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HYDROGELS FOR COLON-SPECIFIC ORAL DRUG DELIVERY: SYNTHESIS AND CHARACTERIZATION

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ABSTRACT

Hydrogels have been synthesized by free radical co-polymerization of acrylamide and maleic acid in the presence of poly(N-vinyl-2-pyrrolidone) in aqueous medium. The presence of a small amount of maleic acid in the polymer network increased the swelling capacity appreciably, thus changing the Fickian swelling behavior to a non-Fickian one. The hydrogels showed good response to pH, ionic-strength and valency of counterions in the external media. The hydrogels demonstrated minimum swelling in the strongly acidic range 1-2 and maximum swelling was observed in the neutral or slightly alkaline medium (7-8). The amount of maleic acid in the hydrogel affected its swelling behavour in a rather unusual way. At pH 7.0, the equilibrium swelling increased up to 123 mM of maleic acid in the system and then started decreasing, while at a low pH, a continuous decrease was observed. The hydrogels underwent a number of deswelling swelling cycles with a pH change from 1.0 to 8.0, respectively. The hydrogels demonstrated temperature-dependent swelling behavior partially, and activation every for the sample with and without maleic acid was found to be 33.1 and 19.9 kJ mol^{-1}. Finally, the pH - dependent swelling behavior makes them suitable for a drug delivery device along the gastrointestinal (GI) tract.

Key Words: Colon-specific drug delivery; Maleic acid; Hydrogels; pH-dependent swelling.

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INTRODUCTION

The common administration route for protein and peptide drugs is parenteral, which results in a rapid increase and subsequent rapid decrease of the blood serum concentration levels. Therefore, the major challenge in the field of protein delivery is to develop a device which can deliver the drug while maintaining the blood concentration for a considerable time period inside the therapeutic region and reduce the number of doses to be administered. Therefore, the oral administration is a convenient route, however, it is very difficult to achieve. One of the major obstacles to oral delivery is the digestion of proteins by gastric and pancreatic enzymes present in the stomach and the small intestine [1]. The pH-sensitive hydrogels are most suitable devices for the oral delivery of peptides and proteins due to their good response to the surrounding environment. It is known that the release of both the high and the low-molecular weight drugs from hydrogels depends upon several factors, such as the hydrophilic/hydrophobic balance of the copolymer, the degree of crosslinking and, especially the degree of swelling [2]. pH-Sensitive hydrogels have a potential use in the site-specific delivery of drugs to specific regions of the gastrointestinal (GI) tract due to pH variations throughout the GI tract. Although a number of workers have made good contributions towards the synthesis and applications of such hydrogels [3-6] for protein drugs delivery yet, additional attention is required in this field.

We have synthesized a new type of pH-sensitive hydrogel composed of poly(N-vinyl-2-pyrrolidone-acrylamide-co-maleic acid) which can be used as a protein drug delivery carrier. At low pH, this hydrogel swells to a minimum, thus protecting the encapsulated drug from the acidic environment of the stomach due to limited release. On the other hand, as the device passes from the stomach to the upper small intestine and then to colon, the drastic pH change will cause the gel to swell and thus the drug loaded will be released. Since the drug release behavior is usually swelling-dependent, the present communication describes only the synthesis and study of the swelling behavior of the proposed system so that this may be used as a site-specific drug delivery device along the GI tract, in the near future.

Maleic acid and Poly (N-vinyl-2-pyrrolidone) (PVP) have been known to be good biocompatable materials and later is used in manufacturing soft contact lenses [7]. The greater hydrophilicity of PVP promotes its use for drug delivery devices. One more significant point about the proposed hydrogel is that synthesis of the polymer matrix does not require a high temperature or use of organic solvent, so the probability of loss of drug activity during the drug incorporation or during the synthesis is minimum [8].

EXPERIMENTAL

Materials

Poly(N-vinyl-2-pyrrolidone (PVP; Sigma, St. Louis, MO), potassium persulfate (KPS; Merck), acrylamide (AAm; Sigma), N,N'-methylene bisacrylamide

(MBA; Sigma) and maleic acid (MA; Sigma) were of analytical grade and used as received. However, the monomer AAm was recrystallized in methanol to remove the inhibitor. The double distilled water was used throughout the investigations.

Synthesis of Cylindrical Gels

A definite amount of PVP was dissolved in 30 mL of doubly distilled water, and to this solution, calculated quantity of the monomer acrylamide along with very small amount of maleic acid (100 to 250 mg) was added. Finally, a definite amount of crosslinker MBA and initiator KPS were added to this solution, and the resulting homogeneous mixture was poured into PVC straws and kept in an electric oven (Tempstar, India) at 65ºC for a period at 3 hours. The resulting semitransparent gels were cut into small cylindrical pieces of a known length. The rod-like gels were washed with deionized water to remove the unreacted salts and then dried at 30ºC for a period of 24 hours in a dust-free chamber and were now ready to be used.

In all, three hydrogel systems were prepared, for which the percent mole ratio AAm/MA was found to be 100.0:0.0, 98.5:1.5, and 96.2:3.8. These samples will be denoted as HG (0), HG (1.5), and HG (3.8). Here, it is worth mentioning that in the preliminary studies the compositions of monomers and amount of crosslinker were already determined to get 100% gelation in each hydrogel system. Hence, the compositions of monomer mixtures in the hydrogel systems is the same as the feed compositions in the reaction mixture at the time of synthesis.

Swelling Studies

Preweighed and completely dried hydrogel samples were placed in a solution of desired pH with the ionic strength 0.1M at a constant temperature 30ºC. The swollen gels were taken out at regular time-intervals, wiped superficially with filter paper, weighed, and placed in the same solution. The mass measurements were continued till the attainment of the equilibrium swelling for each sample. The percentage of mass swelling [$\%S_m$] and volume swelling [$\%S_v$] were obtained using the following formulas [9]:

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

and

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

where m_o and m_t are the initial mass and mass at different time-intervals, respectively; and d_p and d_s are the solvent density and polymer density respectively [10].

Swelling-Deswelling Studies

For this, the initially dried hydrogel sample was placed in an alkaline solution of pH 8.0 and allowed to attain the equilibrium swelling. Then, the swollen gel was removed from the solution and put in a solution of pH 1.0 until it deswelled to give a constant weight. The deswollen gel was again put in the alkaline solution to attain equilibrium swelling, followed by its deswelling in the acidic solution of pH 2.0. This deswelling-swelling cycle was repeated a number of times until the hydrogel sample started to show dissolution tendency. Here, one more significant point to be mentioned is that in order to avoid any possible change in pH of the bathing medium during the swelling and deswelling processes, the experiments were carried out by taking the large volume (i.e., 2 lit.) of the external medium so that the pH of the external solution remained almost constant throughout the experiments. The pH of the external solution was also checked at regular time intervals, and was found to be almost constant throughout the study.

RESULTS AND DISCUSSION

Diffusion

When a glassy hydrogel is placed in a solvent, the solvent diffuses into the polymer matrix, thus causing it to swell. This diffusion process involves migration of water into pre-existing or dynamically formed spaces between macromolecular chains. Swelling of hydrogel involves larger scale segmental motion resulting ultimately into an increased distance of separation between hydrogel chains [11].

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

$$F = \frac{M_t}{M_\alpha} = K \tag{1}$$

where M_t and M_α denote the amount of solvent which diffused into the polymer matrix at time 't' and at equilibrium, respectively; K is a constant related with the structure of the network; and the exponent <n< describes the type of diffusion. For cylindrical shaped gels, n = 0.45 - 0.50 corresponds to 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 plot of ln F versus ln t gives straight lines upto almost a 60% increase in the mass of the hydrogel.

In hydrogel characterization, the diffusion coefficients were calculated from the following relationship:

$$D = 0.049 / (t/4l^2)_{1/2} \tag{2}$$

where D is expressed in $cm^2\ min^{-1}$; t is the time at which swelling is half the equilibrium value and l is the radius of the cylindrical sample.

The intrinsic diffusion coefficient $\bar{D}$ given as:

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

where V is the volume fraction of the solvent penetrating the polymer network by the time t defined above [10].

Figure 1 describes the dynamic uptake of water for the three hydrogel samples in deionized water at pH 7.0 at 30ºC. The percentage mass equilibrium

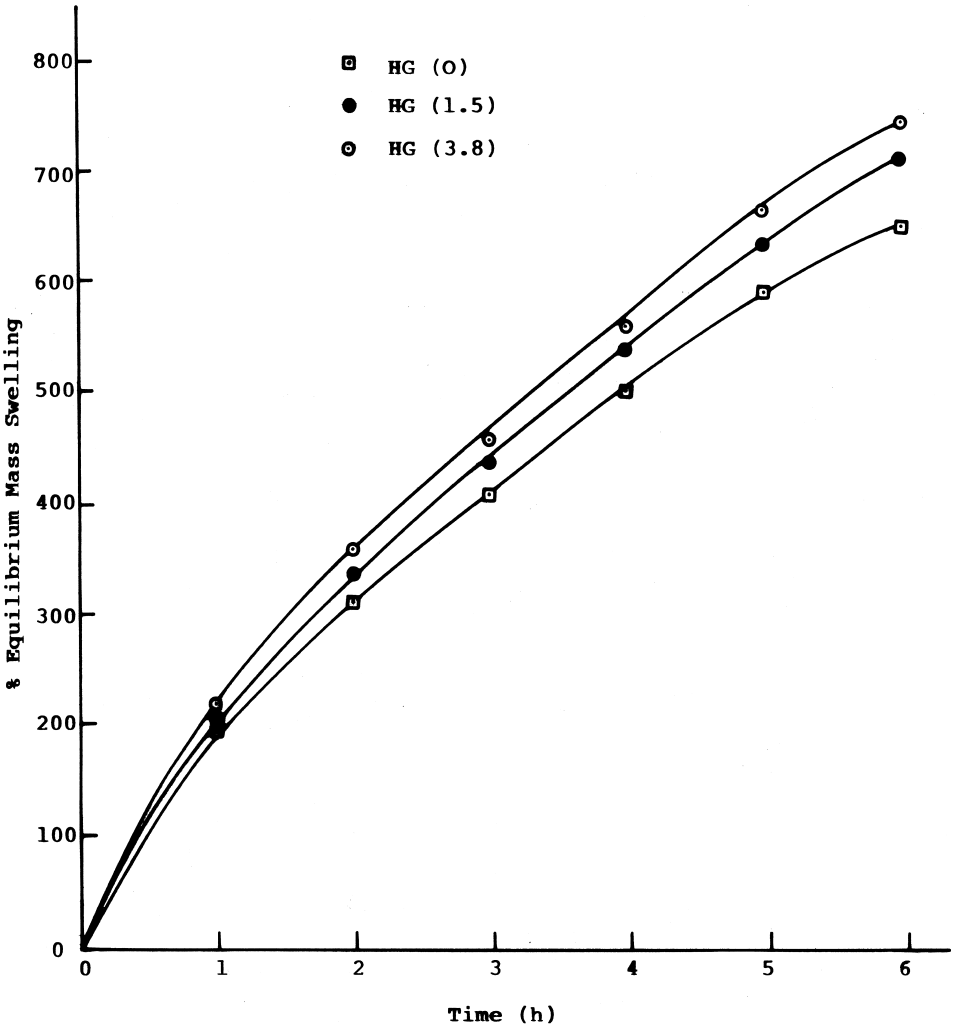

Figure 1. Dynamic mass uptake for the three hydrogel samples HG(O), HG(1.5) and HG (3.8) in the deionized water (pH = 7.0, temperature = 30ºC).

swelling for the three samples were found to be 925, 1270, and 1559, respectively. It shows clearly that the introduction of small amount (100 to 250 mg) of maleic acid causes a great increase in the percent swelling by 300 to 600%.

The values of swelling exponent 'n', as determined from the slope of the straight line plots between ln F and ln t have been listed in Table 1 along with the other swelling parameters such as k, D, and $\bar{D}$. The value of n for the sample HG (0) is 0.52 which shows that the hydrogel follows a Fickian-type swelling behavior while the value for the samples HG (3.8) and HG (1.5) are 0.71 and 0.83, respectively thus showing the non-Fickian type swelling behavior. Therefore, the addition of a small amount of acid into the hydrogel causes the transition from Fickian to non-Fickian swelling behavior. This may be attributed to the fact that for the sample HG (0), which does not contain any ionizable groups in the polymer matrix, the diffusion of water into the hydrogel is the rate limiting, thus imparting almost normal or Fickian swelling behavior to the hydrogel, whereas in the case of samples HG (1.5) and HG (3.8) which contain maleic acid, the ionization of carboxylic groups in the polymer matrix at the experimental pH 7.0 imparts ionic character to the hydrogel. Therefore, not only the ion osmotic swelling pressure π_{ion} increases, but the electrostatic repulsion between the adjacent ionized carboxylate groups also leads to a greater chain relaxation. Now, the former factor encourages the diffusion of water into the gel phase in accordance with the Donnan membrane equilibrium, whereas the later one enhances the macromolecular chain relaxation process. These two factors are comparable, and hence responsible for the anomalous or non-Fickian transport. Similar observations have also been reported elsewhere [12].

Table 1 also shows that the values of the intrinsic diffusion coefficient for the three polymer networks are greater than those for diffusion coefficient because Equation 2 gives a measure not only of diffusion but also of the mass flow of the whole system, while Equation 3 gives the intrinsic diffusion coefficient for the case where no mass action effects enter [10].

pH Effect

If the polymer matrix contains some ionizable groups, which can dissociate or get protonated at some suitable pH values of the external medium, then the

Table 1. Swelling Parameters for the Swelling of the Samples HG(0), HG (1.5), and HG (3.8) in Deionized Water (Temperature = 30ºC, pH = 7.0)

Sample	% S_m	% S_V	n	$K \times 10^2$	$\bar{D} \times 10^6$ $cm^2\ min^{-1}$	$\bar{D} \times 10^4$ $cm^2\ min^{-1}$
HG (0)	925	981	0.52	23.24	14.93	30.89
HG (1.5)	1270	1444	0.71	15.88	10.04	55.87
HG (3.8)	1559	1843	0.83	12.01	07.22	77.21

swelling capacity of the hydrogel is affected by the variation in pH. In the present study, the effect of pH of the swelling media on the swelling behavior of the three hydrogel samples has been studied in the pH range 1-8 at ionic strength 0.1M at 30ºC. It is clear from Figure 2 that the sample HG (0) does not show any change in the equilibrium mass swelling with the pH of the external medium, whereas for the samples HG (1.5) and HG (3.8), which contain small amount of maleic acid, the equilibrium water uptake increases as the pH is increased in the range 1-8. The pH-independent swelling behavior of sample HG (0) may be attributed to the fact that since the polymer matrix is purely non-ionic in nature, it does not contain any ionizable groups and therefore, variation in the pH of the external media does not

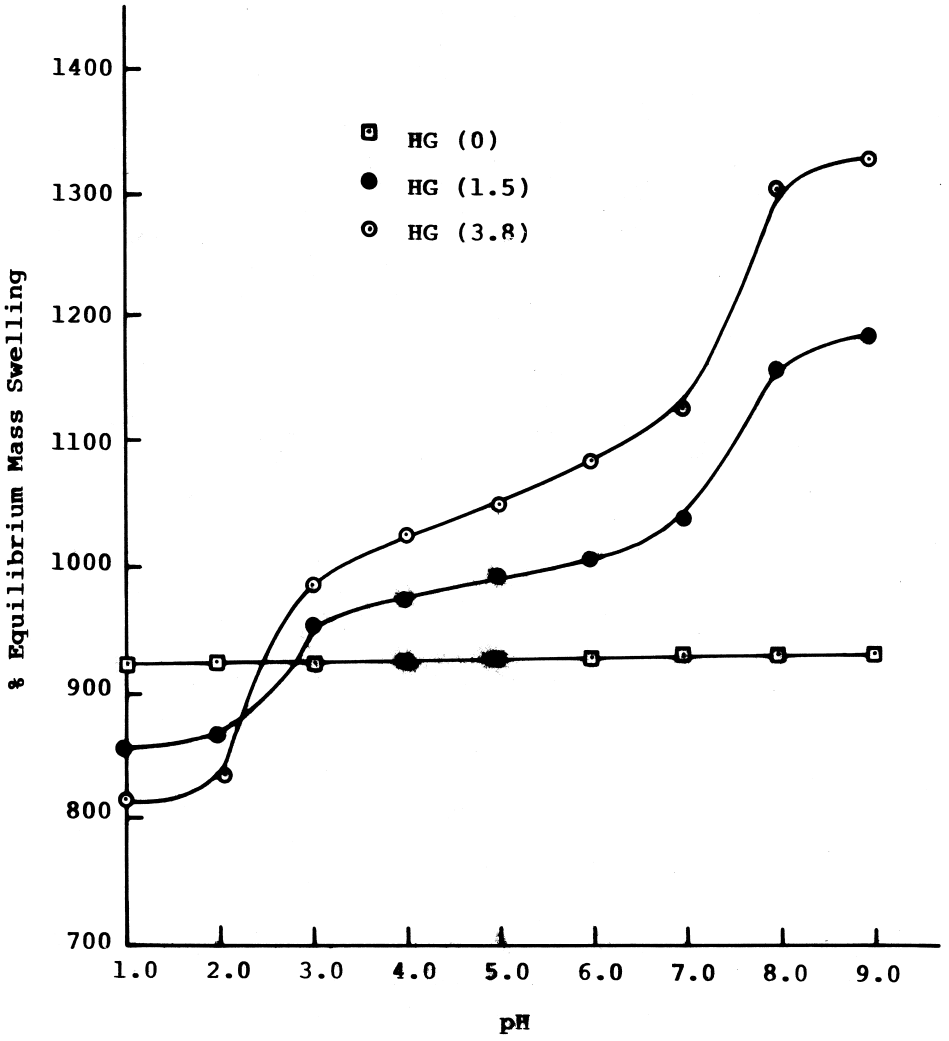

Figure 2. Equilibrium water uptake of the samples HG (1.5) and HG (3.8) as a function of pH of the external medium (temperature = 30ºC, ionic strength = 0.1 M).

change in the swelling capacity. However, the situation is quite different with the samples HG (1.5) and HG (3.8)m which contain carboxylic groups along the macromolecular chains. It is clear from Figure 2 that the increase in the equilibrium water uptake is much more pronounced near the pH 2.0 and 7.0, which may be attributed to the dissociation of the two carboxylic groups of maleic acid around these pH values, because first and second pk_a for maleic acid are 1.85 and 6.06, respectively [13]. Therefore, when the pH of the external medium increases beyond 2.0, the ionization of carboxylic groups in the gel matrix causes a sudden increase in the swelling due to increased ion osmotic swelling pressure, as well as chain relaxation resulting from the electrostatic repulsion among the carboxylate groups along the macromolecular chain. Similarly, when pH of the swelling medium passes through 7.0, again a sudden rise in equilibrium water uptake is noticed which may be attributed to the further ionization of carboxylic groups. The two pk_a values, as determined from the Figure 2 were found to be 2.40 and 7.30, respectively which are slightly greater than the actual values 1.85 and 6.06. This may be due to some hinderance offered in the ionization of carboxylic groups in the polymer matrix due to the crosslinked structure of the polymer matrix. To sum up, the observed increase in equilibrium water uptake with a rise in pH of the external medium arises from the ionization of carboxylic groups of maleic acid which ultimately causes an increase not only in the ion osmotic swelling pressure, but also in the extent of the chain relaxation process.

Effect of Maleic Acid Content

The effect of the amount of maleic acid present in the hydrogel on the equilibrium water uptake has been studied at pH 1.0 and 7.0 at 30ºC at the ionic strength 0.1M (Figure 3). It is clear from the Figure that the swelling behavior of hydrogels, containing varying amounts of maleic acid is quite different at the two experimental pH. At pH 1.0, the equilibrium swelling of hydrogel decreases slightly along with the increasing amount of maleic acid. The observed experimental findings may be attributed to the fact that at the pH 1.0, the carboxylic groups present in the hydrogel are almost in undissociated form (see the pk_a values for the hydrogels), thus imparting non-ionic character to the polymer matrix. Now the hydrophobicity provided by the unionized maleic acid present in the hydrogel discourages the diffusion of solvent into the polymer matrix. Moreover, it has been reported that maleic acid actively participates in the crosslinking of the gel matrix [14] and therefore, the combined effect of the above two factors i.e., hydrophobicity and crosslinking, results in a decrease in the equilibrium swelling of the hydrogel sample. Since the amount of maleic acid is very small, a slight decrease in the swelling is observed (see Figure 3).

However, when the same effect is studied at pH 7.0, the swelling behavior of the hydrogels is found to be quite different. The equilibrium swelling capacity first increases with the maleic acid content up to 123 mM, then it starts decreasing

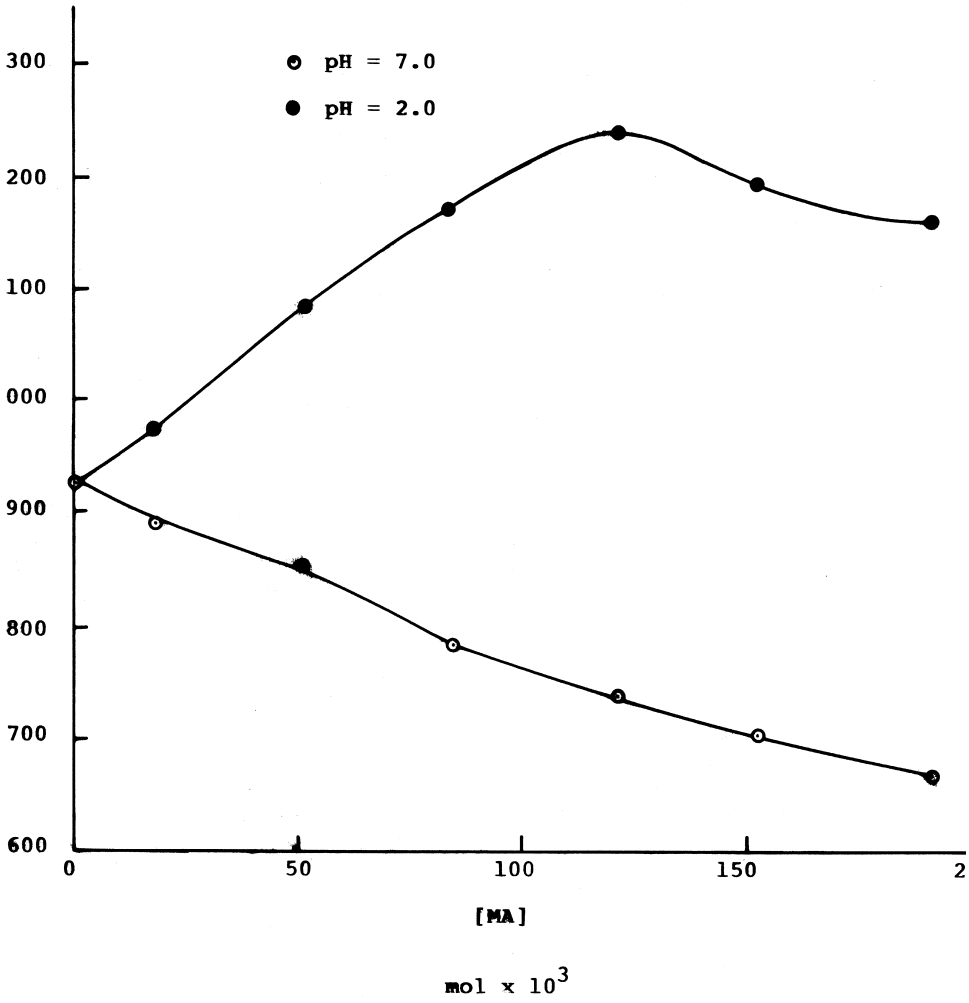

Figure 3. Effect of maleic acid content in the hydrogel on the equilibrium water uptake (pH = 7.0, temperature = 30ºC, ionic strength = 0.1 M).

with a further rise in the maleic acid content. For the lower concentrations of maleic acid in the polymer matrix, the observed increase in equilibrium swelling may simply be due to the almost complete ionization of carboxylic groups, thus resulting in an increase in the swelling due to increased chain relaxation as well as the ion osmotic pressure. However, when the concentration is further increased, the contribution of maleic acid towards the crosslinking of the polymer matrix is almost counterbalanced by the increased ion osmotic pressure and chain relaxation due to electrostatic repulsion among the carboxylate groups along the polymer chain. Henc,e for a very small range of concentration the swelling remains almost constant. Now, with the further increase in the maleic acid content beyond 123 mM, the swelling is observed to decrease due to predominent role of

crosslinking effect and also due to the hydrophobic character imparted by unionized maleic acid to the hydrogel.

Ionic Strength Effect

Figure 4 depicts the equilibrium water uptake of the three hydrogel samples, as studied in a solution of varying ionic strength at pH 7.0 at 30ºC. It is clear from the Figure that as the ionic strength of the bathing medium increases, the equilibrium swelling of the hydrogels samples HG (1.5) and HG (3.8) decreases. This phenomenon is observed most frequently in the swelling behavior of polyelec-

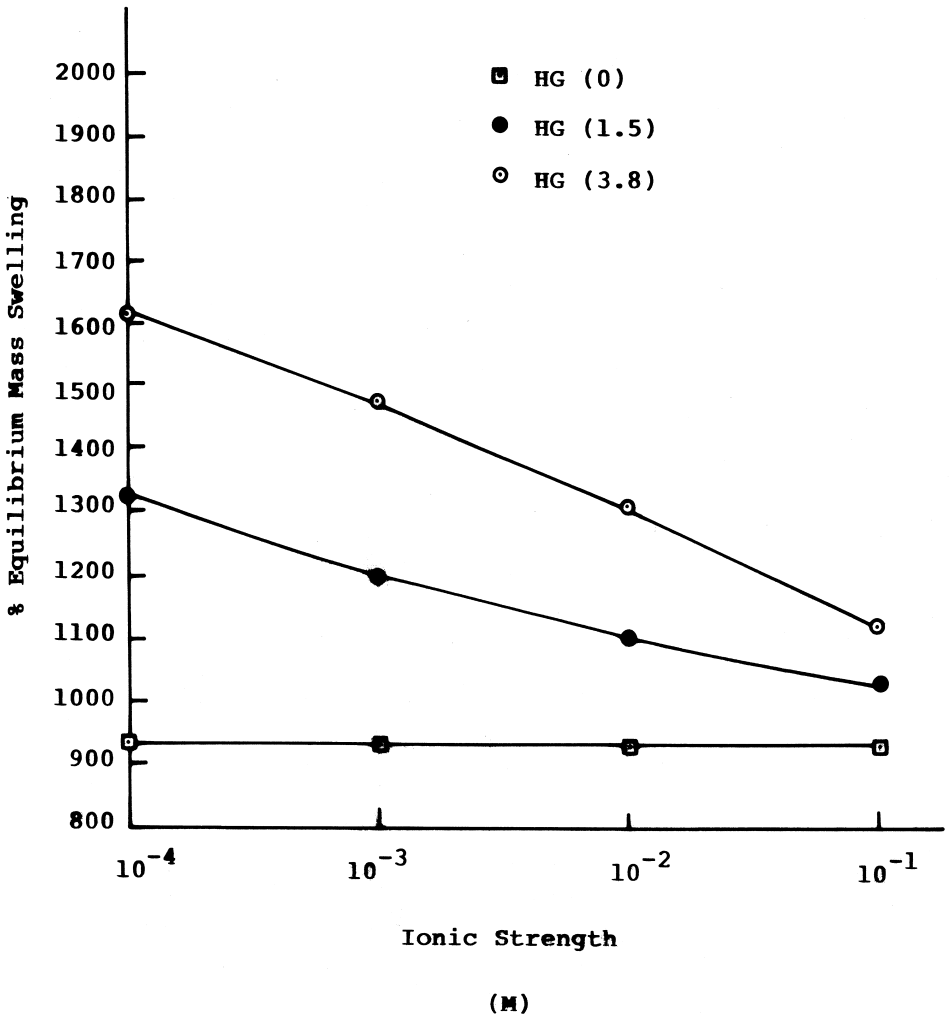

Figure 4. Effect of ionic strength of the external media on the equilibrium swelling of the three hydrogel samples (pH = 7.0, temperature = 30ºC).

trolyte hydrogels. However, the sample with no maleic acid content i.e., HG (0) does not show any change in the equilibrium water uptake with increasing ionic strength. Since the sample HG (0) does not contain any ionizable moiety inside the polymer matrix, it simply behaves like an non-ionic polymer matrix, thus showing no response to the ionic strength of the external media.

For the samples HG (1.5) and HG (3.8), the ionization of carboxylic groups present in the polymer matrix (at the experimental pH 7.0) imparts ionic character to the hydrogels and therefore, the ion osmotic swelling pressure π_{ion} [$= \Sigma(C_g - C_s)$ where C_g and C_s are concentrations of counter/mobile ions in the gel and in the solution phase, respectively] become the governing factor in the overall swelling process. Obviously, with the increase in the ionic strength of the external solution, the value of π_{ion} decreases, which finally reduces the equilibrium water uptake of the hydrogels. In another set of experiments, the same study was carried out at pH 2.0 of the external solution. It was found that all the three samples showed no response to the varying ionic strength of the external media. This may be attributed to the fact that pH of the solution is below the pK_a values, the acid groups of hydrogels remained in almost unionized form, thus providing a 'non-ionic' character to the samples. As a result, no change in the equilibrium mass swelling was observed. Similar results have also been reported elsewhere [15]. The swelling exponent 'n' and gel characteristic constant 'k' at different ionic strength of the external media are listed in the Table 2.

Counter Ion Effect

The effect of valency of the counter ion in the swelling medium on the equilibrium water uptake has been studied by placing the three hydrogel samples in solutions of NaCl and $CaCl_2$ with the varying ionic strength from 10^{-1} to 10^{-3}M at pH 7.0 at 30ºC. The results, as listed in Table 3, clearly show that the sample HG (0) demonstrates almost the same equilibrium swelling in both NaCl and $CaCl_2$ solutions. This may be attributed to the fact that as the polymer sample does not contain any ionizable species in the hydrogel network, the equilibrium water

Table 2. Swelling Exponent 'n' and Constant 'k' for the Swelling of the Samples HG (1.5) and HG (3.8) in Salt Solutions of Various Ionic Strength

Ionic Strength (M)	Swelling Parameters for Sample HG (1.5)		Swelling Parameters for Sample HG (3.8)	
	n	$K \times 10^2$	n	$K \times 10^2$
10^{-1}	0.64	9.44	0.66	8.65
10^{-2}	0.71	8.12	0.76	8.03
10^{-3}	0.74	7.41	0.80	6.71
10^{-4}	0.78	5.62	0.82	5.98

Table 3. Percent Equilibrium Mass Swelling ($\%S_m$) for the Two Hydrogel Samples HG (1.5) and HG (3.8) in Salt Solutions of NaCl and $CaCl_2$ (pH = 7.0; Temperature = 30ºC)

	% S_m in NaCl Solution with Ionic Strength (M)			% S_m in $CaCl_2$ Solution with Ionic Strength (M)		
Sample	10^{-1}	10^{-2}	10^{-3}	10^{-1}	10^{-2}	10^{-3}
HG (1.5)	1036	1104	1203	898	1002	1112
HG (3.8)	1120	1311	1478	1024	1173	1321

uptake remains almost unaffected. However, for the sample HG(1.5) and HG(3.8), the equilibrium swelling decreases as the valency of counter ion increases from 1 to 2. The observed decrease in the equilibrium swelling may be attributed to the presence of ionizable groups in the network. Now, assuming the complete dissociation of carboxylic groups at the experimental pH 7.0, the number of sodium ions required to bind with the carboxylate groups to maintain the electroneutrality condition will almost be double the amount of calcium ions for the same degree of ionization inside the polymer matrix. This results in a decreased ion osmotic swelling pressure and therefore, a decrease in the equilibrium water uptake is observed. The data in the Table also shows that there is not much of a decrease in the swelling as the valency of the counter ion changes. This may be attributed to the fact that the degree of ionization of the carboxylic groups inside the polymer matrix is small. Moreover, since the aqueous electrolytic solution does not have any buffering capacity, this also contributes to a lower degree of ionization [16].

Deswelling-Swelling Study

Figure 5 depicts the successive deswelling-swelling cycles for the hydrogel sample HG(1.5) when it is, after being equilibrated in solution of pH 8.0, allowed to deswell in solution of pH 1.0. The hydrogel was found to undergo a number of such cycles without undergoing any deformation in its shape. The complete deswelling of the hydrogel was observed to take place in nearly 49 hours, while it required almost 37 hours to swell to the equilibrium in the alkaline solution of pH 8.0. This difference in swelling and deswelling times can be explained on the basis of the fact that the hydrogel follows different types of mechanisms in the swelling and deswelling process.

When the completely swollen gel is placed in the external solution of pH 1.0, the deswelling process starts with the formation of unchanged and non-ionic shell layer on the surface and it gradually moves towards the core region of the gel. This dehydrated and non-ionic gel layer retards the further release of water as diffusion barrier. This may be the most probable explanation for the slower deswelling process. However, when the completely deswollen gel is placed in the swelling medium of pH 8.0 (slightly alkaline solution), a more dehydrated and charged

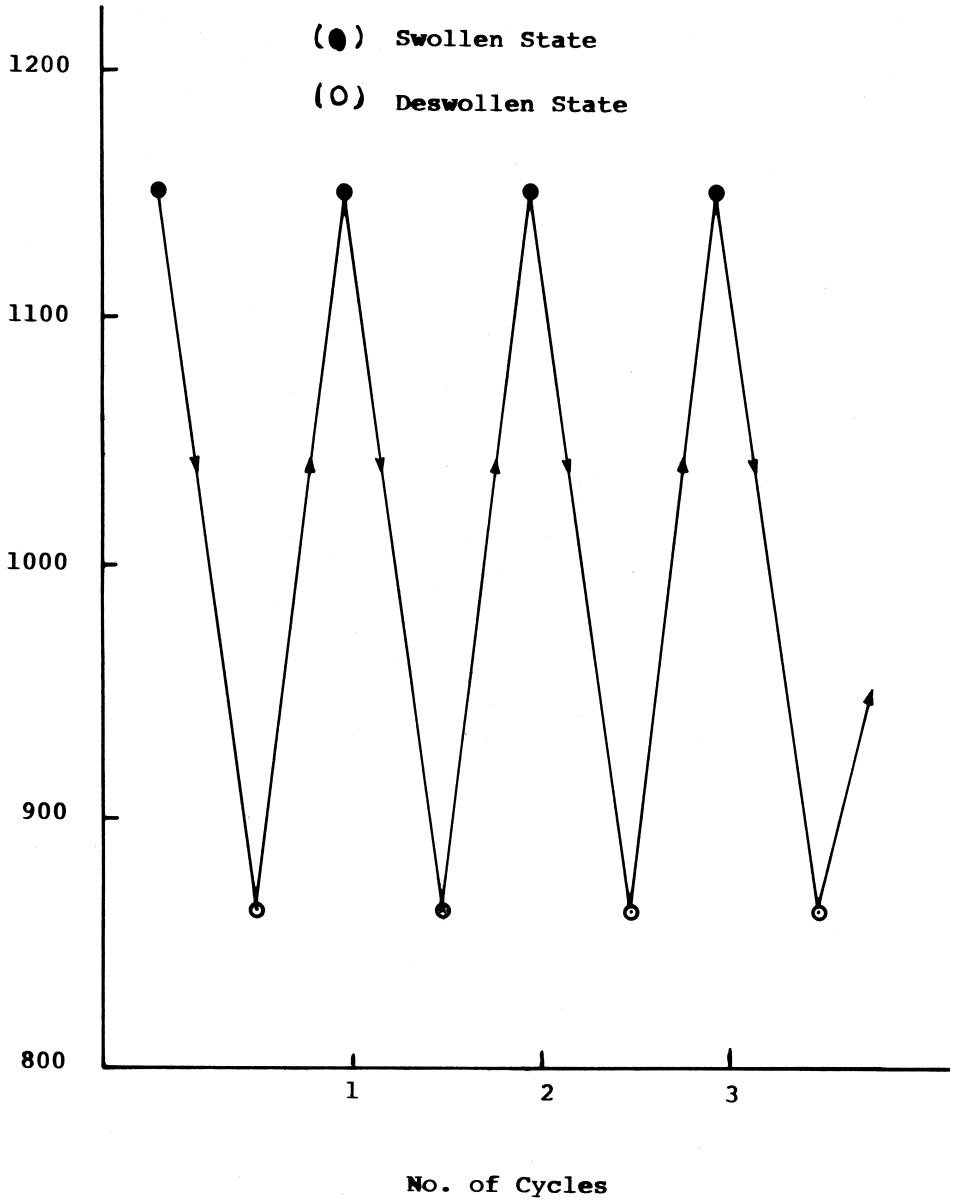

Figure 5. Deswelling-swelling cycles for the hydrogel sample HG (1.5) at pH 1.0 and 8.0, respectively (temperature = 30ºC, ionic strength = 0.1M).

layer (due to the ionization of - COOH groups in the matrix) is first formed on the outer most surface of the gel. Through this, the counter ions can easily be imbided into the collapsed core-region. Therefore, the overall swelling kinetics may be governed by the ion-exchange rate. The proposed mechanism has been well illustrated in Figure 6.

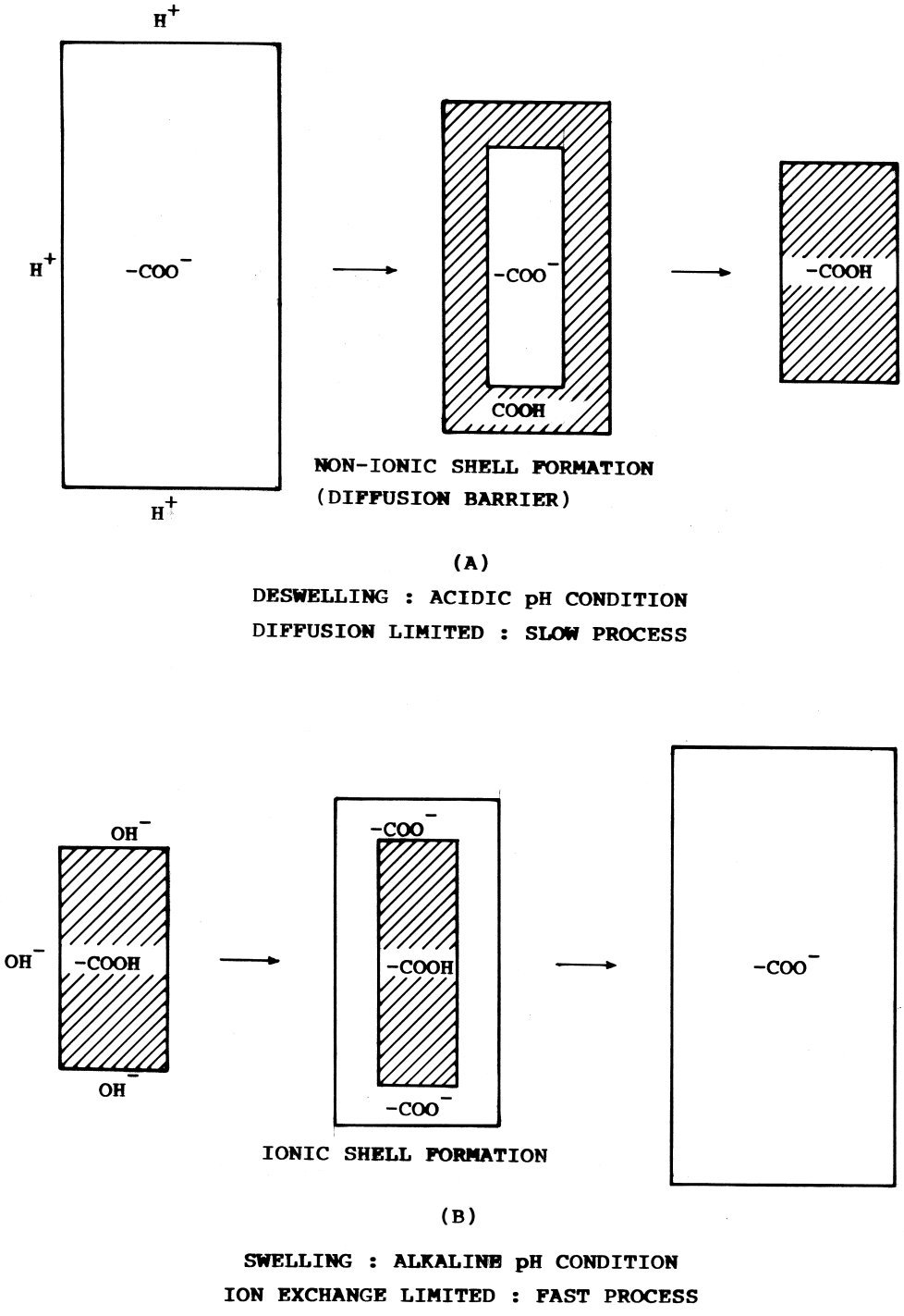

Figure 6. An illustration of the different mechanisms followed by hydrogel during the deswelling and swelling process: (A) Schematic diagram for the deswelling of the hydrogel in the medium of pH 1.0. (B) Schematic diagram for the swelling of the hydrogel in the solution of pH 8.0.

Effect of Temperature

The temperature of the external solution influences the swelling behavior of hydrogels in many ways. If the polymer present in the hydrogel possess a lower critical solution temperature [17], then a sharp volume phase transition is expected across the LCST, otherwise the chemical nature of monomer units within the polymer network decides the swelling trend. However, the increase in temperature is usually accompanied by the enhancement of solvent diffusion into the gel matrix. In the present study, the effect of temperature of the swelling media on the swelling behavior of hydrogel samples HG (0) and HG (1.5) has been studied in the range of 30-50ºC in a solution of ionic strength 0.1M at pH 7.0. The results, as depicted in Table 4, clearly suggest that the value of diffusion coefficient increases with the temperature which is a simple consequence of the increased rate of solvent penetration into the gel matrices. However, the equilibrium water uptake remains almost constant up to 40ºC and then a slight decrease is observed. This behavior may be explained in the light of the fact that the hydrogel is composed of PVP and Poly (acrylamide-co-maleic acid) of which former component PVP possesses lower critical solution temperature between 35º and 40ºC [18]. If the hydrogels were made up of pure PVP, (no other polymer present) then an appreciable volume phase transition would be expected. But the amount of PVP in the hydrogel is nearly 33% (w/w), so a drastic change in gel volume beyond 40ºC is not observed . Therefore, the equilibrium water uptake decreases by a very small amount. The activation energy as determined from the Arrhenius equation was found to be 19.9 and 33.1 kJ $mo1^{-1}$ for the two samples HG (O) and HG (1.5), respectively. Here it should be noted that the average value of activation energy for a simple, non-ion hydrogel film is nearly 8.3 kJ $mo1^{-1}$ [19], while in the present case, the activation energy for non-ionic cylindrical gel HG (O) is 19.9 kJ $mo1^{-1}$, which is sufficiently high. This shows that in the present hydrogel system, the diffusion of solvent into the matrix is quit slow which is in accordance with the Tanaka-Fillmore theory [20]. Moreover, the value of activation energy for the acid containing sample HG (1.5) is 33.1 kJ $mo1^{-1}$ which is greater than that for the plain sample. This may be attributed to the fact that the value is for the entire

Table 4. Equilibrium Water Uptake and Diffusion Coefficients for the Samples HG (O) and HG (1.5) at Different Temperature of the Swelling Medium (pH = 7.0, μ = 0.1 M)

	Sample HG(O)		Sample HG (1.5)	
Temperature (ºC)	$\%S_m$	$D \times 10^6$ cm^2min^{-1}	$\% S_m$	$D \times 10^6$ cm^2min^{-1}
30	925	14.20	1036	11.70
40	918	19.70	1027	19.12
50	830	28.30	995	25.51

process of solvent entry, stretching of the network segments, and consequent large scale dimensional changes in the polymer network [21].

CONCLUSION

It is obvious from the above study that the incorporation of a small amount of maleic acid into the polymer matrix imparts ionic character to the gel and the swelling behavior of the hydrogel undergoes transition from Fickian to a non-Fickian one. The proposed hydrogel system has been found to show minimum equilibrium swelling at lower pH and as the pH of the medium increases, swelling also increases, thus acquiring a maximum value in the pH range 7-8. Moreover, the hydrogels also show a good response to the ionic strength, and valency of the counter ion in the swelling medium. They also undergo a number of deswelling-swelling cycles when placed in an external solution of pH 1.0 and 8.0, respectively.

Thus, looking into the large variation in the equilibrium swelling along with the pH of the external media, the proposed hydrogel can be used as a colon-specific drug delivery device because it will keep the encapsulaled drug protected in the stomach by swelling to the minimum, whereas it will release the maximum amount of drug at the colon (at pH 7.4) by swelling to the maximum. Hence, it may prove to be a good device for the treatment of diseases of colon such as colon cancer. Finally, the great biocompatability of the PVP, plus the mild conditions of gel synthesis and the great variation in the swelling along with the pH of the external media makes the proposed device a potential system for the protein and peptide drug delivery, along the gastrointestinal (GI) tract.

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