Effect of Montmorillonite on the Swelling Behavior and Drug-Release Behavior of Nanocomposite Hydrogels

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Received 10 October 2002; accepted 23 December 2002

ABSTRACT: A series of nanocomposite hydrogels were prepared from various ratios of *N*-isopropylacrylamide (NIPAAm) and organic montmorillonite (MMT). The influence of the extent of MMT in the NIPAAm/MMT nanocomposite hydrogels on the physical properties and drug-release behavior was the main purpose of this study. The microstructure and morphology were identified by X-ray diffraction (XRD) and scanning electronic microscopy (SEM). The results showed that the swelling ratios for these nanocomposite hydrogels decreased with increase in the content of MMT. The gel strength and Young's modulus of the gels also increased with increase in the content of MMT. XRD results indicated that the exfoliation of MMT was achieved in the swollen state. Finally, the drug-release behavior for the gels was also assessed. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 3652–3660, 2003

Key words: hydrogels; clay; nanocomposites; drug delivery systems

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 that sometimes undergo a volume change in response to a change in surrounding conditions such as temperature,[1,2] pH,[3,4] solvent composition,[5–7] and salt concentration.[8] Poly(*N*-isopropylacrylamide) [poly(NIPAAm)] hydrogel exhibits a volume-phase transition phenomenon about 32–33°C.[9,10] This temperature is defined as the critical gel transition temperature (CGTT) or lower critical solution temperature (LCST).

For NIPAAm gel, the amide group will form a stronger hydrogen bond with water when the temperature is below the CGTT. This occurrence makes the gel swell in water. But when the temperature is above the CGTT, the hydrophobic force of the gel increases and the gel will collapse and the bound water in the gel will be released. Because NIPAAm gel has this swell–deswell behavior, it can be widely used in many fields, such as in drug-delivery systems,[11,12] extraction,[13] and enzyme-activity control.[14]

Montmorillonite (MMT) is a natural clay mineral which has a large layer space and has some excellent properties such as good water absorption, swelling, adsorbability, cation exchange, and drug-carrying ability.[15,16] It is well known that a number of organic/inorganic nanocomposites can be prepared by intercalation polymerization from organic polymer and MMT, such as epoxies/MMT, polystyrene/MMT, and polyimide /MMT,[17–21] but a few nanocomposite hydrogels have been investigated in the literature.[22–24] For example, Messersmith and Znidarsich[22] reported stimuli-responsive polymer hydrogel–clay composites by direct copolymerization of NIPAAm with methylene bisacrylamide in aqueous suspensions of Na–MMT. Unfortunately, the nanocomposites retained their thermal responsive behavior only at low clay loadings (to 3.5 wt %). A higher clay solid loading (10 wt %) eliminated the thermal transition. A similar approach was used by Churochkina et al.[23] Their results indicated that clay minerals were found to have no effect, or to have a negative effect, on the swelling behavior of polyacrylamide gels. The results presented by Liang et al.[24] found that the interfacial chemistry between a clay and a polymer could be modified with a coupling agent to favor a more efficient thermal transition. Their results pointed to a new approach to finely tune the thermal transition by controlling the interfacial interactions between the polymers and the nanophase materials.

Thus, one objective of this study was to investigate the effect of MMT on physical properties, such as the microstructure, swelling behavior, and gel strength, of a NIPAAm/MMT nanocomposite hydrogel. The other objective was to investigate the effect of MMT in these gels on the drug-release behavior for drugs with different charges.

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Contract grant sponsor: National Science Council of the Republic of China; contract grant number: NSC 91-28115-C-036-002-E.

Journal of Applied Polymer Science, Vol. 89, 3652–3660 (2003)

TABLE I
Feed Compositions and Characterization of the Present Nanocomposite Gels

Sample	NIPAAm[a] (mol %)	MMT[a] (wt %)	Yield (%)	$G \times 10^2$ (MPa)	Q_{eq} (g/g)
M0	100 (1.1316 g)	0 (0 g)	97.36	6.49 ± 0.16	5.37
M1	99 (1.1203 g)	1 (0.0113 g)	96.11	6.85 ± 0.47	5.35
M3	97 (1.0976 g)	3 (0.0339 g)	91.93	7.07 ± 0.18	5.33
M5	95 (1.0750 g)	5 (0.0566 g)	94.59	7.80 ± 0.36	5.04
M10	90 (1.0184 g)	10 (0.1132 g)	92.33	9.33 ± 0.85	4.90
M15	85 (0.9618 g)	15 (0.1697 g)	95.20	11.42 ± 0.24	4.72
M20	80 (0.9053 g)	20 (0.2263 g)	97.23	7.44 ± 0.45	4.63

[a] Total weight is 1.1316 g (based on NIPAAm + MMT).

EXPERIMENTAL

Materials

NIPAAm (Wako Chemical Co., Osaka, Japan) was recrystallized in *n*-hexane before use. MMT (Cloisite® 30B), which was intercalated by methyl, tallow, and bis-2-hydroxyethyl quaternary ammonium salt (MT2EtOH), was purchased from the Southern Clay Product, Inc. (Gonzales, TX); the *d*-space of intercalated MMT is about 18.5 Å and the cation-exchange capacity (CEC) is 90 meq/100 g clay. Sodium lauryl sulfate (SLS) as a surfactant, *N*,*N*′-methylene bisacrylamide (NMBA) as a crosslinking agent, and ammonium persulfate (APS) as an initiator were purchased from Tokyo Kasei Industries, Ltd. (Tokyo, Japan). *N*,*N*,*N*,*N*′-tetramethylethylenediamine (TEMED) as an accelerator, caffeine, crystal violet (CV), phenol red, and neutral red as model drugs were obtained from the Fluka Chemical Co. (St. Gallen, Switzerland). All solvents and other chemicals were of analytical grade.

Preparation of hydrogels

Various ratios of NIPAAm and MMT were dissolved in 10 mL deionized water. To these solutions, 5 mol % NMBA (0.077 g) and SLS (0.025 g) were well mixed overnight at room temperature in sample vials. Finally, 1 mol % APS and 1 mol % TEMED were added, and then the mixtures were immediately injected into the space between two glass plates. Polymerization was carried out at 15°C for 1 day. After gelation was completed, the gel membranes were cut into disks, 10 mm in diameter, and immersed in an excess amount of deionized water for 4 days to remove residual unreactive components. Swollen gels were dried at 25°C for 1 day and then further dried in a vacuum oven for 2 days. The feed compositions of the nanocomposite gels are listed in Table I.

Swelling experiment

Two dried gel disks were immersed in an excess amount 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 dry weight (W_d) was determined after drying the gel in a vacuum oven for 2 days. The swelling ratio (Q) was calculated from eq. (1):

$$Q = (W_w - W_d)/W_d \tag{1}$$

Swelling and deswelling kinetics

The dried gels were immersed in an excess amount of deionized water. The swelling ratio was obtained by weighing the initial and swollen samples at various time intervals. The amount of water sorbed, *Wt*, was reported as a function of time, and the equilibrium sorption at infinitely long time was designated W_∞. Equation (2) was used to calculate the diffusion coefficient D for $W_t/ W_\infty \leqq 0.8$[25]:

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

where t is the time, and L, the initial thickness of the dried gel. To investigate the diffusion model of the gel, the initial swelling data were fitted to the exponential heuristic eq. (3) for $W_t/ W_\infty \leqq 0.6$[26,27]:

$$\frac{W_t}{W_\infty} = Kt^n \tag{3}$$

where K is a characteristic constant of the gel, and n, an characteristic exponent of the mode transport of the penetrate.

In addition, to investigate the deswelling kinetics of the hydrogel, the dried gels, which used the two disks of the gel membranes, were immersed in an excess amount of deionized water at 25°C and then placed into the deionized water at 37°C until shrinking equilibrium was attained:

$$\text{Shrinking ratio (\%)} = \frac{SR_e - SR_t}{SR_e} \times 100 \tag{4}$$

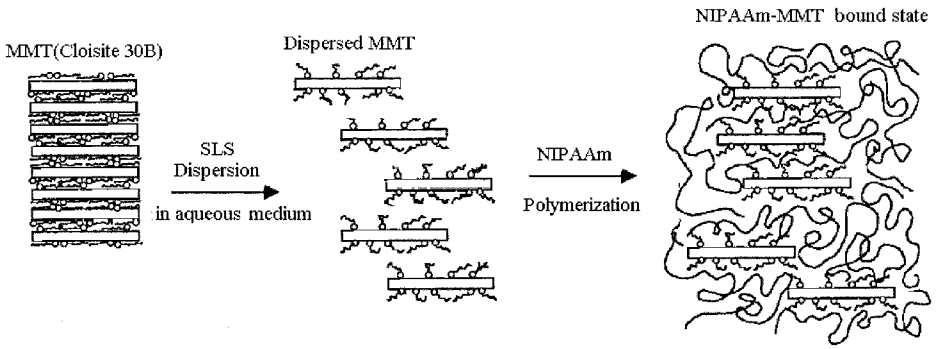

Figure 1 Schematic illustration of the formation of NIPAAm/MMT nanocomposite gels.

where SR_e is the initial equilibrium-swelling ratio of the hydrogel, and SR_t, the swelling ratio of the hydrogel at shrinking time t.

Physical properties measurement

The gel strength of these samples was measured by a uniaxial compression experiment with a universal tester (LLOYD LRX). Equation (5) was used to calculate the shear modulus:

$$\tau = F/A = G(\lambda - \lambda^{-2}) \quad (5)$$

where τ is the compression stress; F, the compression load; A, the cross-sectional area of the swollen gels; and λ, the compression strain (L/L_0). At low strains, a plot of the shear stress versus $-(\lambda - \lambda^{-2})$ would yield a straight line whose slope is the shear modulus (G). Five specimens were measured for each gel.

Drug-release experiment

The dried gels were equilibrated in 30 mg of the drug/10 mL of deionized water at 25°C for 1 day to load the drug into the gels. The drug-release experiment was carried out by transferring previously incubated drug gels into 10 mL deionized water or saline at 37°C. The gels were repeatedly removed and transferred into 10 mL fresh deionized water or saline at each fixed time interval. The released drugs were, respectively, analyzed at 272, 598, 430, and 275 nm for caffeine, CV, phenol red, and neutral red by an ultraviolet spectrophotometer (JASCO V530).

X-ray diffraction analysis

Powder XRD analysis was performed using a Siemens D5000 diffractometer with Cu radiation (40 kV, 30 mA). The scanning speed was 3^0/min. The structure of the clay was determined at different stages of the nanocomposite synthesis. The clay powders were mounted on a sample holder with a large cavity and a smooth surface was obtained by pressing the powders with a glass plate. Analyses of the swollen gels were performed by spreading the mixture on a gel membrane disc (50 mm diameter, 0.5 mm thick) used as a sample holder. It was designed so that a maximum surface could be irradiated at a low angle and gave an optimum intensity to the XRD signal. The nanocomposite plates, produced during the molding process, had a fairly smooth surface.

Morphology

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

RESULTS AND DISCUSSION

Preparation of the nanocomposite hydrogels

MMT is a hydrophilic material: It should be uniformly dispersed in an aqueous medium. However, large interactions on the surface of MMT make it easy to agglomerate. But, using the anionic surfactant, SLS, can make MMT uniformly disperse in aqueous medium. We successfully prepared a nanocomposite hydrogel in aqueous medium using this method at low temperature. Figure 1 shows a schematic illustration of the formation of NIPAAm/MMT nanocomposite gels. This can be compared to a study presented by Liang et al.,[24] who used a coupling agent between MMT and a polymer in organic medium and carried out gelation at high temperature.

Identification of the nanocomposite hydrogels

The XRD patterns of various samples are plotted in Figure 2. A typical diffraction pattern of Na–montmorillonite [MMT(Na^+)] shows a strong peak corre-

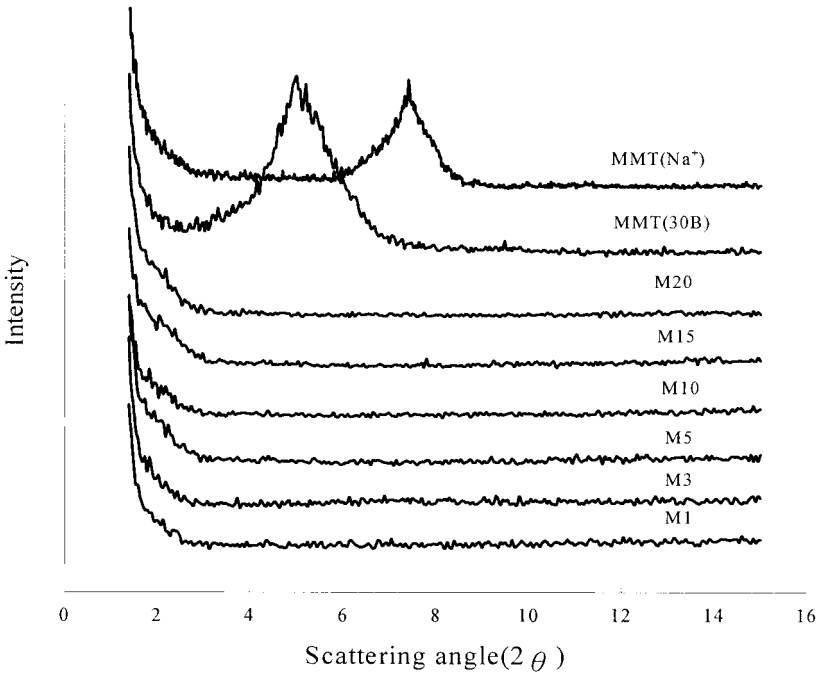

Figure 2 X-ray diffraction patterns of MMT(Na^+), MMT(30B), and various composite hydrogels.

sponding to a basal spacing of 11 Å. After treatment with MT2EtOH, this peak moved to a lower angle ($2\theta = 5.8^0$), corresponding to a basal spacing of 18.5 Å. This shows that the long-chain alkylammonium ions were intercalated between the layers during the cation-exchange process, giving a lateral bilayer structure.

The XRD of the various nanocomposite hydrogels in the swollen state shown in Figure 2 indicates that the diffraction peak disappears in all samples. This result suggests that the MMT minerals in the swollen hydrogels are intercalated and completely exfoliated. This contrasts to the results presented by Liang et al.,[24] who showed that the clay minerals were intercalated and mostly exfoliated in the swollen hydrogels.

Effect of MMT on the nanocomposite hydrogel properties

Fundamental properties, such as the equilibrium swelling ratio, gel strength, and drug-release behavior, for the present nanocomposite hydrogels were investigated.

Effect of MMT on equilibrium swelling ratio

Some characteristics of the present nanocomposite hydrogel with various feed compositions are shown in Table I. The equilibrium swelling ratios for the hydrogels in Table I indicate that the greater the MMT content in the gels the lower was the average equilibrium swelling ratio of the gel, that is, M0 > M1 > M3 > M5 > M10 > M15 > M20. This is because the original hydrophilic MMT modified with MT2EtOH becomes a hydrophobic chain: It makes NIPAAm/MMT nanocomposite hydrogels become more hydrophobic. Hence, the swelling ratio decreases with increase in the content of MMT in the gel. This result conforms to previous results obtained from other researchers, except for Liang et al.'s result. Liang et al.[24] claimed that their gel's swelling ratio increased with increase in the MMT content. We doubt their result, because MMT modified by *N*-tetradecyltrimethylammonium chloride is a hydrophobic chain: It should make the swelling ratio decrease. In addition, the large swelling ratios in their reports are unlikely.

Effect of MMT on gel strength

The average gel strength was assessed by the shear modulus (G) obtained from eq. (5). The results, shown in Table I, indicate that the G values increase with an increase of the content of MMT for the present gels until the content of MMT in the gel reaches 15 wt %. Beyond this content, the gel strength decreases, that is, the gels would become weaker when the content of MMT is over 15 wt %. This is because the excess content of MMT, due to agglomeration, could make the gel matrix discontinuous.

Effect of temperature on swelling ratio

The effect of temperature on the equilibrium swelling ratio for these gels is shown in Figure 3. The results

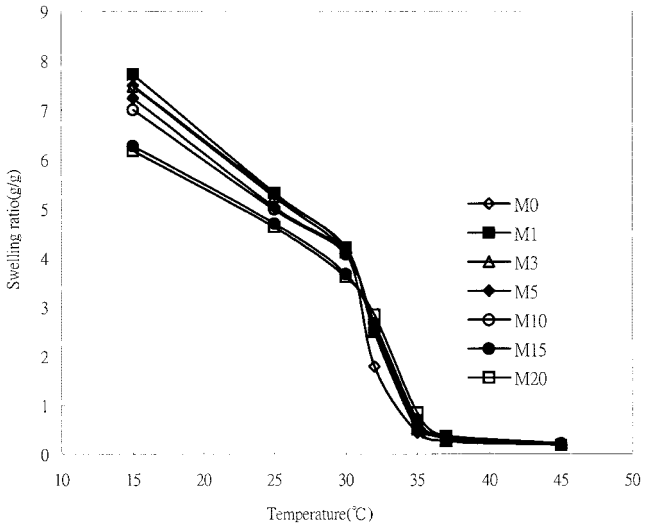

Figure 3 Effect of temperature on equilibrium swelling for the gels in deionized water.

shown in Figure 3 indicate that the higher the temperature the lower is the swelling ratio; however, the gel transition temperature was not obviously affected by the addition of more MMT in the gel. Compared to other studies,[22–24] although the LCST did not obviously change, the gels still showed an excellent thermal response over a wide range of clay loadings: The LCST for the present gels is around 34. Because NIPAAm is the main component in these polymeric gels, the swelling ratio decreases with an increase of temperature.

Effect of MMT on swelling and deswelling kinetics

The swelling ratios, as a function of time for the present gels in deionized water, are shown in Figure 4.

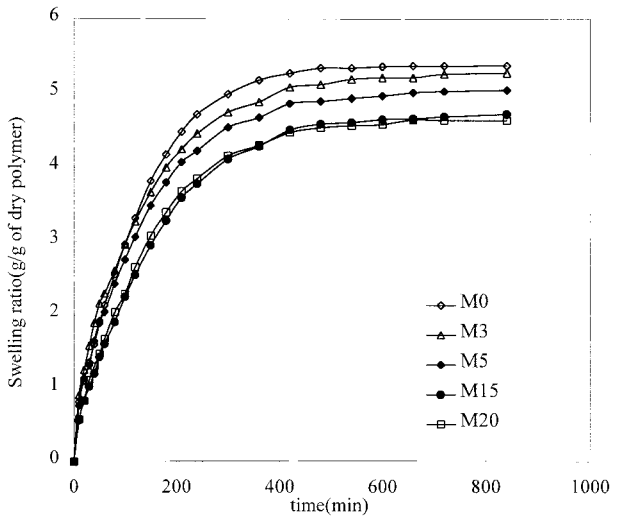

Figure 4 Swelling ratio as a function of time for the hydrogels in deionized water at 25°C.

TABLE II
Initial Diffusion Coefficient of Water *D*, Kinetic Exponent *n*, and Characteristic Constant *k* Through Nanocomposite Gels in Deionized Water at 25°C

Sample	n	$K \times 10^2$	$D \times 10^7$ (cm^2/s)
M0	0.37	2.37	1.05
M3	0.33	3.41	1.07
M5	0.35	2.96	1.06
M15	0.32	3.44	1.1
M20	0.35	2.66	1.06

The n, K, and D values, calculated from eqs. (2) and (3), are listed in Table II. The results show that the diffusion coefficients for these gels in deionized water are not obviously affected by the addition of MMT to the gel. The values of n for the present gels are less than 0.5. According to the classification for the diffusion mechanism presented by Alfrey et al.,[28] the results shown in Table II indicate that the transport mechanism for the nanocomposite hydrogels belongs to Fickian diffusion.

The results, from Figure 5, indicate that the shrinking ratios of the hydrogels at high temperature are affected by their LCSTs. When the swelling poly(NIPAAm) gel is immersed in water above the LCST, deswelling immediately occurs at the gel surface and the gel forms a dense polymer skin layer which retards permeability to water. However, the nanoscale aluminosilicate platelets can uniformly disperse in the polymer matrix and can provide water-release channels which can break the skin layer. So, the shrinking ratios, for these copolymeric gels in deionized water, are in the order of M20 > M15 > M10 > M5 > M3 > M1 > M0. In addition, initial faster deswelling kinetics was observed for the nanocomposite hydrogels as shown in Figure 5. In 10 min, 45 wt % of the water was released from the 20 wt % nanocomposite

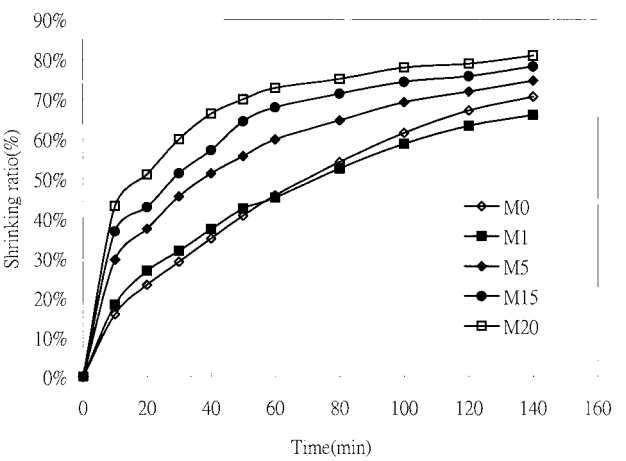

Figure 5 Deswelling ratio as a function of time for the hydrogels in deionized water at 37°C.

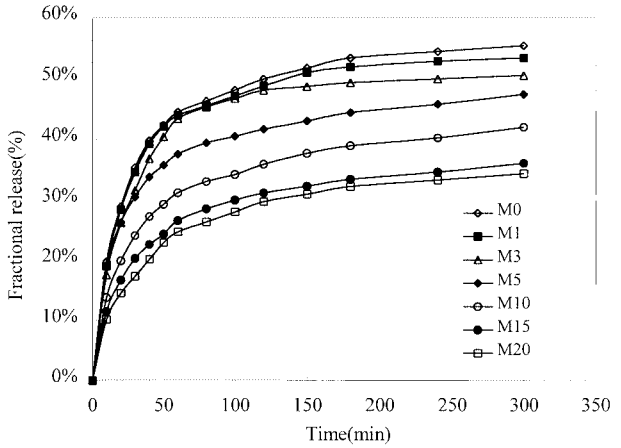

Figure 6 Caffeine-release profiles during loading at 25°C and releasing at 37°C in deionized water.

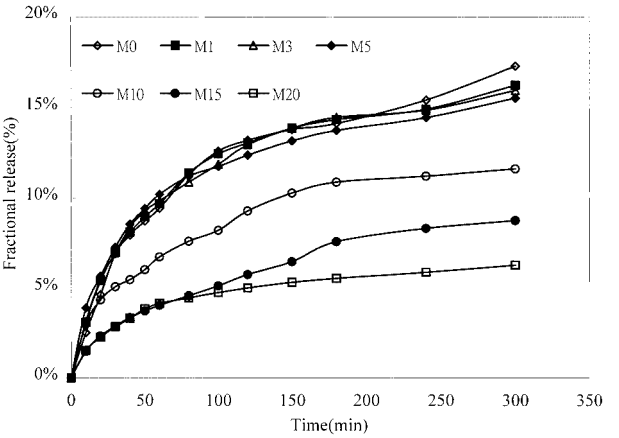

Figure 8 Neutral red-release profiles during loading at 25°C and releasing at 37°C in deionized water.

gel (M20), whereas only 15 wt % of the water was released from pure poly(NIAAm) gel. This phenomenon was also observed in Liang et al.'s study.[24]

Effect of MMT on fractional release of caffeine, CV, phenol red, and neutral red in deionized water or saline

The previous study reported on the investigation of the charge effect on the drug-release behavior for ionic thermosensitive hydrogels.[29] The results showed that the drug-release behavior of the ionic thermosensitive gels is related to their ionicity and drug types. In this study, because MMT bears negative charges on the surface, the nanocomposite hydrogel possesses negative charges. The release profiles of caffeine, CV, phenol red, and neutral red in deionized water or saline solution, for NIPAAm/MMT nanocomposite hydrogels at 37°C, are shown in Figures 6–10, respectively. The loading amount and release amount, and the fractional release of the model drugs in these gels, are shown in Table III.

The results from Figure 6 show that the fractional release of caffeine, for these nanocomposite hydrogels in deionized water at 37°C, is in the order M0 > M1 > M3 > M5> M10 > M15 > M20. From Table III, the caffeine-loading amount increased with an increase in the MMT content in the gel in the 25°C drug solution, but when the gel was transferred to 37°C fresh water, the caffeine was not released accompanied by water molecules while the gel rapidly shrunk. Hence, the fractional release of caffeine exhibited a tendency to decrease while the MMT content increased in the gel composition.

The results of cationic CV and neutral red solutes releasing from the gels in deionized water are shown in Figures 7 and 8, respectively. When the charges of the drug solute and hydrogel are different, electrostatic attraction exists between them. Therefore, the loading amount of CV in the gels increased with increase in the content of MMT (see Table III). But the released amount approximately remained constant. So, the fractional releases of CV in the gel were lower and decreased withan increase in MMT. The same result was observed from neutral red release (see Fig.

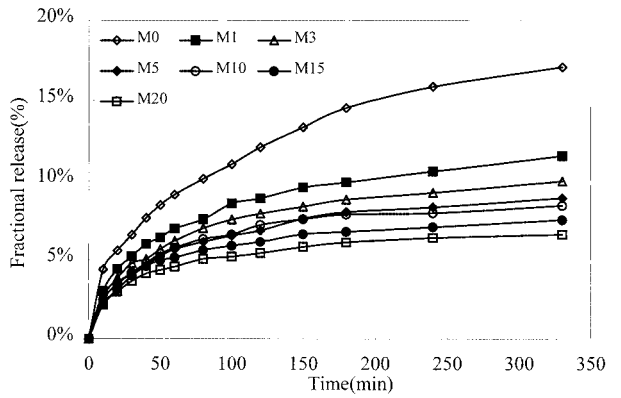

Figure 7 CV-release profiles during loading at 25°C and releasing at 37°C in deionized water.

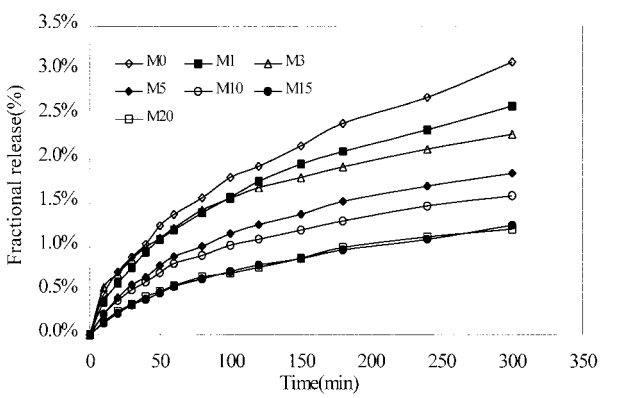

Figure 9 CV-release profiles during loading at 25°C and releasing at 37°C in saline.

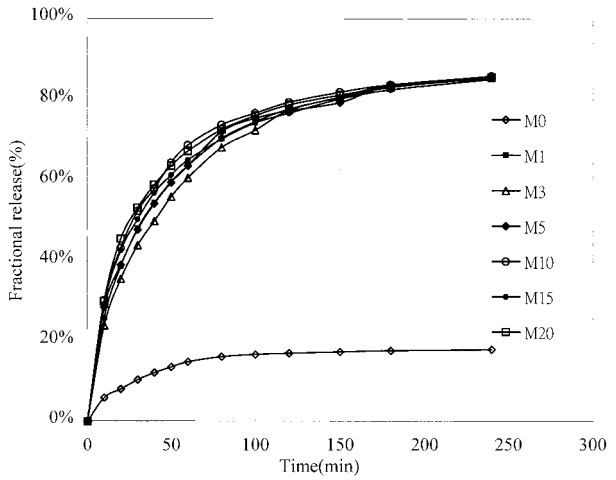

Figure 10 Phenol red-release profiles during loading at 25°C and releasing at 37°C in deionized water.

8). Figure 9 shows the CV-release profile of these gels in saline solution. Because the cationic solutes are difficult to release from the hydrogel in deionized water, we intend to use the ion-exchange technique to improve drug-release behavior. However, the results shown in Figure 9 indicate that CV release was not enhanced in saline solution (compare to Fig. 7). This could be due to a "collapse" of the polymer chains when the gels were transferred from an adsorption medium of low ionic strength to a dissolution medium of high ionic strength.[30] So, the volume of the gel becomes smaller, and the pores on the surface will shrink. Hence, the CV-release ratios are lower in saline solution than in deionized water.

The results of anionic phenol red solutes releasing from anionic gels are shown in Figure 10. When the charges of the drug solutes and hydrogel are the same, the loading amount of phenol red in the gels decreased with an increase in MMT (see Table III). But the released amount of phenol red-like CV in the gels also remains approximately constant. This is because charge repulsion exists between the drug solutes and the gels. The solute is difficult to load into the gel but easily released from the gels. The results in Table III show the lower drug loading in the nanocomposite hydrogels. This is because the nanocomposite hydrogel possesses negative charges and anionic phenol red only adsorbs onto the surface of the gels.

From the above results, we find that the drug-release behavior of NIPAAm/MMT composite hydrogels is profoundly affected by the MMT content, charge of the drug solute, interaction between the gel and the drug solute, and ionic strength of the surrounding medium. These results conform to our previous study.[29]

SEM observation

To understand the microstructure and morphology of the nanocomposite gels, the morphologies of the gels were taken by SEM. The results of the pore size in the

TABLE III
Loading Amount and Releasing Amount and Fractional Release Ratio of the Model Drugs in the Gels

Drug	Sample code	Swelling ratio	Loading amount per milligram xerogel (ppm/mg) at 24 h	Releasing amount per milligram xerogel (ppm/mg) at 300 min	Fractional release at 300 min
Caffiene	M0	5.37	0.47	0.26	55.39%
	M1	5.35	0.52	0.28	53.33%
	M3	5.33	0.59	0.30	50.47%
	M5	5.04	0.70	0.33	47.40%
	M10	4.90	0.96	0.40	41.95%
	M15	4.72	1.05	0.41	39.33%
	M20	4.63	1.27	0.44	34.31%
CV	M0	5.37	1.78	0.29	16.19%
	M1	5.35	1.86	0.21	11.54%
	M3	5.33	2.33	0.23	9.97%
	M5	5.04	2.60	0.23	8.90%
	M10	4.90	2.81	0.23	8.18%
	M15	4.72	2.85	0.22	7.70%
	M20	4.63	2.92	0.18	6.16%
Phenol red	M0	5.37	1.04	0.19	17.91%
	M1	5.35	0.24	0.21	85.78%
	M3	5.33	0.27	0.23	85.48%
	M5	5.04	0.26	0.22	85.57%
	M10	4.90	0.30	0.25	81.84%
	M15	4.72	0.26	0.21	81.51%
	M20	4.63	0.26	0.22	85.44%

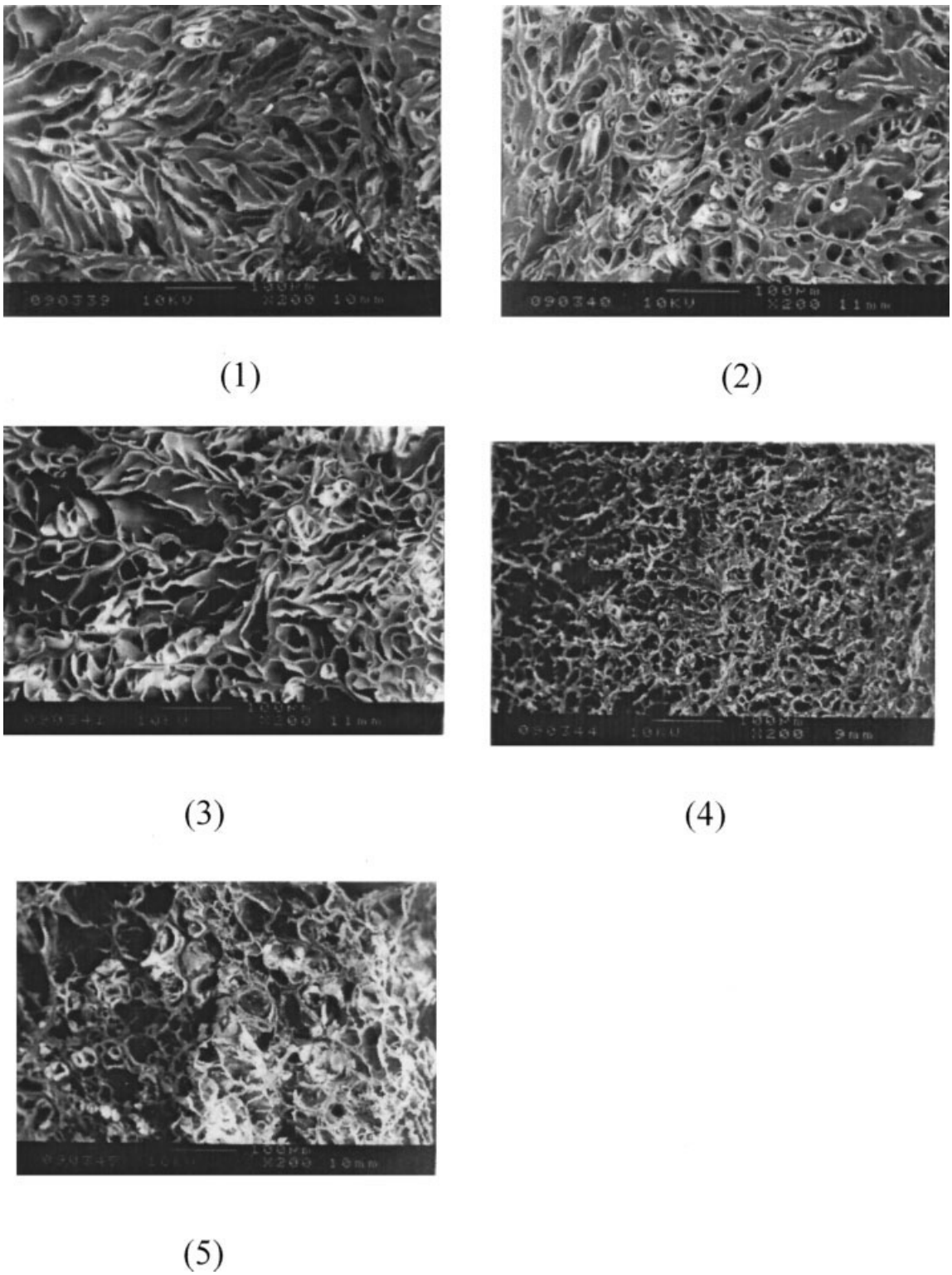

Figure 11 Scanning electron micrograph for the cross section of the gel magnified 200×: (1) M0; (2) M1; (3) M3; (4) M10; (5) M15.

nanocomposite hydrogels are shown in Figure 11. We found that the amount of pores increased with the content of MMT and the pore size decreased with increase of MMT and pore channels formed. These results can explain why the gel strength and shrinking ratios increased with increase of MMT: It is because the amount of pores could improve the gel structure to make the gel strength increase. Due to the formation of pore channels, providing water-release channels, this can improve the gel response.

CONCLUSIONS

NIPAAm/MMT nanocomposite hydrogels were successfully synthesized in this study. From the above discussion, some conclusions can be made as follows: The higher the MMT content, the lower is the swelling ratio of the gels. The shear modulus (G) usually increases with increase in the content of MMT under 15 wt %. The results indicate that MMT could improve the gels' mechanical properties. Because the water-release channels form along an aluminosilicate layer, it could improve the shrinkage rate. The curves of the swelling ratio versus the temperature indicate that the content of MMT does not change the gel transition temperature. The X-ray diffraction experiments show that exfoliation of MMT was achieved.

For drug-release behavior, the results showed that the release ratio of caffeine in the hydrogels was not affected by the ionicity of the hydrogels. The CV strongly interacted with these hydrogels, including the anionic charge of MMT. If the charges of the drug solute and hydrogel are different, electrostatic attraction exists between them and the drug strongly binds in the nanocomposite gels, so the release ratios are lower. Conversely, if the charges of the drug solutes and hydrogel are the same, the release ratio of the gels is higher. When in saline solution, the negative charges on the surface of MMT are neutralized, the volume of the gel becomes smaller, and pores on the surface shrink. The CV-release ratios are lower in saline solution than in deionized water.

The authors gratefully acknowledge the National Science Council of the Republic of China for its financial support (Grant NSC 91-28115-C-036-002-E).

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