Thermoreversible Hydrogels. XII. Effect of the Polymerization Conditions on the Swelling Behavior of the N-Isopropylacrylamide Gel

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ABSTRACT: The swelling behavior for the poly(N-isopropylacrylamide) (NIPAAm) hydrogel prepared in various conditions such as various polymerization media, i.e., deionized water, acetone, and ethanol aqueous solution, and different polymerization temperatures were investigated in this work. The gels were also assessed for suitability in drug-controlled release. The results indicated that the swelling behavior of the gel was dependent on the polymerization media and temperature, that is, the swelling ratios of gel were related to the pore size and the looser or denser structure of the gel. In addition, the pore size of the gel could be controlled by adjusting the surrounding temperature. Hence, the gel can be used to deliver drugs with different sizes. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 78: 1604–1611, 2000

Key words: thermoreversible hydrogel; N-isopropylacrylamide; swelling behavior

INTRODUCTION

Hydrogels are crosslinked hydrophilic polymers that swell but do not dissolve when brought into contact with water. Hydrogels sometimes undergo a reversible discontinuous volume phase change in surrounding conditions with changes such as pH,[1] temperature,[2,3] and solvent composition.[4–8] For example, Tanaka[9] surveyed the critical phase transition behavior of the poly(acrylamide) gel in different temperatures or solution compositions. The swelling behavior of dimethylacrylamide and *n*-butoxymethacrylamide copolymer gel prepared in various polymerization media was reported in our laboratory.[10] The results indicated that the larger the molecular size of the polymerization media, the higher the swelling ratio.

Poly(n-isopropylacrylamide) [Poly(NIPAAm)][11–13] hydrogel exhibits a critical gel transition temperature (CGTT) around 32°C in aqueous solution; that is, the hydrogel exhibits swelling or deswelling at temperatures below or above CGTT. Thus, Poly(NIPAAm) hydrogels have recently been reported to be useful in the field of controlled drug delivery.[13] For example, NIPAAm gel prepared at 4 and 50°C has been studied by Hoffman.[12] The result indicated that the pore size distribution of gel prepared above the CGTT was much larger than that prepared below the CGTT.

Investigation of the influence of different polymerization media, and temperatures under the lower critical solution temperature of poly(NIPAAm) gel, on swelling ratio and diffusion behavior is the main purpose in this article. Furthermore, the utility for drug release or drug delivery of this gel is also assessed.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAAm) (Fluka Chemical Co.) was recrystallized in *n*-hexane before use

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to remove an inhibitor. *N,N*-Methylene-bis-acrylamide (NMBA) (Sigma Chemical Co.), as a crosslinking agent, and ammonium persulfate (APS) (Wako Pure Chemical Co. Ltd.), as an initiator, were further purified by recrystallization. *N,N,N′,N′*-Tetramethylethylenediamine (TEMED) (Fluka Chemical Co.), as an accelerator, was used as received. Crystal Violet (CV) and caffeine as model drugs were obtained from Fluka. All solvents were of analytical grade.

Preparation of Poly(NIPAAm) Hydrogels in Different Polymerization Media

The NIPAAm (679 mg) and 3 mol % NMBA (28 mg) were dissolved in 10 mL of several organic aqueous solutions such as ethanol, acetone, and deionized water, with various volume ratios. To these solutions, 1 mol % APS (14 mg) and 1 mol % TEMED (7 mg) were added as redox initiators, and the mixtures were immediately injected into the space between two glass plates. The gel membrane thickness (2 mm) was controlled by a silicone spacer between the two glass plates. The polymerization was carried out at 5°C for 1 day. After the gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and dried at 40°C for 1 day, then reimmersed in an excess of deionized water for 3 days to remove the residual unreacted component. Swollen polymeric gels were then dried at 40°C for 1 day, and these samples were further dried in a vacuum oven for 1 day at 50°C.

Preparation of Poly(NIPAAm) Hydrogels at Different Polymerization Temperatures

NIPAAm (679 mg) and 3 mol % NMBA (28 mg) were dissolved in 10 mL deionized water. To this solution, 1 mol % APS (14 mg) and 1 mol % TEMED (7 mg) were added as redox initiator, and the mixtures were immediately injected into the space between two glass plates. The gel membrane thickness was controlled by a silicone spacer between the two glass plates. The polymerization was carried out at 15 and 25°C for 1 day. After gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and dried at 40°C for 1 day, then immersed in an excess of deionized water for 3 days to remove the residual unreacted monomer. The swollen polymeric gel disks were dried at 40°C for 1 day, and these samples were further dried in a vacuum oven for 1 day at 50°C.

Measurement of Swelling Ratio

A preweighed dried gel (W_d) was immersed in an excess of deionized water at 25°C until the swelling equilibrium was attained. The weight of 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 formula (1):

$$SR = (W_w - W_d)/W_d \quad (1)$$

Measurement of Thermoreversibility

The thermoreversible behaviors of each sample were characterized by recording the water content of the hydrogel when the temperature changed from 25 to 50°C. The water content (WC) was calculated from the following formula (2):

$$WC\% = [(W_t - W_d)/(W_\infty - W_d)] \times 100 \quad (2)$$

where W_t is the wet weight of the gel at time t, W_d is the dry weight of gel, and W_∞ is the wet weight of the gel at equilibrium state.

Measurement of Dynamic Swelling Behavior of the Gel

The dried gel were immersed in an excess of deionized water at 25°C. The swelling ratio was obtained by weighing the initial and swollen samples at each fixed time interval. The amount of water sorbed, M_t, was reported as a function of time, and the equilibrium sorption at infinitely long time was designated M_∞. Equation (3) can be used to calculate the characteristic constant k, and characteristic exponent, n, for $M_t/M_\infty \leq 0.6$.[14]

$$M_t/M_\infty = kt^n \quad (3)$$

where k is a characteristic constant of the gel, and n is a characteristic exponent of the mode transport of the penetrant.

Equation (4) can be used to calculate the diffusion coefficient D for $M_t/M_\infty \leq 0.8$.[15]

$$M_t/M_\infty = (4/\sqrt{\pi})(Dt/L^2)^{0.5} \quad (4)$$

where t is the time, and L is the initial thickness of the dried sample. Values of n and K were calculated from the slope and intercept of the plot of $\log(M_t/M_\infty)$ against $\log(t)$. In addition, eq. (4) was used to calculate the diffusion coefficient D from

Table I Characterization of the NIPAAm Gels Prepared in Various Ethanol Aqueous Solutions at 5°C

Sample No.	Solvent Volume Ratio (E : W)	Yield (%)	SReq (g/g)	Gel Appearance	Initial Swelling Rate (mg/min)
E1	1 : 9	90.8	10.77	transparent	1.6
E2	2 : 8	91.9	12.39	transparent	2.5
E3	3 : 7	98.1	—	opaque	—
E4	4 : 6	—	—	opaque	—
E5	5 : 5	—	—	opaque	—
E6	6 : 4	—	—	opaque	—
E7	7 : 3	—	—	gelation fail	—

E: ethanol, W: water.

the slope $4\sqrt{D}/\sqrt{\pi}$ of the plot of (M_t/M_∞) against $(t/L^2)^{0.5}$.

Measurement of Drug Diffusion

The dried gels were immersed in an excess of deionized water at 25°C until swelling equilibrium was attained. The preswollen sample was clamped between the two compartments of the diffusion cell. The diffusion drugs were caffeine and crystal violet (CV). At the beginning of the experiment, 25 mL of pure water was poured into the receptor compartment, and 25 mL freshly prepared drug solution of 100 ppm was poured into the donor compartment. To measure the amount of the drugs which diffused through the gel, the released caffeine and CV were analyzed at 270 nm and 561 nm by ultraviolet spectrophotometer (Jasco V-530), respectively.

Measurement of Caffeine Release

To load caffeine into the gel, the dry gels were equilibriated in a caffeine solution (300 mg/100 mL of deionized water) at 25°C for 1 day. The release experiments were carried out by transferring previous drug-incubated gel into 10 mL of deionized water at 50°C. The gels were repeatedly removed and transferred into 10 mL fresh water at each fixed time interval. The released caffeine was analyzed at 270 nm by ultraviolet spectrophotometer (Jasco UV-530).

RESULTS AND DISCUSSION

Characterization of Poly(NIPAAm) Gels Prepared by Various Methods

The characterization of the poly(NIPAAm) gels prepared in various ethanol aqueous solutions (E-series) and acetone aqueous solutions (A-series) at 5°C is listed in Tables I and II, respectively. The results for the E-series in Table I indicate that the appearance of the gels is transparent (a homogeneous state) when the ethanol composition is lower than 20 vol % (E1 and E2). However,

Table II Characterization of the NIPAAm Gels Prepared in Various Acetone Aqueous Solutions at 5°C

Sample No.	Solvent Volume Ratio (A : W)	Yield (%)	SReq (g/g)	Gel Appearance	Initial Swelling Rate (mg/min)
A1	1 : 9	96.8	10.41	transparent	1.7
A2	2 : 8	91.6	10.79	transparent	2.2
A3	3 : 7	99.8	12.22	transparent	2.4
A4	4 : 6	85.4	14.00	transparent	2.8
A5	5 : 5	69.7	—	transparent	—
A6	6 : 4	72.2	—	transparent	—
A7	7 : 3	86.5	—	transparent	—
A8	8 : 2	—	—	gelation fail	—

A: acetone, W: water.

Table III Characterization of the NIPAAm Gels Prepared in Deionized Water at Various Polymerization Temperatures

Sample No.	Polymerization Temperature (°C)	Yield (%)	SReq (g/g)	Gel Appearance	Initial Swelling Rate (mg/min)
W5	5	95.2	8.15	transparent	1.3
W15	15	96.8	13.5	transparent	1.3
W25	25	97.3	14.1	transparent	1.1

the appearance of the gels (E3–E6) is opaque (a heterogeneous state), and the gel becomes too loose to measure swelling ratios when the ethanol composition is over 20 vol % in the polymerization medium. The polymer fails to gelate when the ethanol composition is over 70 vol %.

For the A-series, the results shown in Table II indicate that the gel appearance is transparent (a homogeneous state) when the acetone composition is lower than 80 vol % (A1–A7). But the surface of gel becomes tacky, and the swelling ratios for those gels cannot be measured when the composition of acetone is over 50 vol % (A5–A7). When the acetone composition reaches 80 vol %, polymer gel cannot be formed.

The characterization for the gels (W5, W15, and W25) prepared in deionized water under different temperatures is listed in Table III. The results show that the appearance of the gel is transparent, and yields are over 95%. The swelling ratios increase with an increase in polymerization temperatures, which is below the LCST of NIPAAm (32°C).

Effect of Polymerization Media on Swelling Ratio for Poly(NIPAAm) Hydrogels

In our previous studies,[10,16] we had shown that the larger the molecular size of the polymerization media, the higher the swelling ratio for N-tetrahydrofurfuryl acrylamide (NTHFAAm) gel and dimethyl acrylamide and *n*-butoxymethyl acrylamide (DMA/nBMA) copolymer gels in alcohol homologs. This is due to the fact that the larger molecular size of the polymerization media causes the hydrogel to possess a larger pore size. But we also found that the swelling behavior of the NTHFAAm gel prepared in acetone solution does not follow the above-mentioned rule. Hence, the swelling behavior of the gel not only depends upon the molecular size of polymerization media but also upon the solubility and miscibility of monomer and solvent.[16]

In the present article, the influence of polymerization media on swelling ratio for poly(NIPAAm) hydrogel is shown in Figure 1. The results in Figure 1 indicate that the swelling ratio of E2 gel is higher than A2 and W5 gels. This result is also similar to the result of the NTHFAAm gel in those aqueous solutions. Although the molecular size of acetone is larger than that of ethanol, the gel appearance is opaque when the ethanol content reaches 30%; that is, the gel exhibits a heterogeneous structure (see Table I), and possesses a looser structure and larger pore size. Thus, the gels prepared in ethanol aqueous solution (E series) show larger swelling ratios than those prepared in acetone aqueous solution (A series) and deionized water (W series).

Comparing the initial swelling rates for E2 (Table 1), A2 (Table 2), and W5 (Table 3), the order is E2 > A2 > W5. This result also explicitly indicates that the gels prepared in various polymerization media have different swelling behaviors.

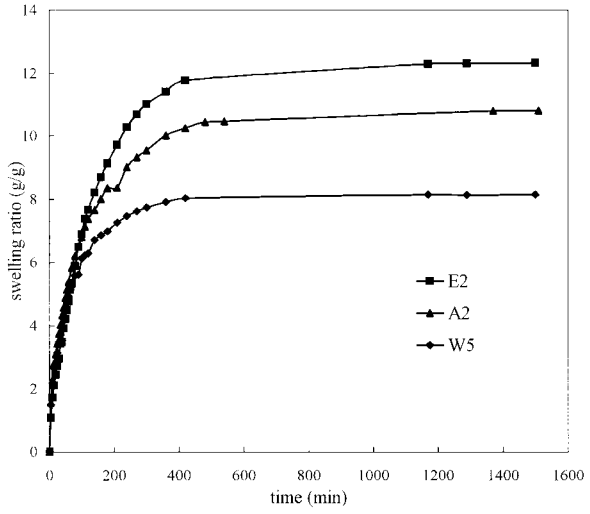

Figure 1 Effect of polymerization medium on swelling ratio as a function of time for NIPAAm hydrogels.

The effect of the ethanol amount in the NIPAAm gel prepared in ethanol aqueous solution at 5°C on swelling behavior was investigated. The swelling ratio as a function of time for E1 and E2 gels in deionized water shown in Figure 2 demonstrates that the swelling ratio increases with AN increase in ethanol content (also see Table I). The result also shows that the initial swelling rate for E2 (3 h) is larger than that for E1. This is due to the larger size of the ethanol molecule. In addition, the NIPAAm gel easily forms heterogeneity in ethanol and makes the hydrogel possess larger pores and a looser structure when the ethanol content increases.

The effect of the acetone amount in the NIPAAm gel prepared in acetone aqueous solution at 5°C on swelling behavior was investigated. The swelling ratios, as a function of time for these gels in deionized water, shown in Figure 3, indicate that the swelling ratio increases with an increase of acetone content. From Table II, the results also show that the initial swelling rate (3 h) increases with increasing the acetone content. This is due to the larger molecular size of acetone. Hence, the hydrogels have larger pores when the acetone content increases. When the acetone content was above 50% (vol %), the structure of the gels was very loose, and the swelling ratio could not be measured.

Effect of Polymerization Temperature on Swelling Ratio for Poly(NIPAAm) Hydrogels

From Table III we can observe that the appearance of the gels is transparent when the gels were prepared in deionized water at 5, 15, and 25°C. The effect of polymerization temperature on swelling ratio for poly(NIPAAm) hydrogels is shown in Figure 4. The results in Figure 4 indicate that the higher the polymerization temperature, the higher the swelling ratio. This is because the higher polymerization temperature would decrease the hydrogen bonding between the water molecules and the amide group in NIPAAm. Thus, the hydrogel easily forms phase discontinuities, causing the hydrogel to become a looser

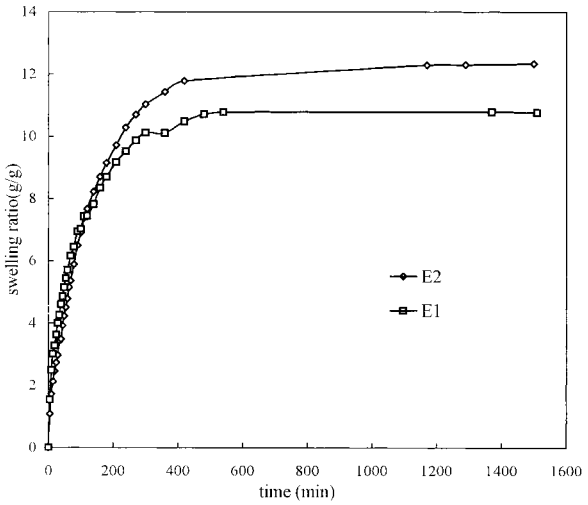

Figure 2 Swelling ratio as a function of time for NIPAAm hydrogels prepared in ethanol solutions at 25°C.

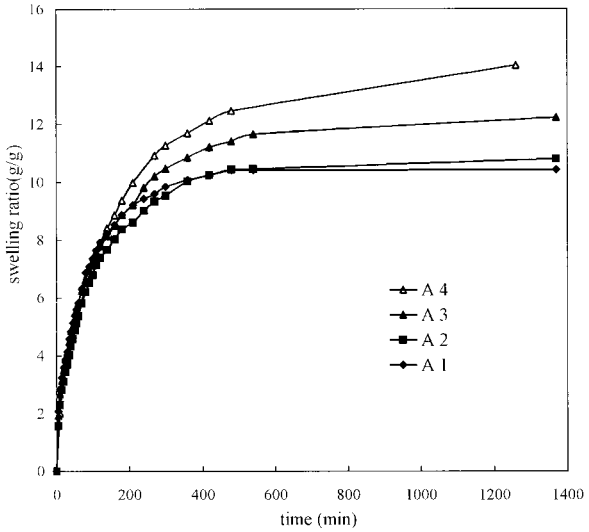

Figure 3 Swelling ratio as a function of time for NIPAAm hydrogels prepared in acetone solutions at 25°C.

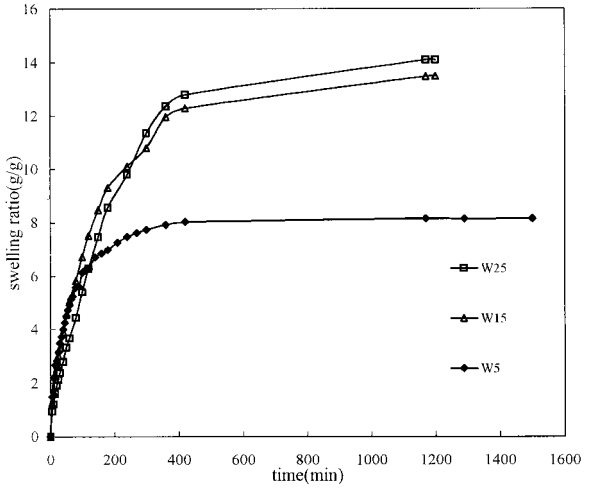

Figure 4 Swelling ratio as a function of time for NIPAAm hydrogels prepared in various temperatures at 25°C.

structure. Hoffman[12] reported that the pore size distribution of macroporous hydrogel prepared above the LCST is much larger than that of the gel prepared below the LCST. Therefore, we know that when the polymerization temperature is below the LCST, the swelling ratio increases with an increase in polymerization temperature.

However, from Table III, the initial swelling rates (3 h) for W5, W15, and W25 have no large differences and do not increase with the swelling ratio, and the initial swelling rates (3 h) for W15 and W25 are not larger than the E series and A series hydrogels. From this above discussion, the results indicate that the initial swelling rate is mainly affected by the pore size of the gel, and the swelling ratio is mainly affected by the structure of the gel.

Effect of Temperature on Swelling Ratio for Different Gels

The dependence of the temperature and swelling ratio for various NIPAAm gels is shown in Figure 5.The swelling ratios show a gradual decrease with increase in temperature. The gel transition temperatures observed from Figure 5 are not significantly affected by the polymerization media.

Thermoreversible Behaviors

The thermoreversible behaviors for hydrogels operated at 25 and 50°C are shown in Figure 6. The operation was repeated for three cycles, and the water content was measured as a function of time. The results in Figure 6 show that the changes of water content for the gels prepared at higher temperatures such as W25 and W15 are 94.5 and 79.7% within 10 min. But the changes of water content for the gels prepared at low temperatures such as E2, A2, and W5, are only 24.9, 19.5, and 16.2% within the same time. Because the changes of water content for these gels are smaller, the reswelling speeds for the gels are more rapid than for gels prepared at higher temperatures (W15 and W25).

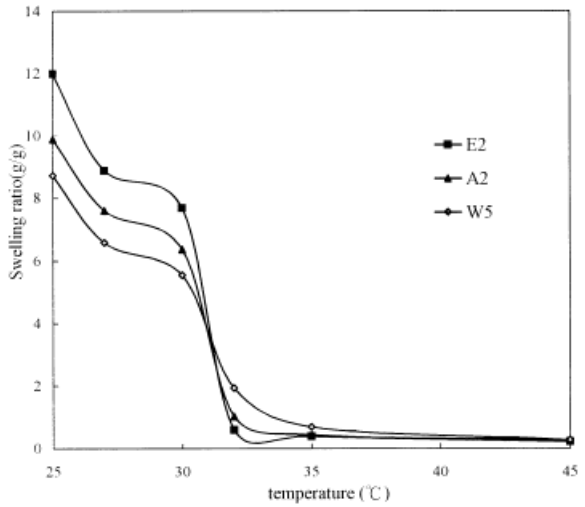

Figure 5 Effect of polymerization medium on swelling ratio of NIPAAm hydrogel at different temperatures in water.

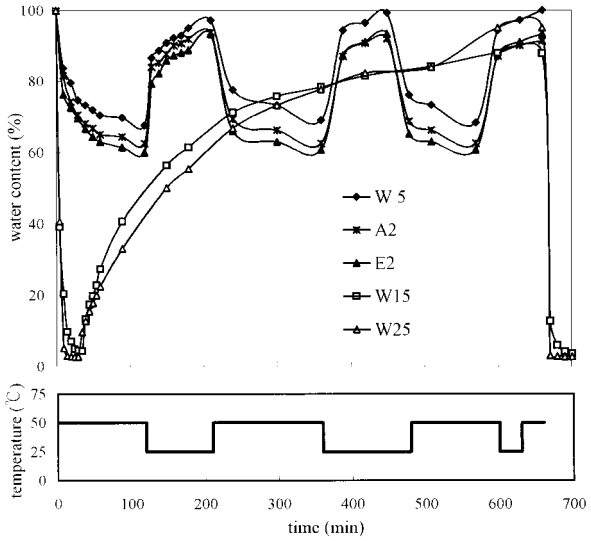

Figure 6 Water content of hydrogels as a function of time with repeated abrupt changes of temperature between 25 and 50°C.

Dynamic Swelling

Table IV shows the diffusion coefficient, D, the characteristic exponent, n, and the characteristic constant, K, for the gels in various polymerization media at 25°C. The results indicate that the values of characteristic exponent n for this series gels at 25°C are in the range from 0.2 to 0.3. This result shows that the swelling transport mechanism is a Fickian transport at 25°C.[14] In addition, the data shown in Table IV also indicate that the characteristic exponents n and diffusion coefficients D increase as the molecular sizes of polymerization media increase. This is because the larger the polymerization media molecule, the larger the pore size of gels, and the faster the diffusion rate.

Effect of Gels on Fractional Release of Caffeine

The release profiles of caffeine in different gels at 50°C is shown in Figure 7. The results shown in

Table IV Initial Diffusion Coefficient, *D*, and Characteristic Exponent, *n*, and Characteristic Constant, *k*, of Solvent Penetrated through NIPAAm Hydrogels at 25°C

Sample No.	Solvent	*n*	*K*	$D \times 10^8$ (cm^2/s)	SReq (g/g)
W5	water	0.20	0.26	3.7	8.15
A1	acetone	0.20	0.25	4.5	10.40
A2	acetone	0.24	0.20	5.8	10.79
E1	ethanol	0.24	0.20	5.8	10.77
E2	ethanol	0.30	0.13	7.8	12.38

this figure can be discussed from two viewpoints. The first result shows that the fractional release of caffeine in gel increases when the polymerization temperature increases, i.e, (W25 > W15 > W5). This occurrence proves that the gel has a loose structure and a larger pore size when prepared at higher temperature. The second result shows that when the molecular size of polymerization media is larger, the release profiles of caffeine in gel is faster, i.e., (E2 >A2 > W5).

From the above discussion we can conclude that the gels prepared at higher temperatures have more and faster release profiles than those prepared in larger molecular size polymerization media. For example, the release profile of caffeine for W25 (the gel prepared in deionized water at 25°C) reaches 80% at 10 min, but for W15 it only releases 50% during the same time interval. In addition, the release profiles for the gels W5, E2, and A2 are only 40, 30, and 20%, respectively. At the same time, we find that the release profiles of caffeine for those gels do not reach 1.0. This is due to water pocket formation in the collapsed gel.[3,13] Hence, caffeine was entrapped in the gel and could not be released completely.

Diffusion of Caffeine and CV

Figure 8 shows the diffusion of caffeine and CV through the E2, A2, and W5 hydrogels clipped in the diffusion cell at 27°C. The results show that the diffusion amount of caffeine or CV is a function of pore size of the hydrogel. It shows that the diffusion of caffeine or CV through these gels increases with increasing the molecular size of polymerization media. The order of the diffusion amount of caffeine and CV is E2 > A2 > W5.

Because the CV molecule is larger than the caffeine molecule, we can observe that the diffusion amount of CV is smaller than that of caffeine in the diffusion system. Figure 9 respectively shows the diffusion of caffeine and CV for E2, A2,

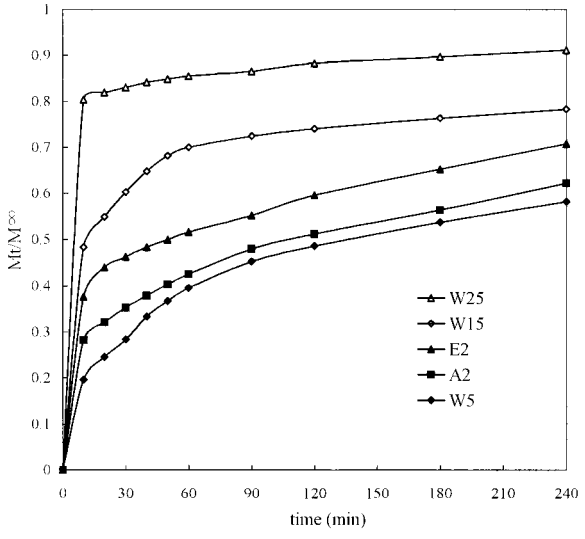

Figure 7 Effect of NIPAAm gels on caffeine release profile during deswelling (50°C).

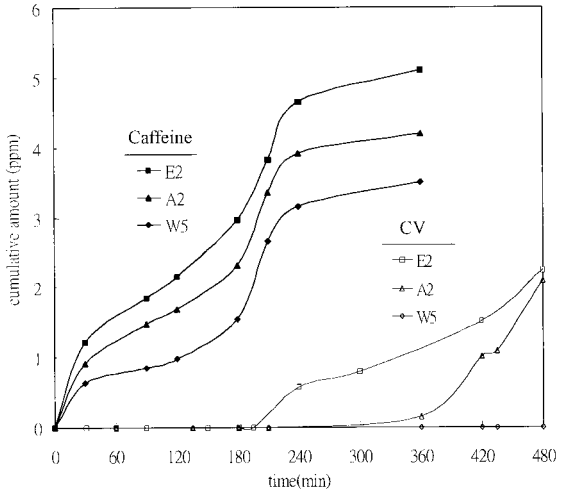

Figure 8 The diffusion behavior in 100 ppm caffeine and CV solution for NIPAAm hydrogel prepared in different media at 27°C.

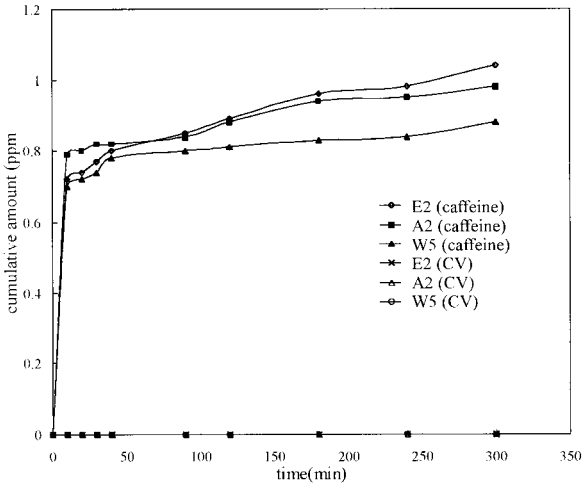

Figure 9 The diffusion behavior in 100 ppm caffeine and CV solution for NIPAAm hydrogel prepared in different solutions at 37°C.

and W5 hydrogels at 37°C. The results also show the order of the diffusion amount of caffeine is E2 > A2 > W5, but the CV does not pass through these gels at 37°C. Hence, when the temperature rises to 37°C, the pore size of the gels becomes smaller so that the CV does not diffuse through these gels.

CONCLUSIONS

The swelling behavior of thermoreversible hydrogels is related to their looser or denser structures and pore sizes, which is dependent on the surrounding temperature, polymerization temperature, and polymerization media. The effect of the polymerization temperature on the swelling ratio for these gels indicates that the higher the polymerization temperature, the higher the swelling ratio and the higher the fractional release of caffeine. The effect of polymerization media on swelling ratio for these gels also shows that the larger the molecular size of the polymerization media, the higher the swelling ratio and the fractional release of caffeine. The initial swelling rate of the gel is mainly affected by the pore size of the gel, but the equilibrium swelling ratio is controlled by the looser or denser structure of the gel. Comparing these two factors, it can be concluded that the effect of polymerization temperature on the swelling ratio and drug release is more predominant than that of the polymerization media. Thus, the influence of the gel structure on the swelling ratio or drug release is greater than that of pore size in the gel.

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REFERENCES

1. Hirokawa, E.; Tanaka, T. J Chem Phys 1984, 81, 6379.
2. Hoffman, A. S. J Controlled Release 1987 6, 297.
3. Bae, Y. H.; Okane, T; Kim, S. W. J Polym Sci Polym *Phys* 1990, 28, 923.
4. Ilavsky, M. Macromolecules, 1982, 15, 782.
5. Beltran, S.; Hooper, H. H.; Blanch, H. W.; Prausnitz, J. M. J Chem Phys 1990, 92, 2061.
6. Ulbrich, K.; Subr, V.; Podperova, P.; Buresova, M. J Controlled Release 1995, 34, 155.
7. Rathjen, C. M.; Chang, P. H.; Goodrich, P. R.; Walagenbach, D. D. Polym Gels Networks 1995, 3, 101.
8. Satyanarayana, D. Chatterji, P. R Polymer, 1993, 4, 3682.
9. Tanaka, T. Polymer, 1979, 20, 1404.
10. Lee, W. F.; Yeh, P. L. J Appl Polym Sci 1998, 68, 1597.
11. Mukae, K.; Bae, Y. H.; Okano, T.; Sung, W. K. *Polym J* 1990, **22**, 206.
12. Yan, Q.; Hoffman, A. S. Polymer 1995, 36, 4, 887.
13. Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. J Controlled Release 1986, 4, 213.
14. Kabra, B. G.; Gehrke, S. H.; Hwang, S. T. J Appl Polym Sci 1991, 42, 2409.
15. Franson, N. M.; Peppas, N. A. J Appl Polym Sci 1983, 28, 1299.
16. Lee, W. F.; Yeh, P. L. J Appl Polym Sci 1997, 65, 909.