Hydrogels for Oral Drug Delivery of Peptides: Synthesis and Characterization

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ABSTRACT: In this study hydrogels were synthesized by the copolymerization of acrylamide and itaconic acid in the presence of poly(*N*-vinyl-2-pyrrolidone) in an aqueous medium. The incorporation of a small amount of itaconic acid resulted in the transition of the swelling behavior from Fickian to non-Fickian. The hydrogels showed good response to the valency of the counterions and pH of the swelling media. The equilibrium water uptake increased with the pH of the external solution, thus attaining a maximum value at pH 7–8. The gels exhibited a number of deswelling–swelling cycles while maintaining mechanical strength and shape stability. The amount of itaconic acid present in the system affected the swelling behavior of the hydrogels in a rather unusual way. At pH 2.0 the equilibrium water uptake increased with the amount of acid monomer up to 15 m*M*, remained almost constant for a very small range of concentrations (i.e., up to 22 m*M*), and then finally decreased with the further increase of the acid content. However, a continuous increase was observed at the pH 7.0 of the swelling media. The hydrogels showed very poor temperature dependency and the activation energies for the samples with and without itaconic acid were 29.09 and 19.92 kJ mol^{-1}, respectively. Finally, the swelling and deswelling processes were explained on the basis of two different mechanisms that were followed by the gels. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 1717–1729, 2002

Key words: itaconic acid; colon-specific drug delivery; pH dependent swelling; gastrointestinal tract

INTRODUCTION

The administration of peptide and protein drugs by frequent injections suffers from the drawback that it results in a rapid increase and subsequent rapid decrease of the blood serum concentration levels.[1] Therefore, it is necessary to make efforts to develop delivery devices that can deliver the drugs while maintaining the blood concentration for a considerable period of time inside the therapeutic region. The oral administration of drugs seems to be the only solution to overcome the problem arising from frequent injections of peptide and protein drugs. However, the major obstacle to oral delivery is the digestion of proteins by gastric and pancreatic enzymes present in the stomach and small intestine.[2] A number of studies were and are being carried out to try to achieve the oral delivery of proteins. These include coadministration of absorption enhancers and the use of stabilizers and coatings to protect the proteins.[3–5]

The ability of pH sensitive hydrogels to respond to their environment makes them suitable

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candidates for the site-specific oral delivery of peptides and proteins along the gastrointestinal (GI) tract, which has pH variations throughout. If the hydrogel consists of a polymer matrix with carboxylic groups along the macromolecular chain inside the network, then the possible dissociation of these acidic groups in a neutral or slightly alkaline pH will result in extensive swelling and subsequent release of the encapsulated drug from the polymer matrix. Such a hydrogel may prove to be an effective device for colon-specific oral drug delivery systems. In a continuous attempt to develop such drug delivery devices[6,7] and to study their drug release behavior in the future, we hereby propose a new type of hydrogel system consisting of poly(*N*-vinyl-2-pyrrolidone) (PVP) and poly(acrylamide-*co*-itaconic acid) (PAAm-*co*-IA), which may prove to be an effective site-specific drug delivery vehicle for the treatment of certain colonic diseases such as Crohn disease, ulcerative colitis, and colorectal cancer. Because the proposed hydrogel system undergoes a drastic change in the degree of swelling with the pH of the swelling media and its components PVP[8] and PAAm-*co*-IA[9] have a fair reputation as biocompatable materials, the proposed hydrogel may be loaded with peptide and protein drugs to be released along the GI tract for the treatment of diseases of the colon.

EXPERIMENTAL

Chemicals

The AAm and IA monomers were obtained from BDH (Poole). The PVP, potassium persulfate (KPS), and the crosslinker *N*,*N*′-methylene bisacrylamide (MBA) were purchased from Sigma (St. Louis). Sodium chloride, sodium hydroxide, and hydrochloric acid were obtained from Loba Chemie Industries. Double distilled water was used throughout the investigations.

Preparation of Hydrogels

In order to prepare cylindrical hydrogels, 2.0 g of PVP were dissolved in water to give a total volume of 30 mL. A calculated quantity of the AAm monomer along with a very small amount of IA (50–130 mg) were added to the PVP–water mixture. Then MBA and KPS were added to this solution, and the resulting mixture was poured into poly(vinyl chloride) straws and kept in an electric oven (Tempstar) at 60°C for a period of 4 h. The resulting semitransparent gels were cut into small cylindrical pieces, which were each 2.54 cm long. The rodlike gels were washed with deionized water to remove the unreacted salts and then dried at 30°C for a period of 24 h in a dust-free chamber. Here it is worth mentioning that in the preliminary studies the compositions of the monomers and the amount of crosslinker were determined by gravimetry[10] to attain 100% gelation in each hydrogel system. Moreover, the consideration for selecting the feed compositions in the present study were the solubility of the monomers and the shape stability of the swollen gels in the equilibrium state.

The gels that were synthesized are denoted as HG (0), HG (0.67), and HG (1.74); the numbers in the parentheses denote the molar percentages of IA in the hydrogel system. Because the gelation is almost 100% in each polymer system, the composition of the monomers in the hydrogels is the same as that in the reaction mixture.

Swelling Studies

Completely dried hydrogel samples of known weight were placed in a 1-L solution of swelling medium of desired pH with an ionic strength of 0.1*M* at a constant 30°C. The swollen gels were taken out at regular time intervals, wiped superficially with filter paper, weighed, and then placed in the same bath. The mass measurements were continued until constant weight was attained for each sample. The percentages of mass swelling (S_m) and volume swelling (S_v) were obtained using the following expressions:

$$S_m = \frac{(m_t - m_0)}{m_0} \times 100$$

and

$$S_v = \frac{(m_t - m_0)}{m_0} \frac{d_p}{d_s} \times 100$$

where m_0 and m_t are the initial mass and mass at different time intervals, respectively; and d_p and d_s are the polymer density and solvent density, respectively.[11] It is worth mentioning that the reason for using a large volume of swelling media was to avoid any possible pH change during the whole swelling process.

Deswelling–Swelling Studies

The initially dry hydrogel sample was placed in a pH 8.0 alkaline solution and allowed to attain equilibrium swelling. Then the sample was withdrawn from the solution and placed in a pH 2.0 solution until it deswelled to gain a constant weight. The deswollen sample was again put in the alkaline solution to attain maximum swelling. In this way, the deswelling–swelling cycle was repeated a number of times.

RESULTS AND DISCUSSION

Diffusion

When immersed in a compatible solvent, a glassy polymer network swells. If the gel is clear, then a distinct boundary between the swollen and dry regions can be observed during the penetration of the solvent into the polymer. The solvent invades the dry network until the transition from the glassy to the rubbery state is complete.[12] The swelling of the hydrogel involves larger scale segmental motion, ultimately resulting in an increased distance of separation between hydrogel chains.[13]

The following equation was used to determine the nature of the diffusion process:

$$F = \frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t and M_∞ denote the amount of solvent that diffused into the polymer matrix at time t and at equilibrium, respectively; k is the gel characteristics constant; and the swelling exponent n describes the type of diffusion. For cylindrical shaped gels $n = 0.45–0.50$ corresponds to the Fickian type diffusion process while $0.50 < n < 1.0$ indicates the anomalous or non-Fickian type diffusion. This equation is applicable to the initial stage of swelling and a plot of ln F versus ln t gives straight lines up to almost a 60% increase in the mass of the hydrogel.

The diffusion coefficients (D, cm^2 min^{-1}) were calculated from the following equation:

$$D = 0.049/(t/41^2)_{1/2} \tag{2}$$

where t is the time at which the swelling is one-half the equilibrium value ($V/V_0 = 1/2$) and l is the radius of the cylindrical sample. The intrinsic diffusion coefficient ($\bar{D}$) may be expressed as

$$\bar{D} = D(1 - V)^{-3} \tag{3}$$

where V is the volume fraction of solvent penetrating the polymer by the t defined above.[14]

Figures 1 and 2 depict the dynamic uptake of water and the plot of ln F versus ln t for the three hydrogel samples in the swelling media at pH 7.0 and 30°C. The various swelling parameters such as swelling exponent n, the D, and the $\bar{D}$ are listed in Table I. It is clear from Table I that the hydrogel sample HG (O), which does not contain the acidic monomer, exhibits Fickian swelling behavior ($n = 0.52$) whereas for samples HG (0.67) and HG (1.74), which contain a small amount of IA in the polymer matrix, the n values were found to be 0.71 and 0.83, which are indicative of the non-Fickian type swelling behavior of these samples. The transition from Fickian to non-Fickian swelling behavior due to the addition of a very small amount of IA may be explained as follows.

For the sample HG (O), which does not contain any ionizable groups inside the polymer matrix, the driving force responsible for the swelling is simply the diffusion of the solvent into the polymer network, which ultimately results in normal or Fickian swelling behavior. However, the situation is quite different in samples HG (0.67) and HG (1.74), which contain ionizable carboxylic groups inside the polymer matrix. At the experimental pH 7.0 these groups undergo almost complete ionization, thus resulting in an increased osmotic swelling pressure {$\pi = RT[\Sigma(C_i^g - C_I^s)]$ where C_i^g and C_I^s are the molar concentrations of the mobile ions or counterions in the gel and the solution phase, respectively} in accordance with the Donnan equilibrium that ultimately causes the gel to undergo extensive swelling. Moreover, the electrostatic repulsion among the carboxylate groups along the macromolecular chains in the gel matrix also plays an effective role in the enhancement of the degree of swelling by causing the chain relaxation process to take place. These two factors (i.e., the osmotic swelling pressure and chain relaxation process) are responsible for the non-Fickian type swelling behavior of samples HG (0.67) and HG (1.74). Similar observations are also reported by other workers.[9]

It is also evident from Table I that the values of the intrinsic diffusion coefficient are greater than those for the diffusion coefficient. This may be

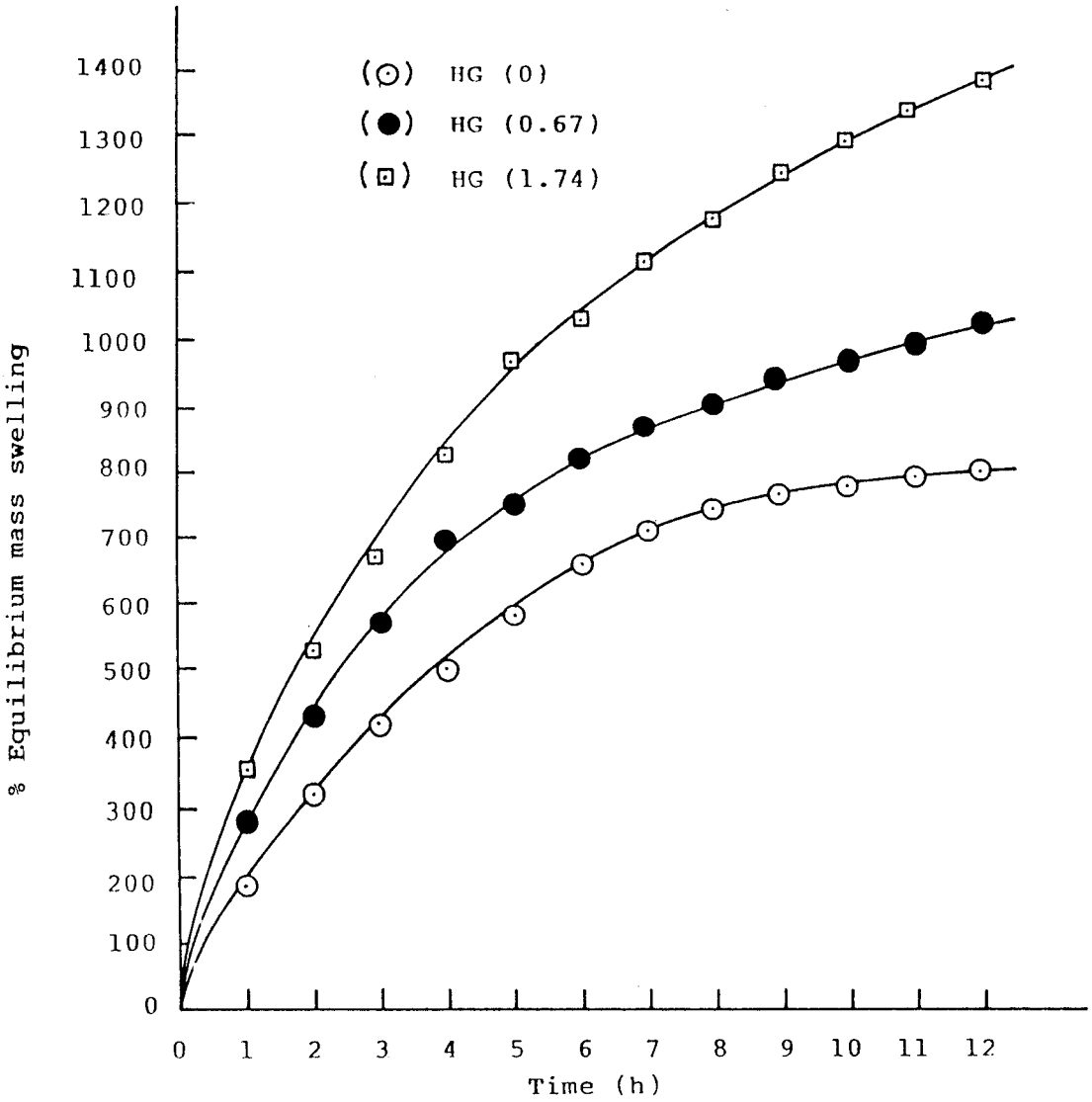

Figure 1 The dynamic mass uptake for the HG (0), HG (0.67), and HG (1.74) hydrogel samples in deionized water at pH 7.0 and 30°C.

attributed to the fact that the diffusion coefficient as given by eq. (2) gives a measure not only of the diffusion but also of the mass flow of the whole system, and eq. (3) gives the intrinsic diffusion coefficient for the case where no mass action affects enter.[11]

Effect of pH

The effect of the pH of the swelling media on the equilibrium water uptake for the three hydrogel samples HG (O), HG (0.67), and HG (1.74) was studied in external solutions of varying pH (1–8) with the ionic strength maintained at 0.1*M* at 30°C. The results are well depicted in Figure 3, which clearly shows that the hydrogel sample with no IA content exhibits behavior that is almost independent of the pH whereas for the other two samples that contain IA the equilibrium water uptake increases with the increase in pH of the swelling media and finally becomes constant in the vicinity of pH 7–8.

The equilibrium water uptake that is independent of the pH for sample HG (O) may be attributed to the fact that because the hydrogel is purely nonionic (i.e., it does not contain any ionizable groups within the gel matrix), the variation in the pH of the external solution does not make any change in the degree of equilibrium swelling

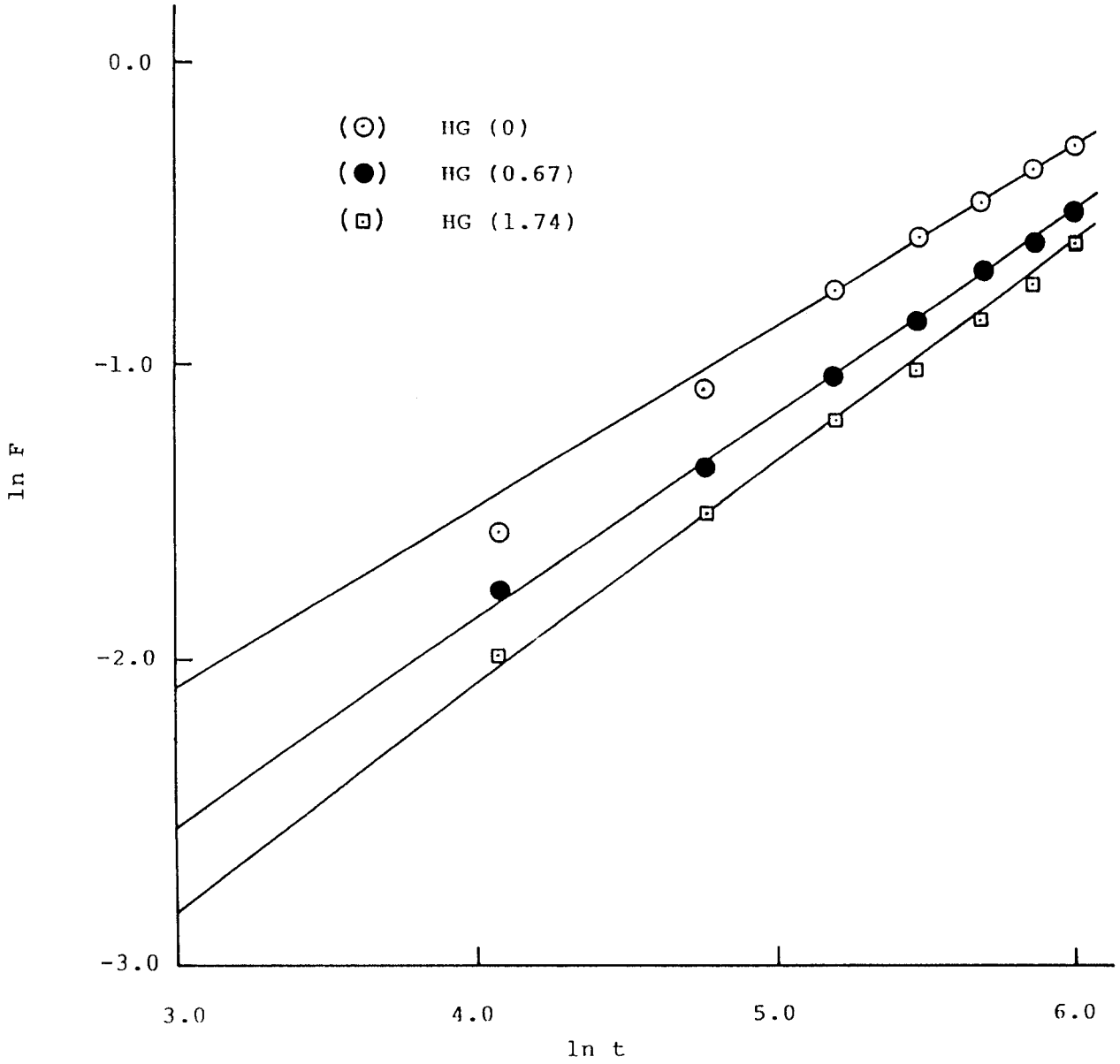

Figure 2 The ln F versus ln t for the swelling of the three hydrogel samples in water at pH 7.0 and 30°C.

of the hydrogel. However, the situation is quite different with the HG (0.67) and HG (1.74) samples that contain small amounts of IA in the polymer matrix. In this case the equilibrium water uptake increases with the pH and a close look at Figure 3 reveals that the curves obtained for the

Table I Swelling Parameters for Swelling of Samples HG (0), HG (0.67), and HG (1.74) in Deionized Water (30°C, pH 7.0)

Sample	S_m (%)	S_v (%)	n	$k \times 10^2$	$D \times 10^6$ (cm^2 min^{-1})	$\bar{D} \times 10^4$ (cm^2 min^{-1})
HG (0)	925	981	0.52	22.52	14.93	30.89
HG (0.67)	1656	1776	0.71	14.65	8.50	99.53
HG (1.74)	2413	2729	0.83	11.38	6.38	287.30

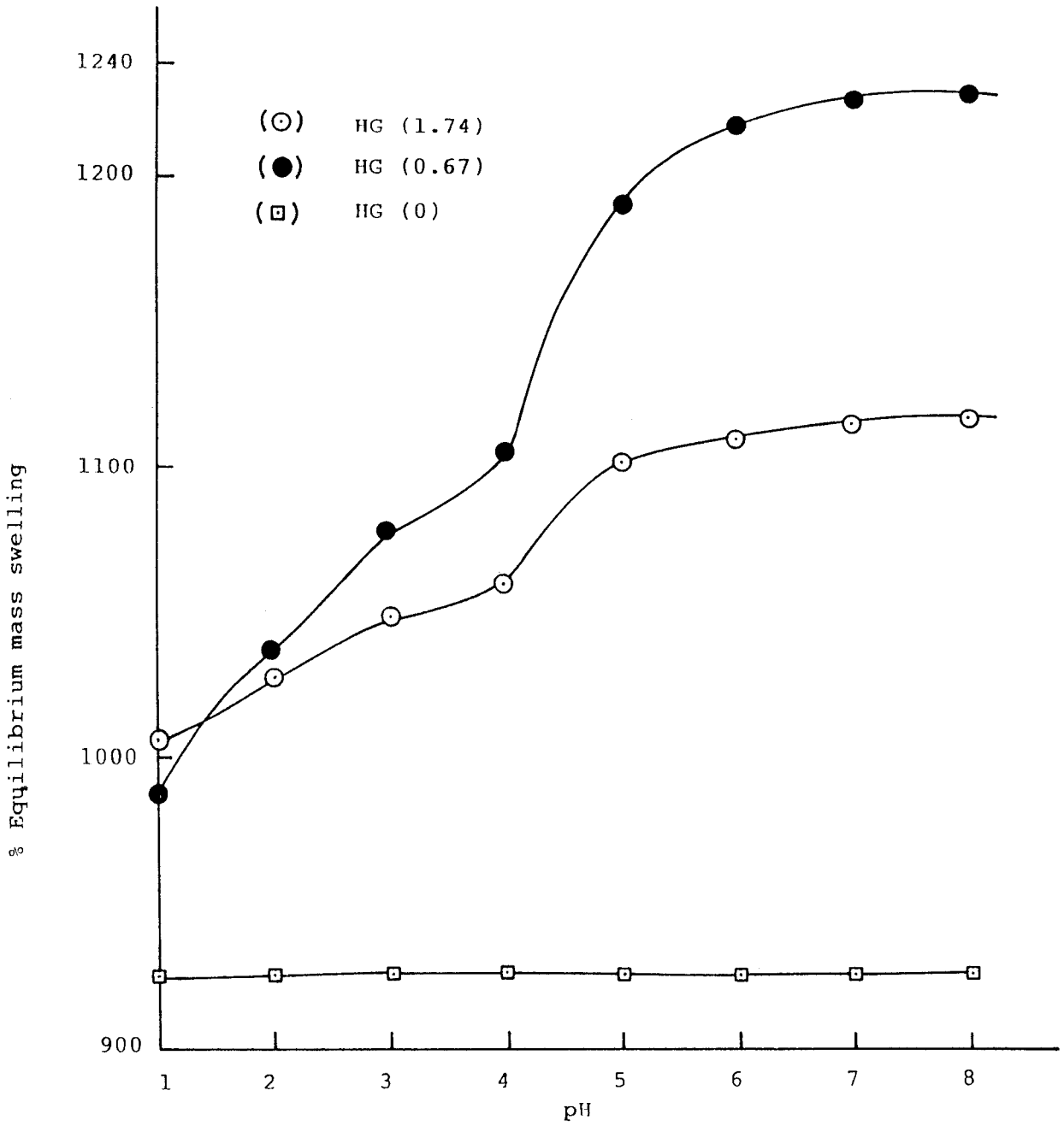

Figure 3 The equilibrium water uptake of the HG (0), HG (0.67), and HG (1.74) samples as a function of the pH of the external medium at 30°C with an ionic strength of 0.1*M*.

samples display single steps with a broadened S shape. The observed increase in the equilibrium water uptake along with the pH of the external media may be attributed to the fact that the two carboxylic groups of IA undergo dissociation in the pH range of 4–7, within which their pK_a values of 3.85 and 5.44 lie.[15] Evidently, this dissociation not only increases the osmotic swelling pressure but also causes enhancement in the chain relaxation process along the macromolecular chains because of the electrostatic repulsion among the carboxylate groups. These two factors are ultimately responsible for the observed increase in the equilibrium water uptake. However, the reason for obtaining a broad single-step rise in the S-shaped curve may be attributed to the

quite close pK_a values of the two carboxylic groups, which subsequently results in the overlapping of the dissociation of the first and second acid groups of the IA in the pH range under study. The observed broadened single-step rise between pH 4.0 and 7.0 (Fig. 3) is thus justified by the proposed explanation based on the overlapping of the two pK_a values in the polymer matrices. Similar types of results were also reported elsewhere.[16]

Effect of IA Content

The amount of IA present in the polymer matrix affects the equilibrium water uptake of the hydrogel in a rather interesting way. Figure 4 depicts the equilibrium mass swelling of the hydrogel samples as a function of the number of moles of IA in the polymer matrix, which was studied at pH 2.0 and 7.0 at 30°C. It is clear from Figure 4 that at the pH 7.0 of the external media, the equilibrium swelling of the hydrogel samples increases with the content of acid monomer in the gel matrix whereas at pH 2.0 the hydrogels exhibit different swelling behavior. In this case the equilibrium swelling first increases with the amount of IA in the hydrogel, it remains almost constant for a small range of concentrations of IA, and then it starts decreasing slowly with a further rise in content of monomer acid in the hydrogel. The observed behavior may be explained on the basis of a hypothesis involving the mutual balancing of hydrophobic and hydrophilic characters imparted to the hydrogel by undissociated IA and ionized carboxylate groups, respectively. Initially, the equilibrium water uptake of the polymer matrix increases with the increase in the acid content up to 15 mM, which may be attributed to the ionization of carboxylic groups (although to a small extent) inside the gel matrix. However, when the amount of acid is further increased, the hydrophilicity imparted to the gel matrix by ionized carboxylate groups is almost counterbalanced by the hydrophopic character of the unionized IA in the hydrogel, thus ultimately causing almost no change in the equilibrium water uptake up to 22 mM. When the concentration of IA in the hydrogel is further increased, the hydrophobicity imparted by unionized IA becomes much more pronounced than the hydrophilic tendency of ionized carboxylate groups in the polymer matrix, which finally causes a slight decrease in the equilibrium swelling of the hydrogel samples. We also reported similar observations with hydrogels containing maleic acid.[6]

However, when the same effect is studied at the pH 7.0 of the external media, the equilibrium water uptake of the hydrogels continues to increase with the molar content of IA in the polymer matrix, which may be due to the fact that at pH 7.0 the carboxylic groups of IA are in almost ionized form, thus causing an increase in the osmotic swelling pressure, as well as the extent of chain relaxation. These two factors ultimately result in an increase in the equilibrium water uptake. Due to the limited solubility of the acid monomer, this effect was only studied up to 37.5 mM of IA in the polymer network.

Deswelling–Swelling Studies

The basic requirement for a protein drug loaded polymeric hydrogel to be used as a site-specific drug delivery system along the GI tract, say in the colon, is that the drug loaded hydrogel should keep the encapsulated drug protected within the matrix in the stomach where the pH of the fluid is nearly 2.0, and it must release the maximum quantity of the drug in the surrounding fluid in the colon where the pH is nearly 7.4. Moreover, the structural integrity and mechanical strength of the drug loaded sample should also be maintained. Thus, in order to have information about the possible mode of action of proposed system along the GI tract, the deswelling–swelling behavior was studied by placing the HG (1.74) hydrogel sample in media of pH 2.0 and 8.0 (Fig. 5). It is very clear from Figure 5 that the equilibrium water uptake in the pH 2.0 medium is nearly 990%, which is a minimum value. When the sample is placed in the pH 8.0 solution, the gel swells to a maximum value of nearly 1600% without undergoing any structural deformation and without losing its mechanical strength. We carried out four such deswelling–swelling cycles and found that the gel maintained its mechanical strength and shape throughout the studies. However, in Figure 5 only two such cycles are shown. One more significant point to be mentioned is that after four cycles the gel started to show a slight tendency toward dissolution. However, the most interesting feature of this study is that the gel takes almost 25 h to swell to a maximum at pH 8.0 while the time required for complete deswelling in the pH 2.0 solution is nearly 71 h. In other words, the swelling process is much faster than the deswelling process, which may be explained on the basis of the fact that the gel follows different mechanisms for the swelling and deswelling processes.

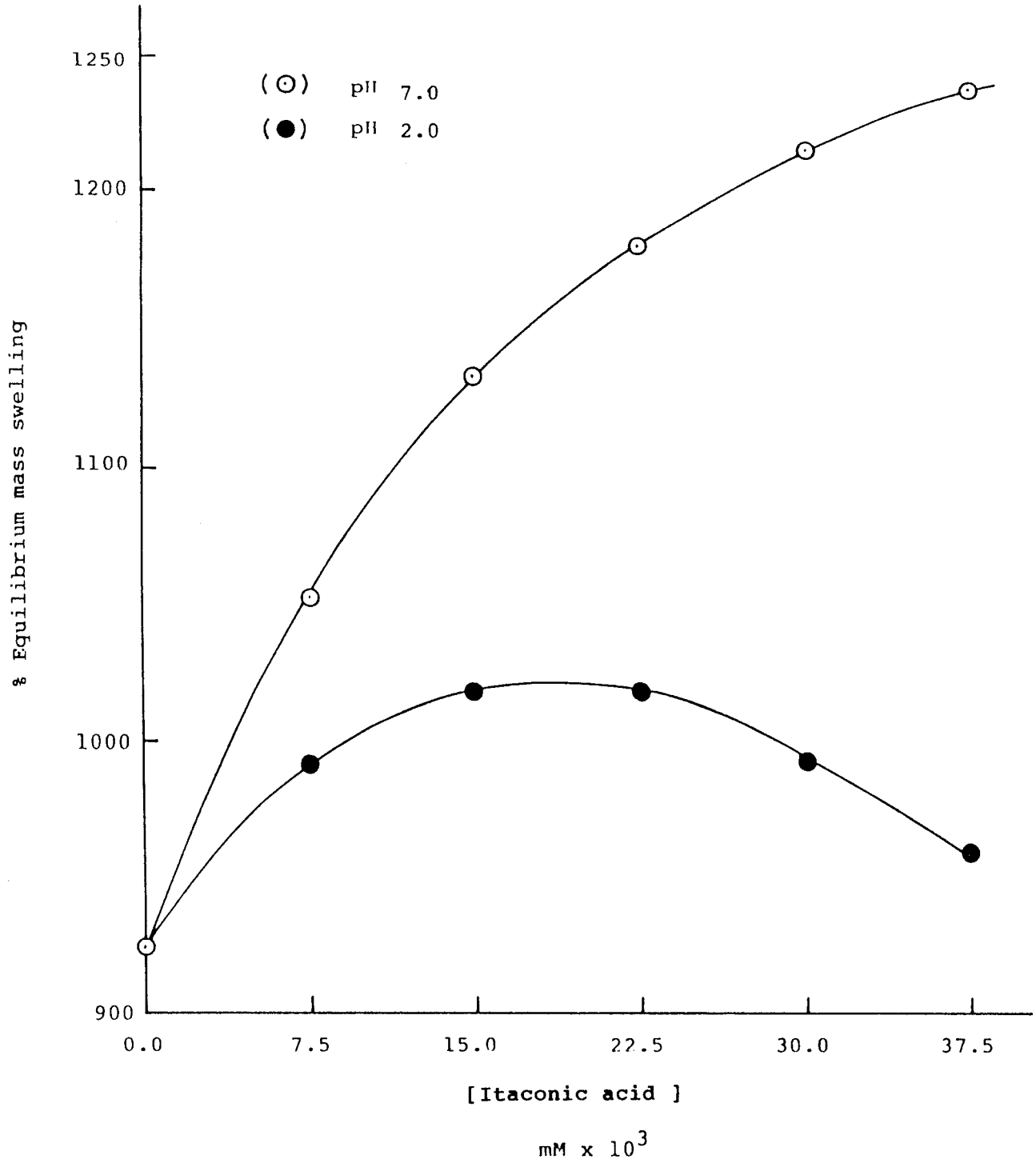

Figure 4 The effect of the itaconic acid content in the hydrogel on the equilibrium water uptake at 30°C with an ionic strength of 0.1*M*.

As depicted in Figure 6(A), when the completely swollen gel is placed in the external medium of pH 2.0, the H^+ ions present in the external medium invade the uppermost surface of the swollen gel containing carboxylate groups, thus resulting in the formation of a nonionic and uncharged shell layer on the surface that gradually moves toward the core region of the gel. This

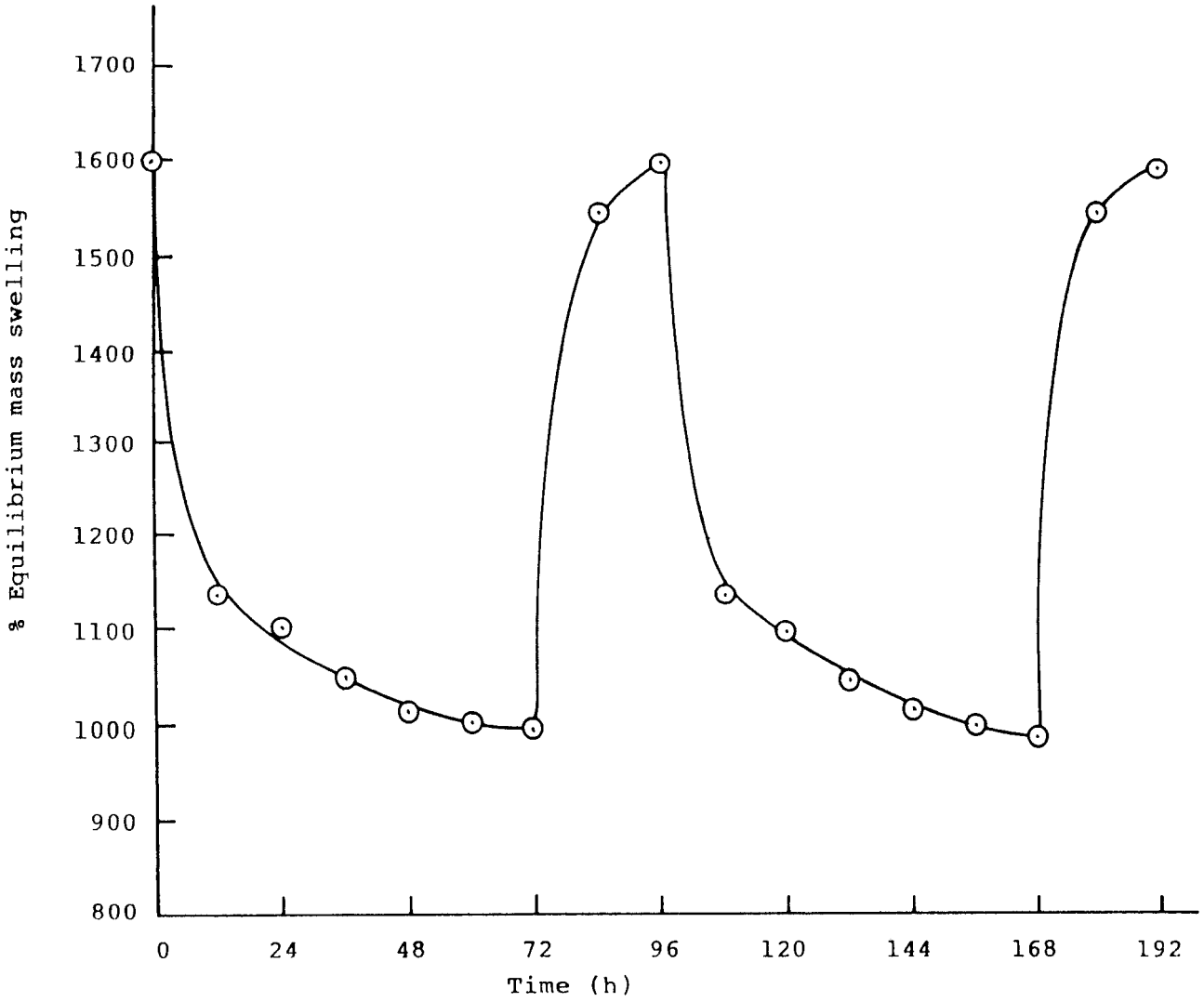

Figure 5 Deswelling–swelling cycles for the hydrogel sample HG (0.67) at pH 2.0 and 8.0 at 30°C with an ionic strength of 0.1*M*.

dehydrated and nonionic gel layer functions as a diffusion barrier for the further release of water from the bulk of the gel into the external medium. This may be the most probable explanation for the slower deswelling kinetics. However, when the completely deswollen gel is placed in a pH 7.4 external solution [Fig. 6(B)], a more hydrated and charged layer is first formed on the surface of the gel due to the ionization of carboxylic groups because the pH of the swelling media (i.e., 8.0) is above the pK_a values of the two carboxylic groups inside the polymer matrix. Through this hydrated and charged layer the counterions along with the solvent molecules can easily be embedded into the collapsed core region, thus causing the gel to swell. Therefore, the overall swelling kinetics may be governed by the ion-exchange rate.

Counterion Effect

The effect of the valency of the counterions in the swelling media on the equilibrium water uptake for the three hydrogel samples was studied in solutions of NaCl and $CaCl_2$ at pH 7.0 with the ionic strength ranging from 10^{-1} to 10^{-3} *M* at 30°C. (Table II). It is clear from Table II that the hydrogel sample without IA does not show any change in its equilibrium swelling with a change in the valency of the counterions from 1 to 2, which may be attributed to the fact that, because the hydrogel sample does not contain any ionizable groups in the polymer matrix, its swelling capacity remains almost unaffected by the nature of the counterions. However, for the HG (0.67) and HG (1.74) samples, which contain IA in the

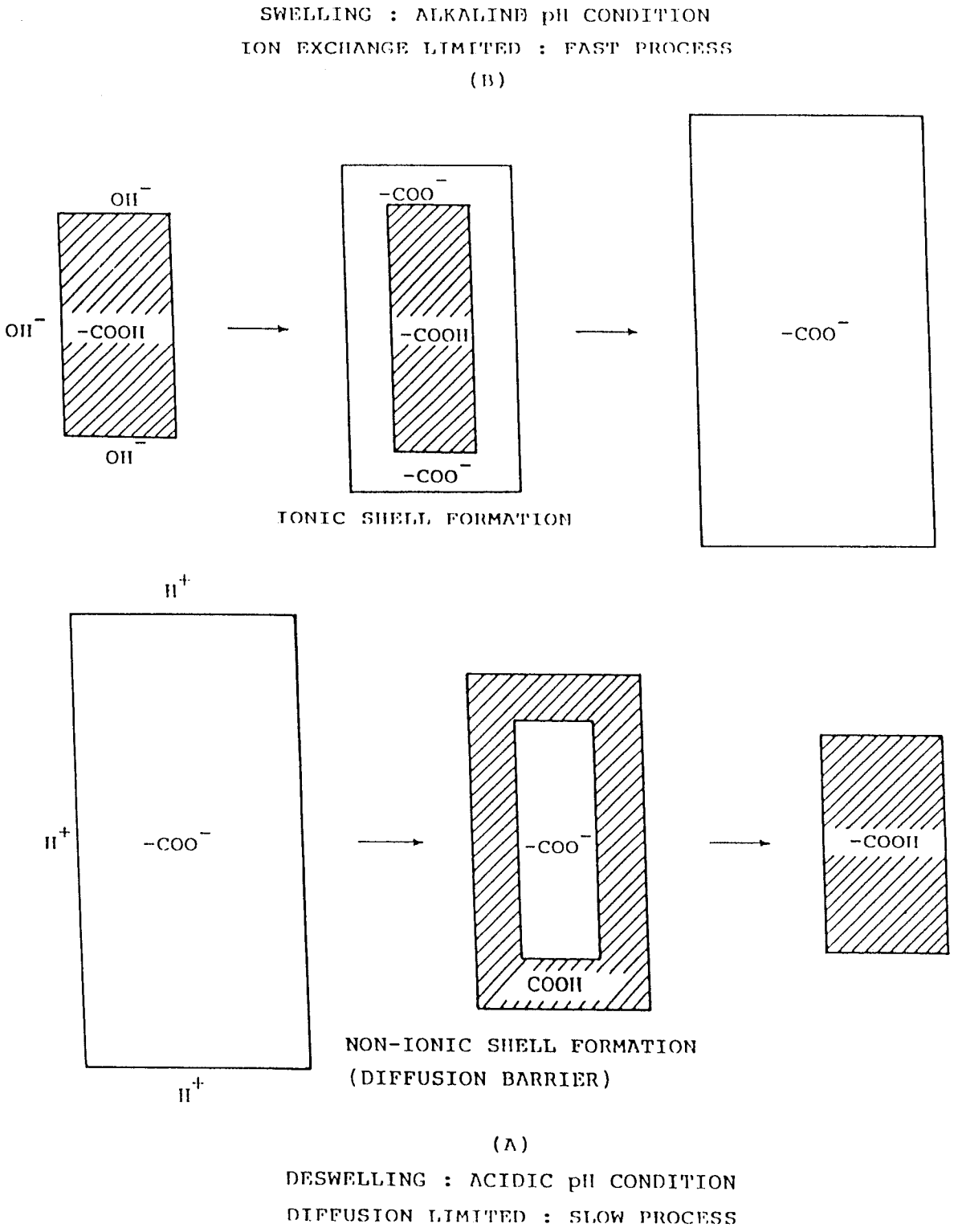

Figure 6 An illustration of the different mechanisms followed by the hydrogel during the deswelling and swelling process: (A) a schematic diagram for the deswelling of the hydrogel in the pH 2.0 medium and (B) a schematic diagram for the swelling of the hydrogel in the pH 8.0 solution.

Table II Percentage of Equilibrium Mass Swelling (S_m) for Samples in Salt Solutions of NaCl and $CaCl_2$ (30°C, pH 7)

	S_m (%) in NaCl Solution			S_m (%) in $CaCl_2$ Solution		
Sample	$10^{-1}M$	$10^{-2}M$	$10^{-3}M$	$10^{-1}M$	$10^{-2}M$	$10^{-3}M$
HG (0)	925	924	926	927	928	923
HG (0.67)	1117	1254	1463	1060	1177	1275
HG (1.74)	1227	1421	1832	1111	1211	1444

gel networks, the equilibrium swelling decreases as the valency of the counterion changes from 1 to 2. The observed decrease in the equilibrium water uptake may be due to the presence of ionizable groups in the hydrogel networks. Now, because the carboxylic groups present in the polymer networks are in the almost completely ionized state at the experimental pH 7.0 of the swelling media, the number of sodium ions required to bind with the carboxylate ions to maintain the electroneutrality condition will be almost double the amount of calcium ions for the same degree of ionization inside the polymer network. This results in a decreased ion osmotic swelling pressure and hence a decreased equilibrium water uptake. However, the observed decrease in the equilibrium mass swelling is not much larger, which ultimately suggests that the degree of ionization of the fixed ionizable groups inside the polymer matrix is very small. In addition, aqueous electrolytic solutions do not have any buffering capacity and this contributes to a lower degree of ionization.[17]

Effect of Temperature

The swelling behavior of polymer networks is affected by the temperature of the swelling media in many ways. If the polymer constituent present in the hydrogel possesses a lower critical solution temperature (LCST),[18] then a sharp volume phase transition is expected across the LCST; otherwise, the chemical nature of the monomer units within the polymer network decides the swelling trend. However, the increase in the temperature of the swelling media is usually accompanied by the enhancement of the rate of solvent diffusion into the gel network. In the present study the effect of the temperature of the swelling media on the equilibrium water uptake of hydrogel samples HG (O) and HG (0.67) was studied in the range of 30–50°C in the solution with an ionic strength of 0.1M at pH 7.0. The results as depicted in Table III clearly suggest that the increase in the temperature causes an increase in the values of the diffusion coefficient, which may simply be attributed to the fact that the rise in temperature causes an increase in the penetration rate of solvent into the gel matrix. However, the equilibrium water uptake remains almost constant up to 40°C and then a slight decrease is observed. This behavior may be explained by considering the nature of the polymeric constituents (PVP and PAAm-*co*-IA) present in the hydrogels. Of these, PVP possesses a LCST between 35 and 40°C[16] whereas the PAAm-*co*-IA does not possess a LCST. If the hydrogel systems were purely made up of PVP (i.e., no other polymer present), then an appreciable volume phase transition would be expected when varying the temperature of the swelling media as was observed in a number of hydrogel networks containing polymeric constituents with a LCST.[19,20] However, in the present case the amount of PVP present in the hydrogel system is nearly 33% (w/w), and hence no sharp volume phase transition takes place beyond 40°C. Therefore, the equilibrium water uptake decreases very slightly due to the partial contri-

Table III Effect of Temperature on Diffusion Coefficient (D) and Equilibrium Mass Swelling (S_m) for Samples (pH 7, 0.1M)

	HG (0)		HG (0.67)	
Temperature (°C)	$D \times 10^6$ ($cm^2\ min^{-1}$)	S_m (%)	$D \times 10^6$ ($cm^2\ min^{-1}$)	S_m (%)
30	14.20	925	15.70	1117
40	19.70	918	21.26	1103
50	28.30	830	30.02	1080

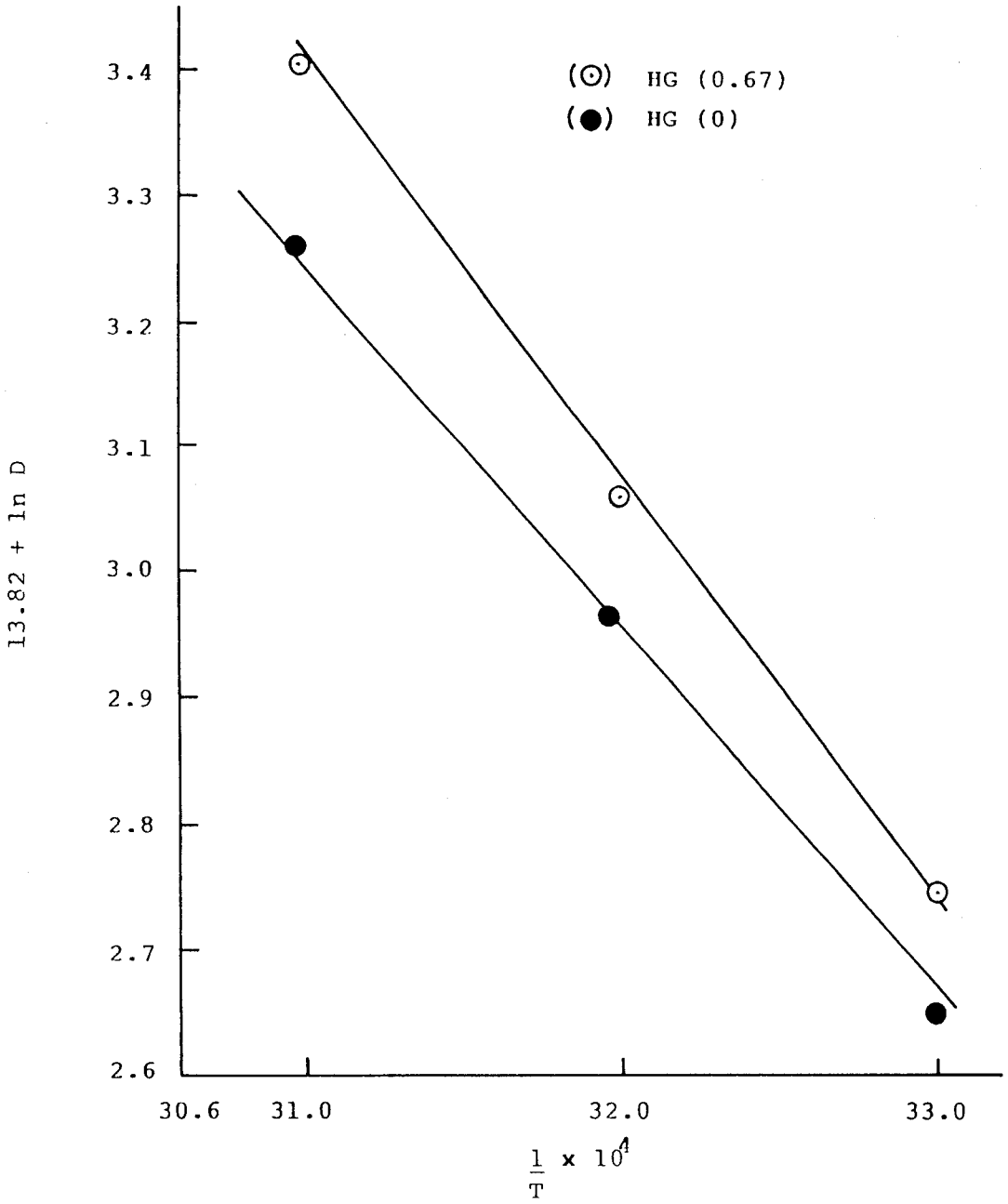

Figure 7 An Arrhenius plot for the HG (0) and HG (0.67) samples with an ionic strength of 0.1*M* at pH 7.0.

bution of PVP toward the volume phase transition. The activation energy, as determined from the Arrhenius plot (Fig. 7), was 19.92 and 29.09 kJ mol^{-1} for samples HG (O) and HG (0.67), respectively. Here it is worth mentioning that the average activation energy value in the literature[21] for a nonionic hydrogel film is nearly 8.3 kJ mol^{-1} while in the present study the activation energy for the nonionic cylindrical hydrogel samples is 19.92 kJ^{-1} mol^{-1}, which is relatively higher. This shows that in the cylindrical hydrogel system the diffusion of solvent into the matrix is quite slow, which is in complete agreement with the predictions made by the Tanaka–Fillmore theory.[22] Moreover, the higher activation energy value for the acid containing samples may be attributed to the fact that the value corresponds to the entire process

of solvent entry, stretching of the network segments, and consequent large-scale dimensional changes in the polymer network.[23]

CONCLUSION

The above study reveals the fact that the incorporation of a small amount of IA into the polymer matrix causes the hydrogel system to exhibit polyelectrolyte type swelling behavior and undergo a transition from the Fickian to non-Fickian type swelling behavior. The hydrogel system studied also shows pH dependent swelling behavior with the minimum swelling near pH 2.0 and the maximum at pH 7–8. Moreover, the hydrogels undergo a number of swelling–deswelling cycles when put in the external solutions of pH 2.0 and 8.0. Finally, the gels are not very sensitive to the temperature of the swelling media and the activation energy for the acid containing hydrogel system is relatively higher than that for the hydrogel with no IA present in the system.

Thus, the proposed hydrogel system exhibits a fairly pH dependent swelling response and is able to undergo a number of swelling–deswelling cycles while maintaining mechanical strength. This makes the system suitable for use as colon-specific drug delivery systems because it will keep the encapsulated drug protected in the stomach where the pH is nearly 2.0 by exhibiting minimum swelling and it will release the maximum amount of drug in the colon at pH 7.4 by swelling to maximum. Therefore, the diseases of the colon such as colon cancer should be curable through oral administration of anticancer drugs encapsulated in the proposed system in the form of nanoparticles, pallets, or other suitable forms. For example, antisense oligonucleotides have proved to be efficient drugs for oral colon-specific delivery for the treatment of cancer.[24] Finally, the good biocompatibility of the constituents and very mild conditions of gel synthesis are also favorable factors to make the proposed device a potential system for protein and peptide drug delivery along the GI tract through oral administration.

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