.12
M20	4	0.76	0.16	2.18
	7	0.78	0.13	2.11
	10	0.86	0.12	2.04

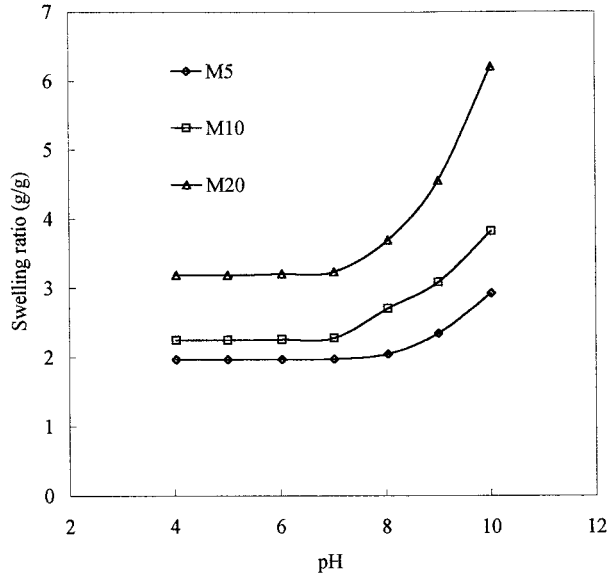

Figure 5 Equilibrium swelling ratio as a function of pH value for the present copolymeric gels at 25°C.

significantly evident. Hence, the pH-reversibility for the said copolymeric gels is dependent on the SA50 content in the gel compositions.

Effect of pH on Fractional Drug Release of for HEMA/SA50 Copolymeric Gels

A polymer gel undergoing rapid dehydration during the deswelling process may have a potential utility in on–off regulation of solute permeation due to the formation of a barrier (skin) layer at the surface of the gel matrix. In this context, the HEMA/SA50 gels may be applicable as a drug-release system responding to pH.

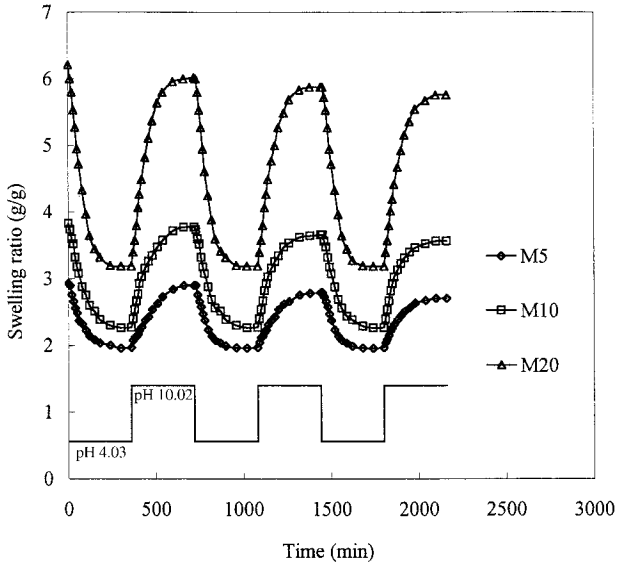

Figure 6 Swelling ratios of various copolymeric gels as a function of time with repeated abrupt change of pH 10.02 and 4.03 in buffer solution.

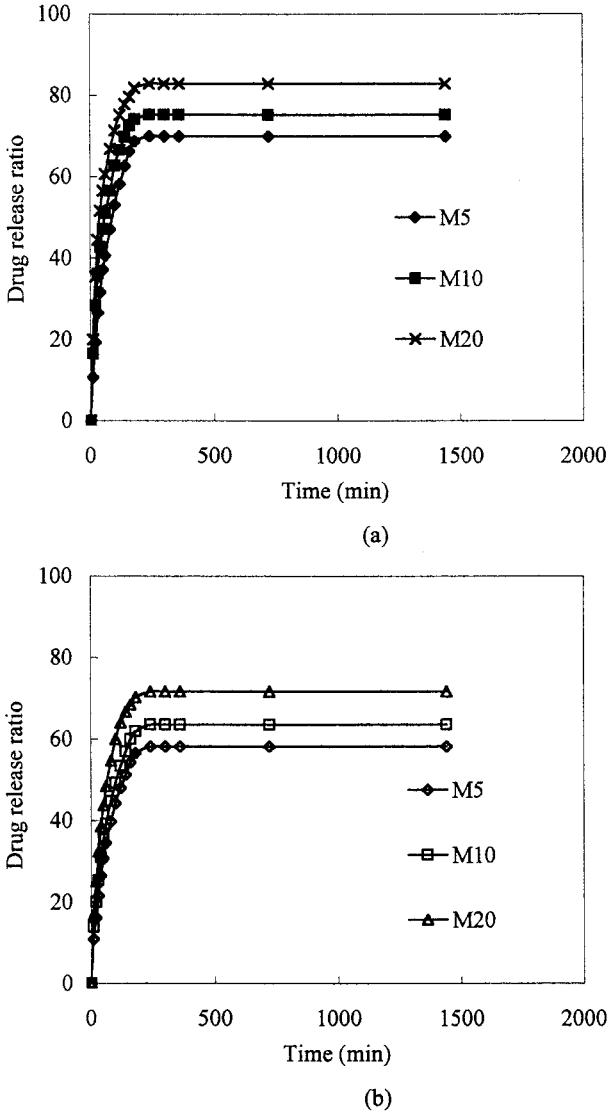

Figure 7 Drug-release profile for the gel incubated at pH 10.02 and released at pH 4.03: (a) caffeine; (b) phenolphthalein.

Drug-release systems with transport across the HEMA/SA50 gels responding to a pH jump in the external milieu were demonstrated using phenolphthalein and caffeine as model drugs and are, respectively, shown in Figure 7(a,b). The results shown in Figure 7 show a rapid release as a function of time for two drugs from the gels in an acid milieu (pH 4.03), and it can be seen that the release rate of the drugs from the gels increases

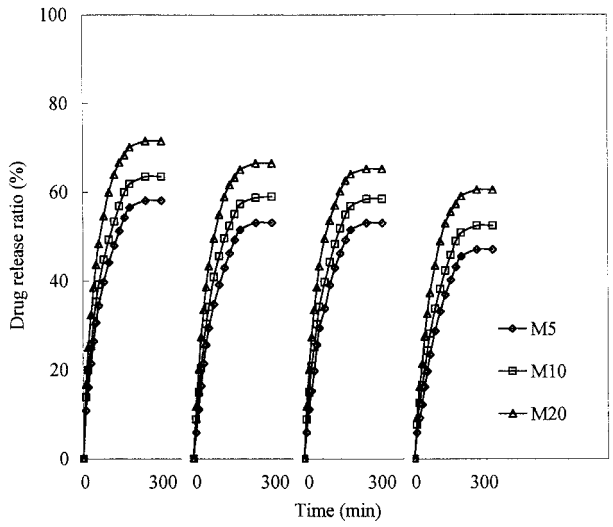

Figure 8 Phenolphthalein delivery profile during swelling at pH 10.02 and deswelling at pH 4.03.

considerably with time. This is because the incorporation of SA50 into the polymer network with a high molar ratio will lead to an increase in the electrostatic repulsive force between charge sites on carboxylate ions and enhance a more extended configuration. The extended structure with more SA50 content might cause a higher amount of the drug incubated into the gel to be released (M20 > M10 > M5). On the other hand, the carboxylate groups of SA50 were protonated and the polymer networks deswelled at acidic conditions. Hence, the drugs were effectively shut off by transferring the gels from an alkali to an acidic milieu, suggesting the formation of a surface barrier layer. Therefore, the drugs released from the gels at pH 4.03 are due to less diffusion of the drug through the deswelled polymer networks. These results also show that the fractional release (Mt/M_∞) of the drugs does not reach 1.0. This occurrence also implies that the drugs were not completely released and some portions were entrapped within the gel.

Effect of SA50 on Phenolphthalein Delivery

Figure 8 shows the result of phenolphthalein delivery over long times between pH 10.02 and 4.03 for M5, M10, and M20. The release amount of phenolphthalein at the first time release is in the order M20 > M10 > M5. This result is similar to the swelling ratios of these three gels. As the gel is released a second time, the release phenolphthalein amounts were lower than they were the first time. But the release amount reached a constant value for the third time release, that is, it reached a stable state, resulting in the equilibrium release amount.

CONCLUSIONS

The swelling ratios of HEMA/SA50 copolymeric gels are increased with an increase of SA50 content, that is, the higher the SA50, the stronger is the affinity of the gels for water. In addition, the minimum equilibrium swelling ratio for PHEMA gradually disappeared with an increasing content of SA50 in HEMA/SA50 copolymeric gels.

In dynamic swelling behavior, the overshooting phenomenon was found in HEMA/SA50 copolymeric gels. The overshooting phenomenon was displayed at lower temperature, for higher HEMA content in copolymeric gels, and shifted to higher temperature, for higher SA50 content in the present copolymeric gels. At the same time, the time for maximum overshooting was shifted from 70 to 100 min.

The swelling transport mechanisms belong to non-Fickian transport for this gel system in deionized water and various pH buffer solutions. Furthermore, the values of D increase with an increase of the temperature and SA 50 content, that is, the rate of diffusion is faster at higher temperature, but decreases with increase in pH. These gels also show that the more SA50 the better is the reversibility with the pH. Finally, gels containing less SA50 exhibit slower caffeine and phenolphthalein release. The gels also show better drug-delivery behavior.

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