Swelling Behavior of Hydrogels for Colon-Site Drug Delivery

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ABSTRACT: Hydrogels based on *n*-alkyl methacrylate esters (*n*-AMA), acrylic acid, and acrylamide crosslinked with 4,4′-di(methacryloylamino)azobenzene were prepared. Swelling behavior of the hydrogels was studied by the immersion of slabs in buffered solutions at pH 2.2–7.4. The diffusion of water into the slabs was discussed on the stress relaxation model of polymer chains. The results obtained are in good agreement with Schott's second-order diffusion kinetics. The constants *A* and *B* of Schott's kinetics equation depend on the balance of hydrophobicity/hydrophilicity, the rigidity/flexibility, and the degree of crosslinking. The factors that exert the greatest influence on the swelling behavior of the gels include the degree of crosslinking, the lengths of the *n*-AMA side chains, and pH values. By adjusting these factors, the degree of swelling of the hydrogels in the small intestine can be controlled, and consequently the drugs may avoid being released before arriving in the colon. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 2835–2842, 2002; DOI 10.1002/app.10259

Key words: hydrogels; swelling kinetics; colonic-specific drug delivery

INTRODUCTION

Much attention has been being paid to the problem that oral protein or peptide drugs are easily digested by gastric and pancreatic enzymes present in the stomach and small intestine. An approach to the solution of this problem is the delivery of proteins or peptides to the colon, where the amount of digestive enzymes is drastically decreased.

It is known that, using hydrogels as carriers of drugs, the release of drugs from hydrogels depends on several factors, such as hydrophilic/hydrophobic balance of the hydrogels, the degree of crosslinking, and, especially, the degree of swelling. pH-sensitive hydrogels have a potential use in the site-specific delivery of drugs to specific regions of the gastrointestinal tract (GIT) attributed to pH changes throughout the GIT.[1–3] However, site-specific drug delivery to the colon cannot be achieved by the use of only pH-sensitive hydrogels, because the pH of the small intestine and large intestine are almost the same.[4]

The ability of drugs to be delivered to the colon is based on the fact that the concentration of microbial flora present in the colon is orders of magnitude higher than that in both the stomach and the small intestine.[4] The azoreductase activity of the colonic bacteria has been exploited for site-specific delivery of protein drugs to the colon.[5] Saffran et al.[5] developed copolymers containing azoaromatic crosslinkers degradable by the azoreductases to deliver insulin and vasopressin to the colon.

Using hydrogels as potential candidates for drug delivery has many advantages, such as their

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biocompatibility, ability to respond to external stimuli under various physiological conditions, and the fact that water retention in the hydrogels provides a suitable drug diffusion pathway by a pore mechanism.[6] An important parameter to consider in the design of hydrogel systems is the behavior of swelling. Not only the swelling-controlled release systems (i.e., pH-sensitive hydrogels[7]) but also the degradation-controlled systems[8,9] are shown to be related to the swelling behavior of hydrogels. Thus the study of swelling behavior of hydrogels is of considerable importance for the development of carriers for site-specific delivery of drugs.

This study focus on the kinetics of hydrogels based on hydrophobic and pH-dependent comonomers containing cecal bacterially degradable azo crosslinkers for site-specific delivery of drugs to the colon. In the low pH range of the stomach, the gels have a low equilibrium degree of swelling ascribed to the control by hydrophobicity and the drugs are protected against digestion by enzymes. In the passage of the gels through the small intestine, the swelling gradually increases because of the increased pH, but no drug or only a little amount releases in the small intestine as a result of the control by the second-order swelling kinetics[10] and steric hindrances of networks. In colon, the swelling reaches such a point at which the crosslinkers become accessible to cecal bacteria. Subsequently, the crosslinkers are cleaved, the gels are degraded, and then the drugs are released. The degradation of the gels in vitro and in vitro by cecal bacteria from rats will be reported later.

EXPERIMENTAL

Materials

All monomers were purified before use. Acrylic acid (AA), methacrylic acid (AAM), *n*-butyl methacrylate (BMA), dodecanol, hexadecanol, methacryloyl chloride, *N,N*-dimethylformamide (DMF), and pyride were distilled before being used. Acrylamide (AM), 4,4′-diaminoazobenzene and 2,2′-azobis(iso-butyronitrile) (AIBN) were recrystallized from ethanol. 4,4′-Bis-(methacryloylamino)azobenzene (DMAAB) was prepared by methacryloylation of 4,4′-diaminoazobenzene as described previously[11] (m.p., 227–228°C). Dodecylmethacrylate (DMA) and hexadecylmethacrylate (HMA) were synthesized as described below.

Synthesis of *n*-Alkyl Methacrylate Esters

DMA and HMA were synthesized by transesterification of methyl methacrylate as described for *n*-butyl acrylate.[12]

$CuCl_2$ (0.344 g, 2.56×10^{-3} mol), dodecanol (18.6 g, 0.1 mol), and *p*-toluenesulfonic acid (0.465 g, 2.70×10^{-3} mol) were added to (methyl methacrylate (20 g, 0.2 mol). The mixture were heated to 110°C in an oil bath, and the formed methanol during the reaction were removed with an all-glass fractionating column. After about 8 h, the excess methyl methacrylate and the lauryl methacrylate were distilled. The yield was 23.37 g (92%), b.p. 285–349°C[13] at atmospheric pressure.

n-Hexyl methacrylate was synthesized by a similar method. The yield: 29.50 g (95.2%), m.p. 310–365°C. The FTIR spectra of *n*-hexyl methacrylate showed bands attributed to C═C, ester and *n*-alkyl groups, that is, 1638 cm^{-1} for C═C; 1721, 1320, 1296, and 1164 cm^{-1} for ester groups; and 2924 and 2853 cm^{-1} for *n*-alkyl groups.

Synthesis of Hydrogels

Each of the terpolymers of acrylic acid, acrylamide, and *n*-alkyl methacrylate esters crosslinked with 4,4′-di(methacryloyamide)azobenzene was prepared by radical copolymerization in various amounts of DMF with AIBN as initiator, as previously described.[14] The compositions of the monomer solutions used for the synthesis of hydrogels are listed in Table I.

Swelling Kinetics of Hydrogels

A slab (about 10.0 mg of its dried weight) cut off from the above-prepared gel was dried first at room temperature for 24 h and then at 60°C in vacuum for another 24 h. The dried gel was weighted and then immersed into a citrate–borate–phosphate buffer system[15] of pH 7.4 at 37°C. The swollen gel was withdrawn at intervals from the buffer solution and weighted after removal of excess surface water by light blotting with a filter paper. Measurements were taken until equilibrium was reached. The degree of swelling (water absorption) was defined as[16]

$$\text{Water absorption } (\%) = 100(W - W_0)/W_0 \quad (1)$$

where W is the weight of swollen gel and W_0 is the weight of dried matrix.

The swelling rate of the hydrogels was described with Schott's second-order swelling kinetics.[10] The equation is

Table I Compositions of Gels and Conditions of the Preparation

Gels	AM (mol %)	AA (mol %)	*n*-AMA (mol %)	DMAAB (mol %)	AIBN (mg)	DMF (g)	Total (g)
A	49.5	40	10 (n = 4)	0.5	30	7	10
B	49.5	40	10 (n = 8)	0.5	30	7	10
C	49.5	40	10 (n = 12)	0.5	30	7	10
D	49.5	40	10 (n = 16)	0.5	30	7	10
E	74.8	20	5 (n = 12)	0.2	30	7	10
F	54.7	40	5 (n = 12)	0.3	30	7	10
G	54.6	40	5 (n = 12)	0.4	30	7	10
H	54.6	40	5 (n = 4)	0.4	30	7	10

$$dH/dt = K(H_\infty - H)^2 \quad (2)$$

where H_∞ is the maximum or equilibrium water uptake, H is the water uptake at time t, and K is the rate constant. If $K = 1/AH_\infty^2$ and H_∞ is replaced by $1/B$, integration between the limits t, H, and 0,0 yields

$$t/H = A + Bt \quad (3)$$

where A and B are two coefficients whose physical sense is interpreted as follows: at a long treatment time, $Bt \gg A$ and according to eq. (3), $B = 1/H_\infty$, it is the reciprocal of the maximum or equilibrium water uptake. On the contrary, at a very short treatment time, $A \gg Bt$ and in the limit, eq. (3) becomes

$$\lim_{t\to 0}(dH/dt) = 1/A \quad (4)$$

Therefore, the intercept A is the reciprocal of the initial swelling rate.

Rearranging and differentiating eq. (3) results in

$$dH/dt = A/(A + Bt)^2 \quad (5)$$

This equation is identical with eq. (2). It indicates that the swelling rate is a function of the treatment time.

RESULTS AND DISCUSSION

The effect of the hydrophobic side-chain length on the swelling kinetics of gels A, B, C, and D is shown in Figure 1. The gels have the same composition but different lengths of the hydrophobic side chains. They hardly swell in the buffer solution of pH 2.2, but drastically swell in the buffer solution of pH 7.4. With the exception of gel D the degree of swelling of gels A, B, and C decreases with an increase in the length of the hydrophobic side chain. These properties of gels are of great significance for the control of no drug release in the stomach.

Generally, the swelling behavior of polyelectrolyte networks is determined by a balance of three primary forces: (1) the free energy of mixing of the network chains with solvent, (2) the osmotic pressure within the network resulting from the mobile counterions surrounding the fixed charged groups (ion osmotic pressure), and (3) the elastic retractile force of the network (network swelling pressure).[17] The copolymeric gels studied here bear weakly carboxyl groups and *n*-alkyl methacrylate ester (*n*-AMA) groups of various chain lengths and crosslinkers degradable by cecal bacteria. Therefore their swelling behavior should result from a balance of the three forces. In the

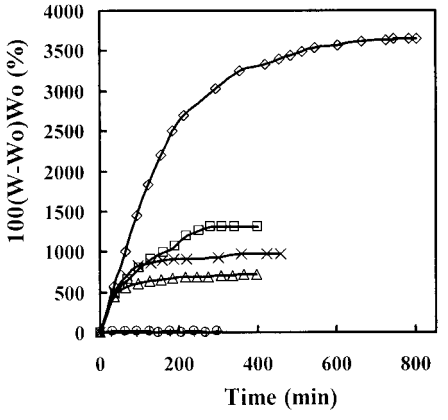

Figure 1 Swelling kinetics of hydrogels A–D in buffered solutions at pH 7.4 and pH 2.2 at 37°C. ◇, A (pH 7.4); □, B (pH 7.4); △, C (pH 7.4); ×, D (pH 7.4); +, A (pH 2.2); ○, B (pH 2.2).

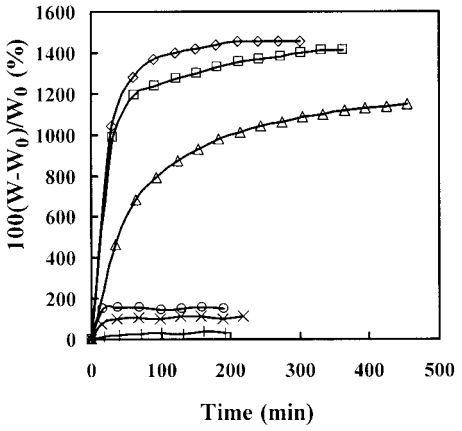

Figure 2 Swelling kinetics of hydrogels E–G in buffered solutions at pH 7.4 and pH 2.2 at 37°C. ◇, E (pH 7.4); □, F (pH 7.4); △, G (pH 7.4); ×, E (pH 2.2); ○, F (pH 2.2); +, G (pH 2.2).

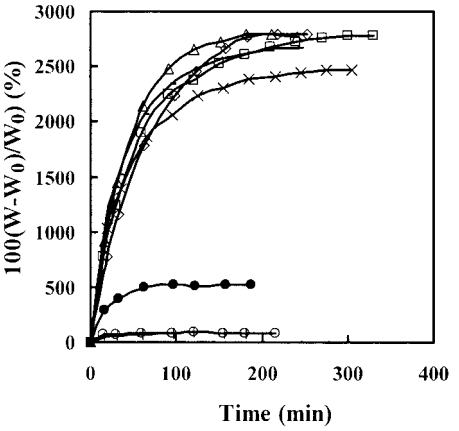

Figure 3 Swelling kinetics of hydrogel H in buffered solutions of various pH values at 37°C. ○, pH 2.2; +, pH 3.0; ●, pH 4.0; ◇, pH 5.0; △, pH 6.0; —, pH 7.0; □, pH 7.4; ×, pH 8.0.

buffer solution of pH 2.2, the gels show almost no swelling that is attributed to the hydrophobicity of both *n*-AMA groups and nonionized carboxyl groups as well as the intensive rigidity of azobenzene crosslinks. While in the buffer solution of pH 7.4, an increase of ionization of carboxyl groups results in increase of the hydrophilicity and osmotic pressure of networks. Therefore, the degree of swelling increases drastically. Again, the degree of swelling results from a balance of the hydrophilic/hydrophobic balance in the buffer solution of pH 7.4; thus, the increase in the length of the hydrophobic side chain leads to the decrease in the degree of swelling of gels A, B, and C. In addition, an increase in the length of the hydrophobic side chain also leads to an increase in network flexibility. In comparison with gel C, a higher degree of swelling for gel D could be attributed to the increase of the relaxation of the segments.

The influence of the crosslinking degree on the swelling kinetics of gels E, F, and G is shown in Figure 2. Obviously, an increase in the degree of crosslinking leads to the decrease of swelling degree, although the gels have the same comonomers.

The influence of pH value of the buffered solution on the swelling kinetics of gel H is shown in Figure 3. In a range of pH 4.0–5.0, an increase of the pH results in a drastic increase of the degree of swelling. In the ranges of pH 5.0–8.0 and pH 2.2–4.0, little influence on the degree of swelling was observed. Similar results were obtained by the measurements of the swelling kinetics of gels G and E at various pH values of the buffered solutions. The change of the equilibrium swelling degree of the gels as a function of the pH value of the buffered solution is shown in Figure 4. A sharp change of the equilibrium swelling degree between pH 4.0–5.0 was observed for the tested gels.

The sharp change of the swelling degree of the gels is attributed to the ionization of carboxyl groups in the buffered solutions. When the pH value changes from the lower to the higher, the ionization of carboxyl groups causes a sharp transition of the network segments from the compact coiled state to the extended state; thereby, the swelling degree of the gels shows an abrupt tran-

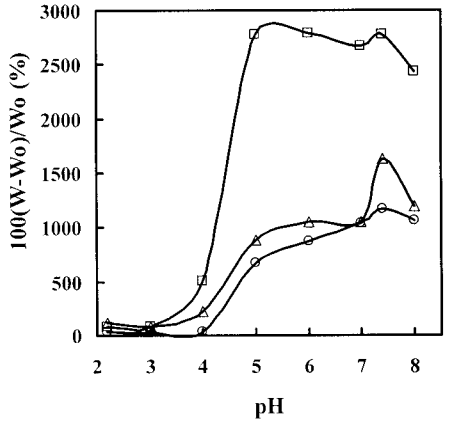

Figure 4 Variation of equilibrium degree of swelling with the pH values of buffered solutions at 37°C. □, H; ○, E; △, G.

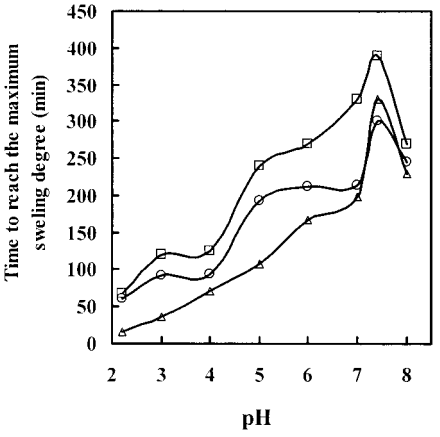

Figure 5 Average time necessary to reach maximum degree of swelling by immersion of samples H, E, and G into buffered solutions of varying pH values at 37°C. □, H; ○, E; △, G.

sition. A slight increase of the equilibrium swelling degree at pH 7.4 for the three gels is attributed to the electrostatic repulsive forces between the carboxyl anions, in which protons were neutralized in alkaline media. Subsequently, with the increase of the pH a decrease of swelling degree was observed because of the screening of the charges in the networks.

Figure 5 is a plot of the average time necessary for the swelling equilibrium versus pH values of buffered solutions. Generally, the average time increases with the increase of the pH in the range of pH 2.2–7.4. A maximum of the average time was obtained at pH 7.4. In the case of the same pH values, the longest average time to reach the swelling equilibrium was found for gel H with shortest hydrophobic side chains; gels E and G followed. The dependence of the average time for gels to reach the swelling equilibrium on the equilibrium swelling degree is obviously ascribed to the hydrophobic/hydrophilic balance and the degree of crosslinking. Gel G showed the shortest average time to reach the swelling equilibrium that would be attributed to the degree of crosslinking, although both gel G and gel E have the same hydrophobic side chains.

In general, the swelling process of polymeric gels is a stress relaxation of the macromolecular segments responding to the osmotic pressure. This results in a progressive softening of the system as the buffered solution permeates into the polymeric matrix, giving rise to a continuous change of the swelling rate with time. The change of the swelling rate (dH/dt) of gel H as a function of the swelling time is shown in Figure 6. In all cases the swelling rate reaches a maximum just after the immersion of the dry samples into the buffered solution and decreases exponentially with time until the equilibrium is reached. In the range of pH 2.2–5.0 the swelling rate is very sensitive to the pH of the medium and increases with the increase of pH, whereas there was almost no influence of pH on the swelling rate in the range of pH 5.0–8.0. These phenomena can also be explained by the ionization of carboxyl groups; for example, carboxyl groups were in the nonionized state at pH 2.2 and dH/dt is almost zero.

The influence of the length of the hydrophobic side chain on the swelling rate is shown in Figure 7. Generally, the longer the hydrophobic side chains, the lower the swelling rates. Gel A with the shortest hydrophobic side chains, shows the highest swelling rate compared with that of gels B, C, and D. By way of exception, gel D with the longest hydrophobic side chains shows a slight higher swelling rate than that of gel C. Apparently, this is related to the flexibility of the hydrophobic side chains of the gels.

The influence of the degree of crosslinking on the swelling rate is shown in Figure 8. The declining tendency of the swelling rates decreases in the following order: E > F > G. It indicates that the lower the degree of crosslinking, the faster the decline of the swelling rate. This reason could be attributed to the rigidity of the networks and the interaction between the chain segments as well as the stress relaxation of the chain segments.

The swelling process of rigid polymeric gels does not follow Fick's first-order swelling kinetics

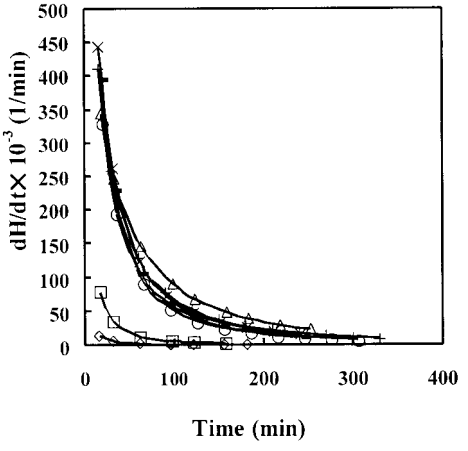

Figure 6 Variation of swelling rate dH/dt as a function of swelling time at 37°C for gel H in buffered solutions of varying pH values. ◇, pH 3.0; □, pH 4.0; △, pH 5.0; ×, pH 6.0; —, pH 7.0; +, pH 7.4; ○, pH 8.0.

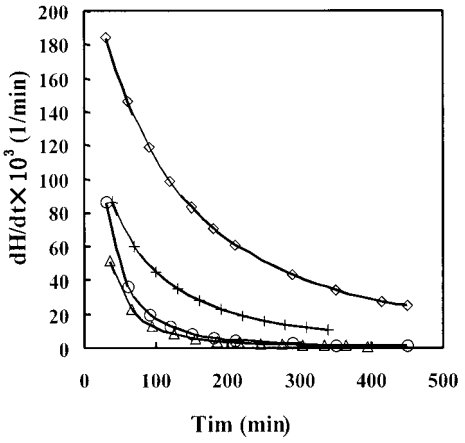

Figure 7 Effect of length of hydrophobic groups on change of swelling rate (dH/dt) as a function of swelling time for hydrogels A–D in pH 7.4 buffered solutions at 37°C. ◇, A; +, B; △, C; ○, D.

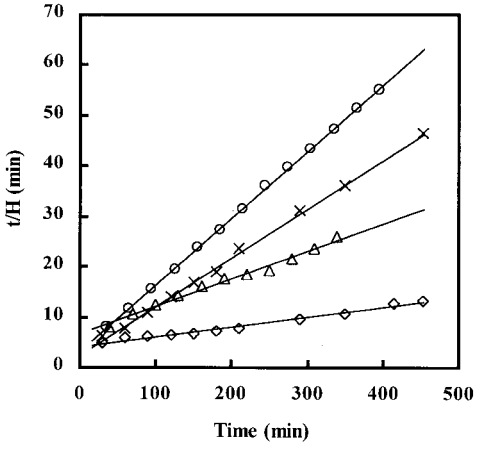

Figure 9 Variation of reciprocal rates of swelling [defined in eq. (3)] as a function of the swelling time for different lengths of hydrophobic groups of hydrogels A–D in pH 7.4 buffered solution at 37°C. ◇, A; △, B; ○, C; ×, D.

because Fick's law considers that the diffusion coefficient D of penetrating agent (solvent or solution) and sample volume remain constant during the entire swelling process.[18–20] However, for an extensive swelling system the volume obviously does not remain constant. Schott[10] has proposed a theoretical model for the swelling system, considering that the swelling system follows second-order swelling kinetics. By the application of the swelling data of the above eight gels to eq. (3), a straight linear relation between the reciprocal of the average rate of swelling (H/T) and the swelling time is obtained in Figures 9, 10, and 11. This result demonstrates that the swelling process of this system follows Schott's swelling theoretical model,[10] independent of the pH of the medium. It also reveals that the phase transition of the gels caused by the pH of the medium is not controlled kinetically, but by a complex mechanism.

From eq. (3), it is known that the swelling process depends on the two constants A and B, that is, the initial rate of swelling and the swelling equilibrium, respectively, which control the entire swelling process. The initial swelling is related to the relaxation rate of the chain segments of the dry gel, which involves the rigidity/

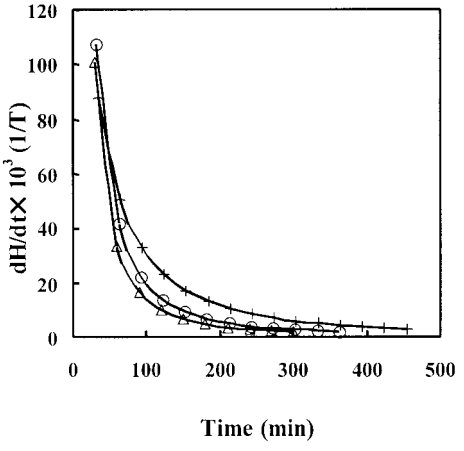

Figure 8 Effect of degree of crosslinking of hydrogels E–G on variation of swelling rate dH/dt as a function of swelling time in pH 7.4 buffered solutions at 37°C. △, E; ○, F; +, G.

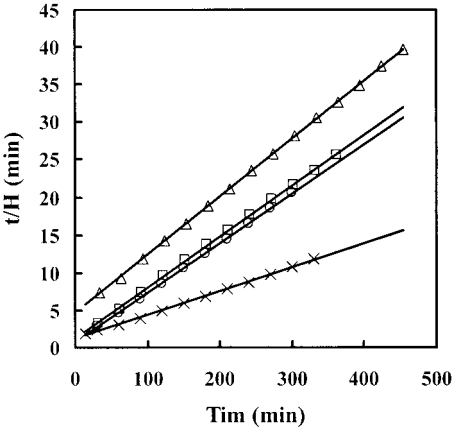

Figure 10 Variation of reciprocal rates of swelling [defined in eq. (3)] as a function of the swelling time for different degrees of crosslinking of hydrogels E–H in pH 7.4 buffered solution at 37°C. ○, E; □, F; △, G; ×, H.

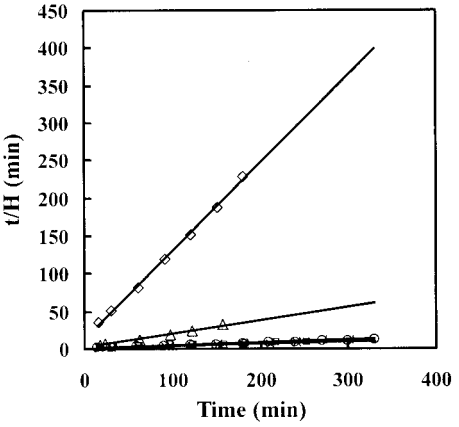

Figure 11 Variation of reciprocal rate of swelling [defined in eq. (3)] as a function of the swelling time for hydrogel H in buffered solutions of varying pH values at 37°C. ◇, pH 3.0; △, pH 4.0; □, pH 5.0; ×, pH 6.0; —, pH 7.0; ○, pH 7.4; +, pH 8.0.

flexibility, the hydrophobic/hydrophilic balance, the degree of crosslinking, the amorphous regions/crystalline domains, and the thickness of the dry gel. Much attention has been paid to the influence of the amorphous regions/crystalline domains and the thickness of the dry gels in the literature.[21,22]

The effect of the hydrophobic side chain on constants A and B is shown in Figure 9. The values of constant A are 4.1788 for gel A, 6.7003 for gel B, 3.1346 for gel C, and 2.5178 for gel D, respectively. The value of constant A for gel A is less than that of gel B, mainly because of the higher hydrophobicity of gel B. The values of constant A decrease in the following order: gel B > gel C > gel D, which is ascribed to the gradual increase in the flexibility of the hydrophobic side chains. The values of constant B increase in the following order: 0.0195 (gel A) < 0.0549 (gel B) < 0.0967 (gel D) < 0.1324 (gel C). This order again clarifies the effects of the hydrophobicity and flexibility of the hydrophobic chains on the swelling rates.

The effect of the crosslinking degree on constants A and B is shown in Figure 10. The values of constant A increase in the following order: 0.7382 (gel E) < 1.2337 (gel F) < 4.6448 (gel G). This result indicates that the relaxation of gel networks becomes slow because of the increase in the interaction between the chain segments and the rigidity of the networks with the increase in the degree of crosslinking. In accordance with the order of constant A, the order of constant B is: 0.0657 (gel E) < 0.0675 (gel F) < 0.0771 (gel G), respectively.

The effect of pH on constants A and B is shown in Figures 11 and 12. In acidic media, the values of constant A for gel H decrease in the following order: 13.543 (pH 3) > 2.2111 (pH 4) > 1.7901 (pH 5) > 1.0435 (pH 6) > 0.9879 (pH 7). It indicates that as pH increases, the initial swelling rate also increases as a result of the increase in the extent of ionization of the carboxyl groups. The values of constant A in alkaline media are 0.9879 (pH 7), 1.3222 (pH 7.4), and 1.1303 (pH 8), which indicate that the initial swelling rate decreases with the increase in pH. The constant A value at pH 7.4 is higher than that at pH 8.0. This is possibly the reason that, in alkaline media, the carboxyl groups at the surface of the dry gel are completely neutralized, and the concomitant drastic increase in the net charges increases the rigidity at the surface and coils being more compact inside the gel. With the further increase in the pH, the increase of flexibility at the surfaces caused by the screening effect of the cations leads to the decrease of constant A. In acidic media the values of constant B are 1.1654 (pH 3), 0.1814 (pH 4), 0.0275 (pH 5), 0.0307 (pH 6), and 0.0329 (pH 7). In alkaline media the constant B values are 0.0329 (pH 7), 0.0314 (pH 7.4), and 0.0364 (pH 8). From these data, a drastic increase in the equilibrium degree of swelling between pH 5.0 and 6.0, a slight decrease at pH 7.0, a maximum at pH 7.4, and some decrease again at pH 8.0 were observed. This result is in complete accord with that from Figure 4.

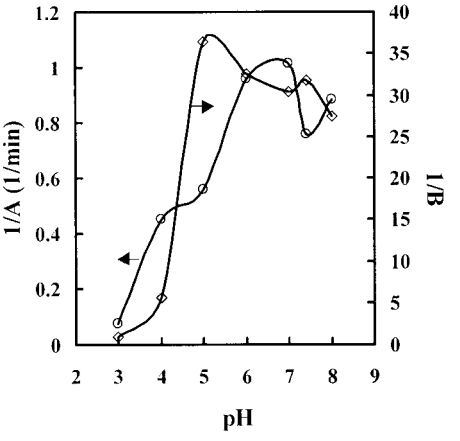

Figure 12 Variation of initial swelling rate ($1/A$) and maximum degree of swelling equilibrium ($1/B$) of hydrogel H with pH of buffered solution at 37°C. ○, H ($1/A$); ◇, H ($1/B$).

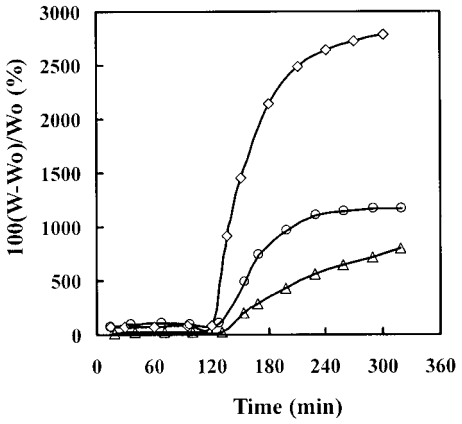

Figure 13 Swelling kinetics of hydrogels H, E, and G in buffered solution of pH 2.2 for 2 h and in buffered solution of pH 6.0 for 3 h at 37°C. ◇, H; ○, E; △, G.

The pH range in the human stomach is between 1.0 and 3.5, in which the gels show very low degree of swelling. Using the gels as the drug carriers, drugs can be protected against the release in the stomach. The entire swelling process of the gels occurs mainly in the small intestine and colon, where the range of pH is between 5.0 and 7.0. Generally, the transit time of drugs in the human small intestine is about 3 h. Therefore, the swelling kinetics of the gels for 3 h is of great significance. Figure 13 shows that the swelling kinetics of gels H, E, and G in the buffered solution of pH 2.2 for 2 h, and subsequently in the buffered solution of pH 6.0 for 3 h. The three gels hardly swell in the buffered solution of pH 2.2. The swelling degree in the buffered solution of pH 6.0 decreases in the following order: gel H > gel E > gel G. This result reveals that the drugs inside the gels might not be released in the small intestine (or a little amount in the small intestine) by the control of the swelling degree, namely adjusting the composition or the chain lengths of hydrophobic groups of the gels.

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