Effect of Fluorinated Hydrophobic Monomer on the Drug Release Behavior for the Thermosensitive Hydrogels

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ABSTRACT: Three series of copolymeric gels based on *N*-isopropylacrylamide (NIPAAm) and perfluoroalkyl methacrylate such as 2,2,3,3,4,4,5,5-octafluoropentyl methacrylate (OFPMA), 4,4,5,5,6,7,7,7-octafluoro-2-hydroxy-6-(trifluoromethyl)heptyl methacrylate (OFHHMA), and 3,3,4,4,5,6,6,6-octafluoro-5-(trifluoromethyl)hexyl methacrylate (OFHMA), were prepared by emulsion polymerization. The effect of perfluoroalkyl methacrylate and sodium lauryl sulfate (SLS), which can act as a surfactant and a pore-forming agent, on the equilibrium swelling ratio and mechanical properties of the present hydrogels was investigated. Results show that hydrophobic monomers made the swelling ratio of the gel decrease and the mechanical property of the gel increase; however, SLS exhibits a contrary result. In addition, the effect of perfluoroalkyl methacrylate on the drug release behavior was also investigated. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 100: 4661–4667, 2006

Key words: hydrogel; perfluoroalkyl methacrylate; drug release behavior

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymeric networks that swell but do not dissolve when brought into contact with water. There are hydrogels that sometimes undergo a volume change in response to a change in surrounding conditions such as temperature,[1,2] pH,[3] and different concentration and kind of ions in the solution.[4,5] Those effects would cause differences of swelling ratios and volume variation, which could be applied in separation of solute and control of drug delivery.[6–11] In recent years, these hydrogels have often been used in drug release and some applications of biomedical materials.

The volume variation of the general temperature-sensitive gels is caused by different hydrophilic and hydrophobic characteristics of polymeric chain at different temperatures. It is well known that poly(NIPAAm) gel undergoes a dramatic volume phase transition in water above the lower critical solution temperature (LCST), (32–33)°C. When a swollen poly(NIPAAm) hydrogel is immersed into water above the LCST, deswelling immediately occurs at the gel surface. On the contrary, poly(NIPAAm) gel becomes hydrophilic when immersed in water below the LCST. Because poly(NIPAAm) has afore-mentioned properties, it is often used for temperature-sensitive gels.

In recent years, much research in hydrogels has been focused on drug release and drug delivery. In addition to their inertness and good biocompatibility, the ability of hydrogels to release entrapped drug in an aqueous medium and the ease of regulating such drug release by controlling water swelling and crosslinking density have made hydrogels particularly suitable as drug carriers in the controlled release of pharmaceuticals.[12] The permeability and releasing rate of drugs are influenced by the type of releasing agent and swelling ratio in hydrogels.[13] Despite the high water content of the hydrogels, the system might also be used for the release of drugs that are poorly soluble in water. Solute transport through a polymer membrane is either via the pore or partition mechanism. In the pore mechanism, the solute diffuses through the water filled pores. In the partition mechanism, the solute transport is presumed to occur by a process involving the dissolution of the solute within the polymer followed by the diffusion through the membrane.[14]

Conventionally, fluorinated copolymer hydrogels with high oxygen permeability for contact lenses are prepared by UV irradiation.[15–20] However, fluorine-containing thermoreversible hydrogels have not been investigated in the literature. Hence, a series of thermoreversible hydrogels based on NIPAAm and perfluoroalkyl methacrylate were prepared by emulsion polymerization process. The effect of hydrophobic perfluoroalkyl methacrylate moiety and content of

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TABLE I
Equilibrium-Swelling Ratio and Feed Compositions of the Hydrogels

Sample code	NIPAAm (mol %)	OFPMA (mol %)	OFHHMA (mol %)	OFHMA (mol %)	SLS (mol %)	Yield (%)	Q (g/g)
A	99.8	0.2	—	—	0.5	95	6.26
B	99.8	0.2	—	—	2.5	98	6.12
C	98.0	2.0	—	—	2.5	98	5.67
D	99.8	—	0.2	—	0.5	98	6.02
E	99.8	—	0.2	—	2.5	97	6.00
F	98.0	—	2.0	—	2.5	99	5.74
G	99.8	—	—	0.2	0.5	98	5.91
H	99.8	—	—	0.2	2.5	99	6.18
I	98.0	—	—	2.0	2.5	90	6.05
N	100	—	—	—	0	95	5.42

The concentration of the polymerization solution was 1.2*M*.

surfactant on the drug release behavior for the copolymeric gels is the main purpose in this study.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAAm) (Wako Chemical Co. Tokyo, Japan) was recrystallized in *n*-hexane before use. The fluorinated monomers, such as 2,2,3,3,4,4,5,5-octafluoropentyl methacrylate (OFPMA), 4,5,5,6,7,7,7-octafluoro-2-hydroxy-6-(trifluoromethyl)heptyl methacrylate (OFHHMA), and 3,3,4,4,5,6,6,6-octafluoro-5-(trifluoromethyl)hexyl methacrylate (OFHMA) (Aldrich Chemical Co. St. Mo.) were used directly. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED; Fluka Chemical Co. Buchs, Switzerland) as an accelerator. *N*, *N*′-methylenebisacrylamide (NMBA) as a crosslinking agent and ammonium persulfate (APS; Tokyo Kasei Industries, Ltd. Tokyo, Japan) as an initiator were used as received. Caffeine and vitamin B_{12} as model drugs were obtained from Fluka Chemical Co. All solvents and other chemicals used were of analytical grade.

Preparation of hydrogel

Various molar ratios of NIPAAm and fluorinated monomer and 3 mol % NMBA based on total monomer were dissolved in fixed capacities of deionized water that could fill whole silicon spacer spaces. APS (0.5 mol %) and 1 mol % TEMED as redox initiators were added. Sodium lauryl sulfate (SLS), $NaHCO_3$ (0.01 g), and 1*M* HCl 0.1 mL were also added. The mixture was immediately injected into the space between the two glass plates. The membrane thickness of gel was adjusted with a silicon spacer between the two glass plates. Polymerization was carried out at 20°C for 24 h. After gelation was completed, the gel membrane was cut into discs, 8.5 mm in diameter, and immersed into an excess amount of deionized water for a week to completely remove SLS and residual unreacted monomer. Swollen polymer gels were dried at 40°C for 3 days, and these samples were further dried in a vacuum oven for 1 day. The feed compositions and sample codes for the representative copolymeric gels are listed in Table I.

Measurement of swelling ratio

The preweighed dried gels (W_d) were immersed in deionized water at 25°C until the gels approached equilibrium. Each gel was removed from the water bath, tapped with delicate task wipers to remove excess surface water, and weighed as the wet weight of gel (W_t). The swelling ratio (Q) was calculated from the following equation:

$$Q = (W_t - W_d)/W_d \quad (1)$$

Drug release experiment

The dried gels were equilibrated in 30 mg drug/100 mL of deionized water at 25°C for 2 days to load drug into the gels. The drug release experiments were carried out by transferring previously incubated-drug gels into 10 mL deionized water at 37°C. The gels were repeatedly removed and transferred into 10 mL deionized water at each fixed time interval. The released drug was analyzed at 272 and 360 nm for caffeine and vitamin B_{12}, respectively, by an ultraviolet spectrophotometer (JASCO V530 Tokyo, Japan).

Physical properties measurement

The gel strength of these samples was measured by a uniaxial compression experiment with universal tester (LLOYD LRX, Fareham, UK). The following equation was used to calculate the shear modulus (G):

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

where τ is compression stress, F is compression load, A is cross-sectional area of swollen gels, and λ is compression strain ($\Delta L/L_0$) where ΔL is difference between the thickness of the dried gel and swollen gels. L_0 is the thickness of the dried gels. At low strains, a plot of shear stress versus -($\lambda - \lambda^{-2}$)would yield a straight line whose slope was shear modulus (G). The effective crosslinking density (ρ) could then be calculated from the shear modulus and polymer volume fraction (υ_2) as follows:

$$\rho = G/(\upsilon_2^{1/3} \times \mathrm{RT}) \quad (3)$$

where R is the gas constant and T is the absolute temperature.

Morphology

The dried specimens were examined for morphological details by using scanning electron microscopy (SEM) (JOEL JSM-6300, MA, USA) with an acceleration voltage of 15 kV. The specimens were coated with a gold metal layer to provide proper surface conduction.

RESULTS AND DISCUSSION

Effect of hydrophobic monomer on swelling ratio

The equilibrium-swelling ratios for the present copolymeric hydrogels are shown in Table I. According to Flory's swelling theory for nonionic gels, the following equation was given[21]:

$$Q^{5/3} = \left[\frac{(1/2-\chi_1)}{V_1}\right]/(\mathrm{v}_e/V_0) \quad (4)$$

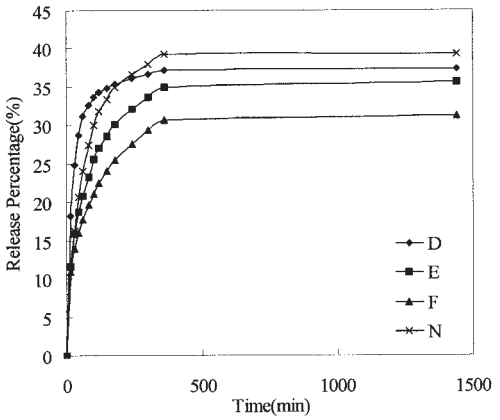

Figure 2 Caffeine release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFHHMA in deionized water.

where Q is the equilibrium swelling ratio and $(1/2-\chi_1)/V_1$ is the affinity of the hydrogel and ν_e/V_0 is the crosslinking density of the hydrogel. Hence, the swelling ratio only has a relation to the crosslinking density and the affinity of the gel toward water.

The equilibrium swelling ratios for the present copolymeric gels in deionized water shown in Table I indicate that the swelling ratio increases when the perfluoroalkyl methacrylate monomer was added into the NIPAAm gel by emulsion polymerization (see sample codes A, D, G, and N; B, E, H, and N; C, F, I, and N). In general, the hydrophobic monomer incorporated into the NIPAAm gel would decrease the swelling ratio of the copolymeric gels. This phenomenon can be observed from the present gels such as B and C; E and F; or H and I gels. It is surprising that the hydrophobic fluorinated monomer can enhance the swelling ratio of the poly(NIPAAm) gel. That is, the swelling ratios for these all copolymeric gels are

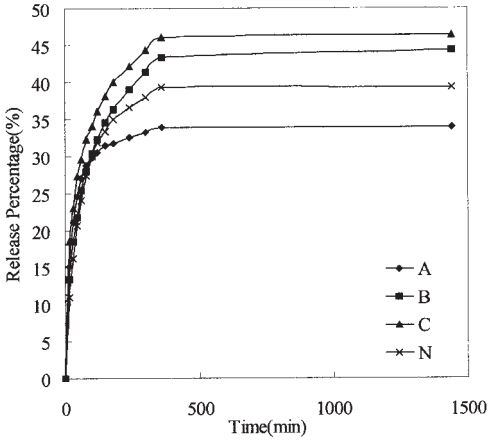

Figure 1 Caffeine release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFPMA in deionized water.

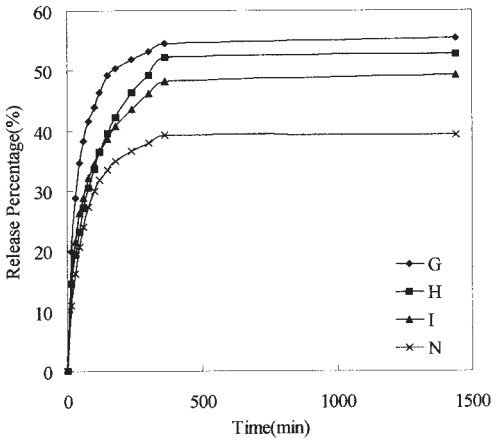

Figure 3 Caffeine release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFHMA in deionized water.

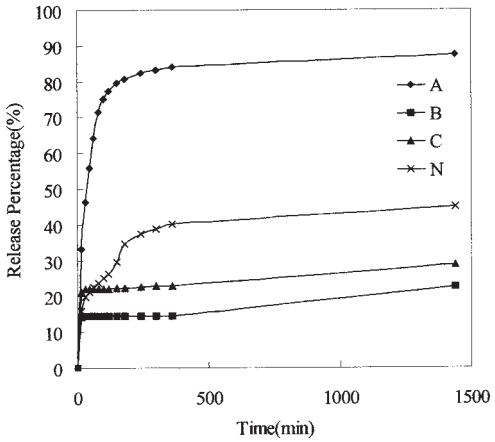

Figure 4 Vitamin B_{12} release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFPMA in deionized water.

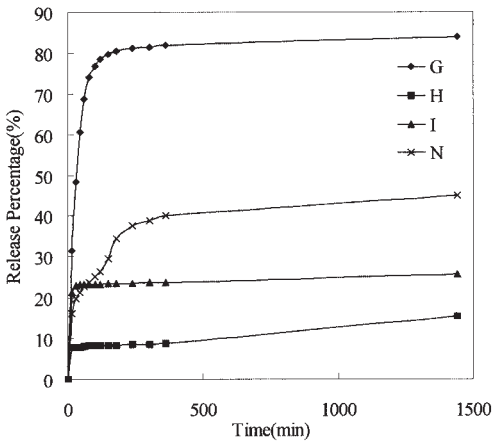

Figure 6 Vitamin B_{12} release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFHMA in deionized water.

higher than that for pure poly(NIPAAm) gel. Hence, we think the main effect resulting in this result is attributed to the polymerization process, i.e., emulsion polymerization effect. This is because SLS has both emulsification and pore-forming effect simultaneously. On the other hand, the different fluorinated monomers required different content of SLS to emulsify them. The results in Table I also show that the swelling ratios for the gels, such as A and B; D and E; G and H, are not significantly affected by increasing SLS. Similarly, the effect of the structure of perfluoroalkyl methacrylate on the swelling ratio for the copolymeric gels is also not obvious.

Drug release

Caffeine and vitamin B_{12} were chosen as model drugs in drug release experiment. The concentrations of the two drug solutions were 300 ppm. The dry gels were equilibrated in drug solution at 25°C for 2 days to load drug into the gels.

In general, drug-loading capacity is proportional to the swelling ratio of the gel, but the drug-releasing behavior is also concerned with the temperature and pore-forming agent etc. Figures 1–3 show respectively, the caffeine releasing profile during loading at 25°C and releasing at 37°C for these three series fluorinated hydrogels in deionized water. An unusual tendency for these gels was observed from the caffeine release behavior, which was affected by emulsification and the pore-forming effect of SLS. This unusual tendency in caffeine release depended on the type of fluorinated monomers, but did not depended on SLS. We also find a phenomenon from these figures that the release ratio of caffeine for the copolymeric hydrogels containing OFPMA, was improved by more pore-forming agent, SLS (C > B > A). However, a contrary result was observed for other two series gels; i.e., D > E > F and G > H > I. Hence, we supposed that this phenomenon

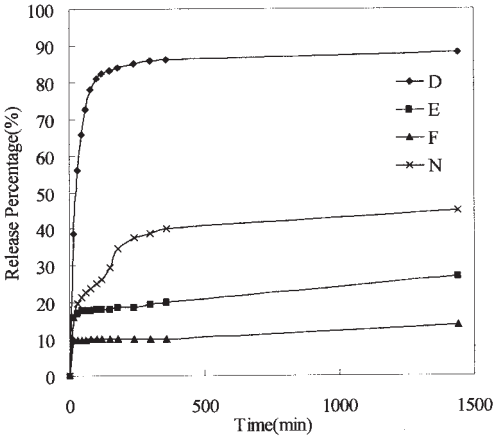

Figure 5 Vitamin B_{12} release profile during loading at 25°C and releasing at 37°C for the hydrogels containing OFHHMA in deionized water.

TABLE II
Releasing Profile for the Present Gels for Caffeine

Sample code	Caffeine		
	Loading amount (ppm/g)	Releasing amount (ppm/g)	Releasing ratio (%)
A	703	238	33.8
B	534	237	44.3
C	514	238	46.4
D	650	242	37.3
E	661	235	35.6
F	692	216	31.2
G	533	295	55.3
H	618	326	52.7
I	704	346	49.2
N	836	329	39.3

TABLE III
Releasing Profile for the Present Gels for Vitamin B_{12}

Sample code	Vitamin B_{12}		
	Loading amount (ppm/g)	Releasing amount (ppm/g)	Releasing ratio (%)
A	240	213	88.9
B	209	74	35.5
C	282	93	33.0
D	210	188	89.6
E	212	77	36.1
F	339	64	19.0
G	236	201	85.0
H	314	69	22.0
I	390	108	27.8
N	264	126	47.6

depended on the degree of emulsification. In other words, 0.2 mol % OFPMA can be completely emulsified by 0.5 mol % at even 2.5 mol % SLS, but OFHHMA and OFHMA cannot be completely emulsified by SLS. Excess amount of SLS can create more and larger pores of the gel. The release amount for the present gels, such as A, B, C, approximately kept constant. Hence, a gel (C) with lower loading amount had a higher releasing ratio for OFPMA system in a fixed releasing amount.

Contrary results were observed from other two series gels such as D, E, F and G, H, I gel. The caffeine-loading amount for these two series gels increases with increase in OFHHMA and OFHMA content. But the releasing ratios decrease with an increase of the content of OFHHMA and OFHMA in the copolymeric gels in a similar releasing amount.

From the earlier mentioned results, we find some regularity in the different fluorinated monomers. The chemical structures for OFPMA and OFHHMA (or OFHMA) are different. The OFPMA has 8 *F* atoms, but the OFHHMA (or OFHMA) has 11 *F* atoms in respective the structures. Hence, OFHHMA (or OFHMA) has more hydrophobicity. So the degree of emulsification is a decisive factor in drug releasing system.

TABLE IV
Crosslinking Densities of the Present Gels

Sample code	G (g/cm^2)	ρ (mol/cm^3)
A	792	4.99 E −05 ± 2%
B	693	4.58 E −05 ± 11%
C	788	4.67 E −05 ± 1%
D	767	4.91 E −05 ± 3%
E	690	4.60 E −05 ± 7%
F	731	4.71 E −05 ± 5%
G	825	5.05 E −05 ± 1%
H	680	4.48 E −05 ±8%
I	782	4.74 E −05 ± 6%
N	823	5.32 E −05 ± 6%

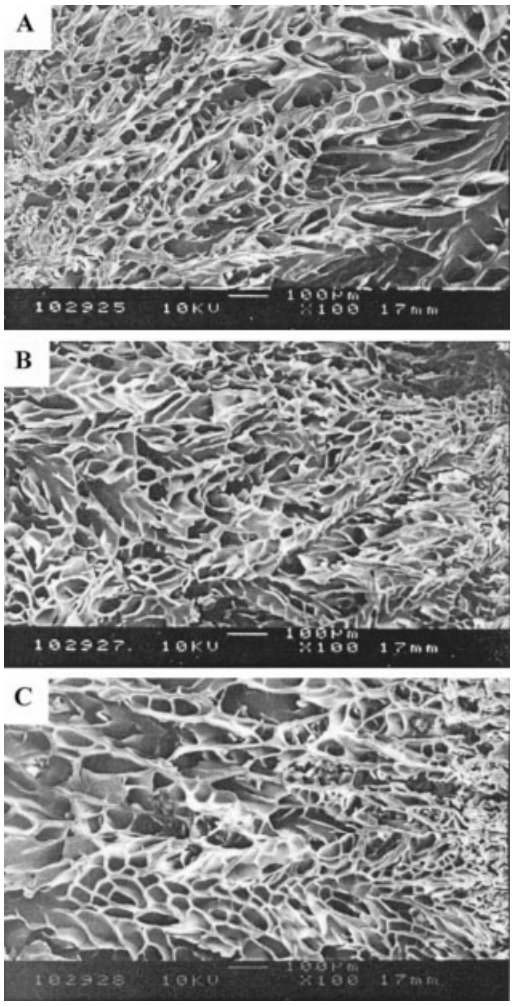

Figure 7 SEM morphologies for the hydrogels containing OFPMA.

However, another drug-vitamin $B_{12,}$ for which net charge is zero, has releasing profiles for the present gels as shown in Figures 4–6. The results in Figures 4–6 also showed that the releasing ratios for the gels with low SLS content such as A, D, and G gel, were highly larger than those for other gels with high SLS content. But, the releasing ratios for the gels were not significantly affected by the content of the perfluoroalkyl methacrylate in the gel composition. This is because the gel volume dramatically shrunk when the gel A, D, and G, was transferred from 25 to 37°C. But, for other gels, the gel volume was almost kept constant when they were transferred from 25 to 37°C.

Tables II and III show the loading amounts and equilibrium releasing amounts and releasing ratios for the present gels. Comparing Tables II and III, the release ratio of caffeine for the gel, such as A, D, and G gel with low SLS content, was larger than of vitamin B_{12}, but the loading amount exhibited a contrary result. This result explicitly shows that smaller caffeine molecule can easily load into the inside of the gel, but

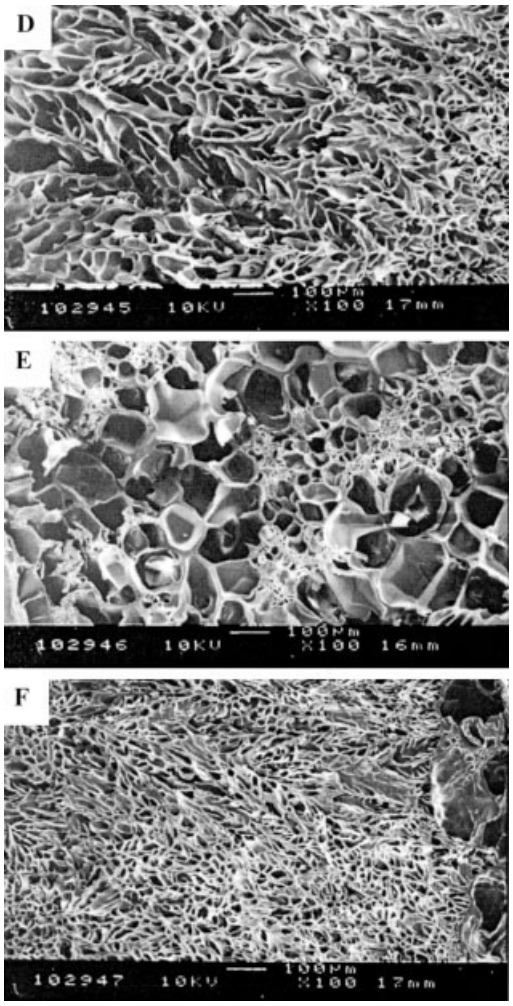

Figure 8 SEM morphologies for the hydrogels containing OFHHMA.

larger vitamin B_{12} molecule can only load into the surface layer of the gel. Because the gel with low SLS content shrank quickly at 37°C, vitamin B_{12} in surface layer of the gel was easily released, but the caffeine loading inside the gel cannot be easily released. The gels with high SLS content shrank slowly at 37°C, so the deciding factor for determining the release ratio is the molecular size of drugs and gel volume variation. Therefore, the release ratio of caffeine was larger than that of vitamin B_{12} for the gels with high SLS content.

Crosslinking density

Table IV shows the gel strength and crosslinking densities of the present gels. The result shows that the gel strength increased with an increase of the content of the fluorinated hydrophobic monomer (compare B and C gel), but decreased with increase in SLS (compare A and B gel). This is because SLS, as a pore-forming agent, could destroy the gel matrix and the fluorinated hydrophobic monomer can make the gel volume easily shrink. The results in Table IV also showed that the crosslinking densities of the present gels were smaller than pure NIPAAm gel, this is mainly due to SLS addition into the present gel preparation.

Morphology

Figures 7–9 showed microphotographs for the present gels by scanning electron microscopy (SEM). The pore size of the gels was not obviously changed with increasing content of SLS (see Fig. 7), except for the gels containing OFHHMA (D and E). This is because the OFHHMA has a hydroxyl group in its chemical structure (see Fig. 8). The pore size of the gels becomes smaller with increasing content of fluorinated hydrophobic monomer (H and I, see Fig. 9), except for the gels containing OFPMA (B and C). This is because 2.5 mol % SLS can completely emulsify 2.0 mol % OFPMA. In addition, the gel wall becomes thinner and the gel strength decreased with increasing content of

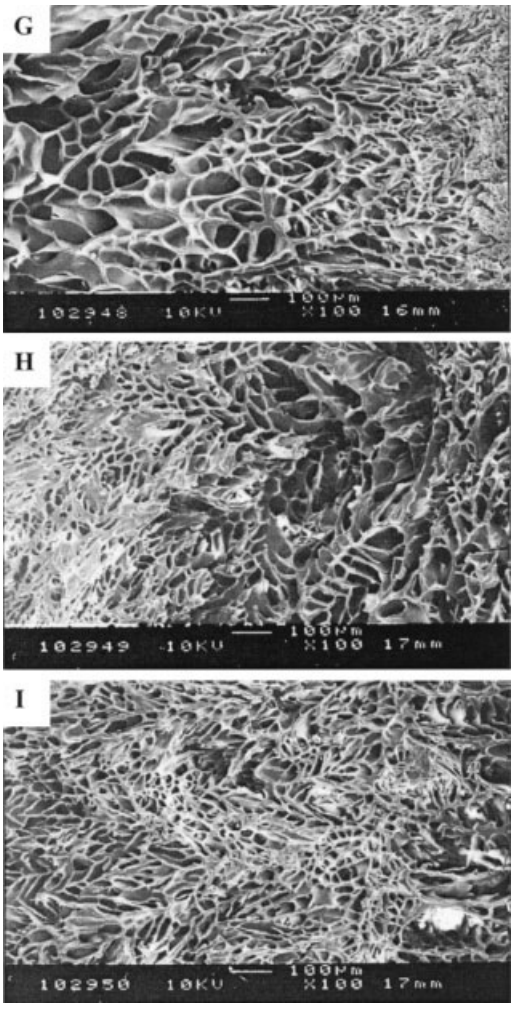

Figure 9 SEM morphologies for the hydrogels containing OFHMA.

SLS. The gel wall thickened and the gel strength increased with increasing content of fluorinated hydrophobic monomer. This is because SLS can aggregate more water molecule, but the perfluoroalkyl methacrylate exhibits a contrary result.

CONCLUSIONS

In drug release for the present copolymeric gels, the main factor is the different fluorinated monomers not a swelling ratio. Each fluorinated monomer has a hydrophobic chemical structure. In this hydrogel system, the difference in these three fluorinated monomers is the number of *F* atoms. In caffeine release, the release ratio for the more hydrophobic fluorinated monomers (OFHHMA or OFHMA) is lower than that for the less hydrophobic fluorinated monomer (OFPMA). The different hydrophobicity causes a different emulsifying degree with a fixed amount of SLS. Hence, we can say that the emulsifying degree of the fluorinated monomer decides the tendency of the drug release. The crosslinking density increases with increase in the content of the fluorinated monomer. From SEM, gel structures will be strengthened with increase in the content of the fluorinated monomer, but weakened with an increase in the content of SLS.

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