We have developed a pH-sensitive terpolymeric hydrogel system based on acrylamide, methacrylamide and acrylic acid by aqueous polymerization. The hydrogels exhibited a fair pH-dependent swelling behaviour with transition from Fickian \((n = 0.43)\) to non-Fickian \((n = 0.83)\) as the pH of the swelling medium varied from 1.0 to 8.0. The gel exhibited a number of swelling-deswelling cycles as the pH of the swelling medium was varied from 7.4 to 1.0. The equilibrium water uptake was found to increase with the amount of acrylic acid in the gels when studied in the media of pH 7.4. However, at pH 1.0, the degree of swelling was observed to decrease with monomer acid content. The activation energy for the swelling process, as calculated from the Arrehenius plot, was found to be 15.52 kJ mol\(^{-1}\). The gel also showed a good swelling response when put in the media of continuous varying pH. The minimum swelling in the acidic pH was explained on the basis of formation of complex structure within the gel network due to H-bonding interactions between -COOH and -CONH\(_2\) groups.

**ABSTRACT**

We have developed a pH-sensitive terpolymeric hydrogel system based on acrylamide, methacrylamide and acrylic acid by aqueous polymerization. The hydrogels exhibited a fair pH-dependent swelling behaviour with transition from Fickian \((n = 0.43)\) to non-Fickian \((n = 0.83)\) as the pH of the swelling medium varied from 1.0 to 8.0. The gel exhibited a number of swelling-deswelling cycles as the pH of the swelling medium was varied from 7.4 to 1.0. The equilibrium water uptake was found to increase with the amount of acrylic acid in the gels when studied in the media of pH 7.4. However, at pH 1.0, the degree of swelling was observed to decrease with monomer acid content. The activation energy for the swelling process, as calculated from the Arrehenius plot, was found to be 15.52 kJ mol\(^{-1}\). The gel also showed a good swelling response when put in the media of continuous varying pH. The minimum swelling in the acidic pH was explained on the basis of formation of complex structure within the gel network due to H-bonding interactions between -COOH and -CONH\(_2\) groups.

**INTRODUCTION**

Oral administration of drugs by conventional pharmaceutical formulations is the most convenient and effective delivery system and it is preferred over parental medication as the latter suffers from the drawback that it results in the rapid increase and subsequent rapid decrease of the blood serum concentration levels[1]. However, the oral administration of protein and peptide drugs is not so easy to achieve, possibly because of their sensitivity to gastric acid and their vulnerabili-
ty to gastrointestinal enzymes [2]. Therefore, the major challenge in the field of drug delivery is to develop a device that 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.

The site-specific oral delivery of drugs to the target receptor site has the potential to reduce the side effects and to increase pharmacological response. One of the interesting areas to target drugs orally for the systemic drug delivery is the colon, the proximal part of the large intestine. In addition, there are a number of local pathologies where direct release of drugs in the colon would not only improve pharmacotherapy but also reduce potential toxicity and side effects. The treatment of disorders of the large intestine, such as irritable bowel syndrome, colitis, Crohn’s disease, colon cancer and local infectious diseases, where a high concentration of active agent is needed, can be markedly improved using colon-specific drug delivery systems [3].

Because of the unique physiological characteristics of the large intestine, drug delivery to the colon can be achieved in different ways. One such feature is the colonic microflora, which consists mainly of anaerobic or facultative anaerobic microorganisms and produces a variety of enzymes in the colon [4]. This has led to the development of a new class of drug delivery vehicles that release the drug through enzymatic degradation [5-8].

Another approach to the colon-targeted drug delivery is based on the fact that the luminal pH of the healthy distal colon is slightly higher than that of the proximal small intestine and this, in fact, has led to the development of oral dosage forms that are intended to release the drug at the colonic pH (i.e., in the pH range 7-8). These devices are, in fact, pH-sensitive polymeric hydrogels which swell to minimum in the acidic pH (i.e., pH of the stomach), thus giving almost complete protection to the encapsulated drug and undergo maximum swelling in the slightly alkaline pH to release most of the drug. In recent past, a number of studies have been carried out by different workers [9-13] on pH sensitive hydrogels for gastrointestinal drug delivery.

Using hydrogels as potential candidates for drug delivery has many advantages such as their 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 [14]. An important parameter to consider in the design of hydrogel system is the behaviour of swelling. Not only the swelling-controlled release systems (i.e., pH-sensitive hydrogels [15]) but also the degradation-controlled systems [16] are shown to be related to the swelling behaviour of hydrogels. Therefore, the study of swelling behaviour of hydrogels is of considerable importance for the development of carriers for site-specific delivery of drugs.

The possibility of using a pH-sensitive hydrogel for gastrointestinal drug delivery depends upon its ability as to how quickly it responds to change in pH of the swelling medium and the extent to which it undergoes volume transition. Therefore, in order to propose a pH-responsive polymeric hydrogel for oral delivery along GI tract, it is necessary to carry out a detailed study of its swelling behaviour so that it can be used for release of active pharmaceutical agents to target a receptor site through oral delivery. Although a number of attempts have been made to investigate the swelling behaviour of vinyl monomers based pH-sensitive hydrogels [17-19]. However, we feel that it requires more attention to be paid on the mechanism involved in swelling-deswelling process of such systems. With this object, we hereby propose the detailed study of swelling behaviour of a new ternary co-polymeric pH-sensitive hydrogel system, consisting of acrylamide, methacrylamide and the acidic monomer acrylic acid.

Although numerous reports have been published on the swelling behaviour of AAm-AAc based hydrogels, but a thorough survey of the literature reveals that no studies have been carried out on a ter-polymeric system involving AAm, AAc, and MAm. The advantage of ter-polymeric hydrogels system is that the swelling (and hence drug release) properties of gel can be better controlled by varying the relative concentrations of three monomers involved. Methacrylamide is a water soluble monomer whose hydroxypropyl derivative is bio-compatible, non-immunogenic [20] and it has been frequently used to synthesize polymer-drug conjugates for drug delivery [21-22]. Since methacrylamide is relatively hydrophobic, the relative concentrations of AAm, AAc, and MAm monomers can provide better hydrophilic-hydrophobic balance within the polymer
matrix and hence provide better control over the swelling properties of the gel.

EXPERIMENTAL

Chemicals
The monomers acrylamide (AAm), methacrylamide (MAm), and acrylic acid (AAc), were obtained from BDH (Poole, UK). The cross-linker N,N'-methylene bisacrylamide (MB), and initiator potassium persulphate (KPS) were obtained from Research Lab (Bombay, India). The monomers AAm and MAm were distilled in methanol to remove the inhibitor while AAc was vacuum distilled at 47°C/7mm Hg. The double distilled water was used throughout the investigations.

Preparation of Hydrogels
In order to prepare cylindrical hydrogels, definite quantities of monomers MAm, AAm, and AAc were dissolved in water to give a total volume of 5 mL. To this, pre-calculated quantity of cross-linker MB was added, followed by the addition of initiator KPS. The resulting reaction mixture was poured into PVC straws, kept in an electric oven (Tempstar, India) at 60°C for a period of 2 h. The resulting hydrogels were cut into small pieces, each of length 2.54 ± 0.1 cm, washed extensively with water and dried in a dust-free chamber at 30°C for a period of 24 h. Here, it is worth mentioning that before synthesizing hydrogels for final studies, we synthesized a large number of samples by taking varying amounts of monomers AAm, MAm, and AAc and cross-linker MB and then for each sample prepared the percentage gelation (i.e., percent conversion of monomers into polymeric hydrogel) was determined from mass measurements [23] using the following expression:

\[
\text{Gelation} = \left( \frac{\text{total mass of monomers in the feed mixture}}{\text{total mass of dry polymer formed}} \right) \times 100
\]

For this, the gels synthesized were dried completely and this mass was taken using analytical balance. In this way, the range of monomers yielding almost complete gelation (98 ± 1.8 percent) was determined.

The hydrogel samples are denoted as HG (x), where the number in parenthesis denotes the percent mole of acrylic acid with respect to total monomer concentration. The amounts of monomers, cross-linker and initiator, used for synthesizing various samples have been given in the Table 1. We synthesized seven samples in all to carry out the whole investigations. Finally, the aspect ratio for the samples synthesized was found to be 10.4 ± 0.2.

Swelling Studies
The completely dried pre-weighed hydrogel sample was placed in 500 mL of buffer solution of desired pH at 30°C. The swollen gel was taken out at regular time intervals, wiped superficially with filter paper to remove surface-water, weighed and then placed in the same bath. The mass measurements were continued till the attainment of the equilibrium. The percentage of mass swelling (SM) was determined using the following expression:

\[
S_M (%) = \frac{(m_t - m_o)}{m_o} \times 100
\]

where, \(m_o\) and \(m_t\) are the initial mass and mass at different time intervals, respectively. For pH 4.0, citric acid-trisodium citrate buffer (0.05 M), was used while for pH 7.4 phosphate buffer (0.1M) was used. In both cases ionic strength was maintained at 0.1M. For pH 2.0, HCl of 0.01 M was used and ionic strength was maintained to 0.1 M by the addition of NaCl. All the

Table 1. Compositions of various samples synthesized (concentrations are shown in 5.0 mL of the reaction mixture).

<table>
<thead>
<tr>
<th>Sample</th>
<th>AAm (mM)</th>
<th>MAm (mM)</th>
<th>AAc (mM)</th>
<th>MB (mM)</th>
<th>KPS (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>7.04</td>
<td>5.88</td>
<td>9.00</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>13.04</td>
<td>5.88</td>
<td>3.00</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>3</td>
<td>8.54</td>
<td>5.88</td>
<td>7.50</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>4</td>
<td>4.04</td>
<td>5.88</td>
<td>12.0</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>5</td>
<td>1.04</td>
<td>5.88</td>
<td>15.0</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>3.52</td>
<td>9.38</td>
<td>9.0</td>
<td>0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>7</td>
<td>11.26</td>
<td>1.64</td>
<td>9.0</td>
<td>0.16</td>
<td>0.11</td>
</tr>
</tbody>
</table>

(*) Standard sample
experiments were carried out with three samples.

**Deswelling-swelling Studies**
The dry sample was placed in the buffer solution of pH 7.4 and the swelling process was followed gravimetrically till the attainment of the equilibrium. Now the swollen gel was placed in the solution of pH 1.0 and the deswelling was also monitored gravimetrically, till the gel attained constant weight. This swelling-deswelling process was repeated a number of times.

**RESULTS AND DISCUSSION**

**Dynamic Swelling**
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 [24].

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

\[ F = \frac{M_t}{M_\infty} = k t^n \]  

(1)

where, \( M_t \) and \( M_\infty \) denote the amount of solvent which diffused into 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 hydrogel.

In hydrogel characterization, the diffusion coefficients were calculated from the following relationship [25]:

\[ D = \frac{0.049}{(t/4 \times l^2)^{1/2}} \]  

(2)

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

The intrinsic diffusion coefficient \( \overline{D} \) was given as:

\[ \overline{D} = D (1-V)^3 \]  

(3)

where, \( V \) is the volume fraction of the solvent penetrating the polymer network by the time \( t \) defined above.

Figure 1 depicts the dynamic uptake of water by the hydrogel samples HG (0) and HG (41) in the buffer medium of pH 7.4 (phosphate buffer, ionic strength 0.1M) at 30°C. The values of various swelling parameters such as \% \( S_M \), \( n \), \( k \), \( D \), and \( \overline{D} \) have also been listed in the Table 2. It is clear from the Table 2 that sample HG (0), which does not contain acidic monomer, exhibits nearly Fickian type (\( n = 0.58 \)) swelling behaviour while the sample HG (41) which contains acrylic acid within the polymer network demonstrates non-Fickian (\( n = 0.84 \)) swelling behaviour. This indicates that addition of carboxylic acid containing monomer into the hydrogel system causes a transition from almost Fickian to non-Fickian or anom-
alous swelling behaviour. The observed finding may be explained as below:
when the sample HG (0), which does not contain any ionizable groups within the network, is placed in the swelling medium of pH 7.4, the hydrogels swell due to diffusion of solvent molecules into the gel network through micro-pores and this results in almost Fickian swelling behaviour with equilibrium mass swelling 650 %. However, situation is quite different in the case of the hydrogel sample HG (41) which contains COOH groups within the network. As the pH of the swelling media is 7.4, these groups undergo ionization, thus resulting in an increased osmotic swelling pressure \[\pi_{\text{ion}} = RT \sum(C_{i}^{g} - C_{i}^{s})\], where \(C_{i}^{g}\) and \(C_{i}^{s}\) are molar concentrations of mobile ions in the gel and the solution phase, respectively] in accordance with the Donnan equilibrium, that ultimately causes the gel to undergo extensive swelling. In addition to this, the electrostatic force of repulsion among similarly charged -COO- groups along the macromolecular chains also causes the polymeric segments to become unfolded or relaxed, followed by enhanced degree of swelling. These two factors, namely osmotic swelling pressure and chain relaxation process are responsible for the gel to exhibit non-Fickian type of swelling behaviour with equilibrium mass swelling of 2055 %.

Table 2 reveals one more fact that values of \(\overline{D}\) (i.e., intrinsic diffusion coefficient) are greater than those for \(D\) (diffusion coefficient) which may be attributed to the fact that the diffusion coefficient as given by eqn (2) gives a measure not only of the diffusion but also of the mass flow of the whole system, while eqn (3) gives the intrinsic diffusion coefficient for the case where no mass action effects enter [26].

**Effect of pH**
If the polymer matrix contains some ionizable groups, which can dissociate or become protonated at some suitable pH of the swelling media, then the degree of swelling of hydrogel undergoes appreciable change with external pH. Figure 2 depicts the dynamic uptake of water by the sample HG (41) in the buffer media of pH 2.0, 4.0, and 7.4, with ionic strength maintained on 0.1 M at 30°C. It is very clear from the Figure 2 that gel exhibits minimum swelling in the medium of pH 2.0, and as the pH of the swelling medium becomes 7.4, the degree of swelling at different time intervals increases. The values of swelling exponent ‘n’, as determined from the double logarithmic plot, were found to be 0.43, 0.57, and 0.84 for the swelling in the media of pH 2.0, 4.0 and 7.4, respectively. These values suggest that gel demonstrates almost Fickian type of swelling behaviour in the media of pH 2.0, and 4.0, while it exhibits anomalous or non-Fickian behaviour when allowed to swell in the media of pH 7.4. This can be well explained on the basis of the fact that when the gel is allowed to swell in the media of pH 2.0, the -COOH groups presence within the network remain almost non-ionized, thus imparting almost non-polyelectrolyte type behaviour to the gel.

![Figure 2. Dynamic uptake of water as a function of time for the hydrogel HG (41) in the media of pH 2.0 (○), pH 4.0 (●) and pH 7.4 (△) with I = 0.1 M at 30°C.](image-url)
Moreover, there exists strong H-bonding interactions between carboxylic groups and amide groups, which are present within the network due to presence of acrylic acid and acrylamide/methacrylamide. These H-bonding interactions, as depicted in Figure 3, result in the formation of a compact or tight structure which does not permit much movements of polymeric segments within the hydrogel network. This results in minimum swelling of hydrogel. Such type of explanations which accounts for minimum swelling at lower pH have also been offered elsewhere [27].

However, in the medium of pH 7.4, the almost complete ionization of -COOH groups results in extensive chain relaxation due to repulsion among similarly charged -COO− groups present along the macromolecular chains. Moreover, the dissociation also causes an increase in ion osmotic swelling pressure. These two factors are thus responsible for higher degree of swelling in the medium of pH 7.4.

There is also a qualitative supporting evidence in the favour of the above observed finding that gel exhibits non-Fickian type of swelling behaviour in the medium of pH 7.4 and Fickian in the swelling media of pH 2.0 and 4.0. Figure 4 depicts the plot between $M_t / M_\infty$ and $(t)^{1/2}$, which comes out to be almost linear for the swelling of the gel in the medium of pH 2.0. However, for the pH 4.0, some deviations from linearity is observed and this is most prominent in the case of swelling of the gel in buffer medium of pH 7.4. This is also a qualitative evidence to support the experimental findings.

Satyanarayana et al. [28], after carrying out gamma scintigraphic studies on guar gum tablets using 99mTc-DTPA as tracer in human volunteers reported a mean gastric emptying time of $1.08 \pm 0.11$ h and the mean colonic arrival time of $2.83 \pm 0.33$ h. Hence, it means that small intestinal transit time is likely to be $1.75 \pm 0.25$ h, thus suggesting that the formulation should enter the colon between 1.75 and 3.75 h of administration. Relying on this data, we opted to expose the hydrogel for a period of 2 h at pH 2.0 and 4.0 each and then for the next 6 h in the medium of pH 7.4 thus mimicking the transition of formulation from stomach to colon. The results, as depicted in the Figure 5 indicates that, out of total swelling of 825% percent in the first ten hours, the hydrogel swelled to only 5.7% percent in the first two hours in the medium of pH 2.0, then 5.6% percent in the next two hours in the solution media of pH 4.0 and finally 88.7% percent in the rest 6 hours in the buffer medium of pH 7.4. This suggests that the proposed hydrogel, if loaded with a suitable protein drug (which is of course next part of our study), should also behave in almost similar way during the process of drug release. Therefore, the device has a potential to be used for the colon targeted drug delivery.

Finally, the effect of the pH of the swelling media

![Figure 3. Complex structure of hydrogel in the medium of pH 2.0. Dotted lines (-------) showing the H-bonding interactions between carboxylic and amide groups.](image)

![Figure 4. $M_t / M_\infty$ versus $(t)^{1/2}$ plots for the swelling of the hydrogel HG (41) in the medium of pH 2.0 ( ), pH 4.0 ( ), and pH 7.4 ( ) with ionic strength of 0.1 M at 30°C.](image)
on the equilibrium water uptake for the three hydrogel samples HG (34), HG (54) and HG (68) was studied in the swelling media of varying pH (1-8) with the ionic strength 0.1 M at 30°C.

A close look at the Figure 6 reveals that up to pH 3.0, the equilibrium water uptake was very low (70% to 360%) which may be attributed to the fact that at lower pH, the almost non-ionized -COOH groups’ presence within the network not only impart non-ionic character to the gel but also form compact structure through H-bonding interactions with amide groups. Moreover, when pH > 6, the carboxylic groups on the copolymer backbone were converted to salt form (basic) and maximum degree of swelling was achieved.

However, in the swelling media of pH ranging between 3-6, the equilibrium water uptake increases almost linearly with pH of the solutions. Within this pH range, the acid and salt forms of the carboxylic groups on the polymer backbone are both present. Hence, these two forms, which are present within the polymer matrix, constitute a “hydrogel buffer” system.

Under such conditions, the Handerson-Hasselbalch equation can be used:

\[
pH = pK_a + \log \left(\frac{\text{base form of carboxylic group}}{\text{acid form of carboxylic group}}\right)
\]  

(4)

Now, since the degree of swelling varies linearly with the pH of the media in the range 3-6, and pH of the “hydrogel buffer” may be determined from the ratio of the two forms (using above equation), we may conclude that at half the equilibrium swelling, the ratio of two forms must be unity and the corresponding pH will give the value of pK_a of polymer matrix. The equilibrium water uptake values for the three samples HG (34), HG (54), and HG (68) was found to be 1147%, 1547%, and 1609%, respectively. Hence from the Figure 6, at half the equilibrium water uptake, the corresponding pH (and hence pK_a) value comes out to be approximately 4.5±0.1. This value is in close agreement with the previously reported values for acrylic acid containing polymeric systems [29-30].

**Acid Content Effect**

Amount of acrylic acid, present within the hydrogels, affects the equilibrium water uptake in a rather interesting way. Figure 7 depicts the equilibrium mass swelling of hydrogel samples as a function of number of moles of acrylic acid and it is very clear that in the...
swelling medium of pH 7.4, the equilibrium water uptake continues to increase with the content of acid monomer in the whole concentration range studied, while the water uptake is found to decrease when the same hydrogels are allowed to swell in the swelling media of pH 2.0.

The observed behaviour may be explained as follows:

When the hydrogels, with increasing number of moles of acrylic acid, are placed in the swelling media of pH 7.4, the ionization of -COOH groups present along the macromolecular chains causes an increase in the osmotic swelling pressure. Moreover, the mutual electrostatic repulsion among -COO- groups also causes the polymeric chains to relax. These two factors, ultimately, result in an increase in the equilibrium water uptake of the polymer matrices. However, when these gels are placed in the swelling medium of pH 2.0, the carboxylic groups, present within the network, remain non-ionized thus imparting non-polyelectrolyte type behaviour to the gels. Now, the decrease in the equilibrium water uptake can be attributed to the minimum osmotic swelling pressure, the higher hydrophobicity of unionized acrylic acid as compared to the hydrophilic acrylamide and methacrylamide, and the H-bonding interactions between unionized acrylic acid molecules and amide groups of both acrylamide and methacrylamide. These factors cause the degree of swelling to decrease with increase in AAc content.

Similar observations have also been reported elsewhere [31]. A close look at the Figure 7 reveals one more interesting fact that in the medium of pH 7.4, the increase in swelling is especially steep between 7.5 mM and 12.0 mM of acrylic acid, while between 3 mM and 7.5 mM there is not much increase in swelling capacity. This may be attributed to the fact that when the AAc content is sufficiently low (i.e., between 3 mM and 7.5 mM), the charges are shielded by counter ions present in the buffer and this results in low degree of electrostatic repulsion among -COO- groups and hence the macromolecular chains do not relax to a great extent. However, for higher content of AAc (i.e., between 7.5 mM and 12.0 mM) the charge density is so high that the counter ions are not sufficient to provide proper shielding. In other words, degree of shielding is not sufficient and, therefore, the chain relaxation of polymeric segments takes place to a greater extent. This causes a large increase in degree of swelling. Finally, it is also evident that the more AAc the polymers contains, the larger the difference between swelling at low and high pH and the more pH sensitive the gel.

Counter Ion Effect

The effect of valency of counter ions present in the swelling media on the equilibrium water uptake of the sample HG (41) was studied in the aqueous solution of NaCl and CaCl₂ at pH 7.4 with ionic strength varying from 0.1 M to 1.4 M at 30°C. The swelling behaviour of sample HG (0) which does not contain ionizable groups was also studied in NaCl solutions of the same concentration range. The results, as depicted in the Figure 8 clearly indicate that the equilibrium water uptake of sample HG (0) remains almost the same in the solutions of NaCl thus indicating that swelling capacity of sample HG (0) is not affected by the change

![Figure 7](image-url)  
**Figure 7.** Equilibrium water uptake as a function of acrylic acid content in the hydrogels in the media of pH 1.0 (■) and pH 7.4 (●) with ionic strength of 0.1 M at 30°C.

![Figure 8](image-url)  
**Figure 8.** Equilibrium water uptake of the sample HG (41) in solutions of NaCl (■) and CaCl₂ (▲) of varying concentrations. The equilibrium swelling of sample HG (0) in NaCl solutions (●) of the same concentration range is also shown.
in concentration of ions (i.e., Na\(^+\) ions) in the swelling media. This may be attributed to the fact that the hydrogel sample HG (0) does not contain any ionizable groups within the network and hence the swelling capacity remains almost the same for all concentrations of Na\(^+\) ions in the swelling media. However, in the case of HG (41) which contains ionizable -COOH groups due to the presence of acrylic acid, the equilibrium mass swelling is observed to decrease as the valency of counter ions changes from 1 to 2. The observed decrease may be attributed to the fact that since the carboxylic groups, present within the network, are in almost ionized state at the experimental pH 7.4, number of Na\(^+\) ions required to bind to the carboxylate ions to maintain the electro-neutrality condition will almost be double the number of Ca\(^2+\) ions for the same degree of ionization inside the hydrogel network. As a result, the ion osmotic swelling pressure decreases with subsequent decrease in the equilibrium water uptake. A close look at the Figure 8 also reveals that the observed decrease in the percent mass swelling is sufficiently large. This indicates that the degree of ionization of fixed ionizable groups (i.e., -COOH groups) inside the polymer matrix takes place to an appreciable extent. Finally, Figure 8 also reveals that when concentration of ions of the same valency is increased, the equilibrium water uptake of HG (41) also decreases (This can be seen for solutions of NaCl as well as CaCl\(_2\)). This may simply be attributed to the fact that with the increase in concentration of counter ions (of same valency) in the external media, the osmotic swelling pressure decreases which ultimately causes a decrease in the water uptake of the sample HG (41). In this way, the equilibrium water uptake of HG (41) is affected by the valency of the counter ions as well as by the concentration of counter ions of same valency.

**Activation Energy For Swelling Process**

The energy of activation for the swelling process was determined by carrying out the swelling kinetics of the sample HG (41) in the buffer medium of pH 7.4 at three different temperatures in the range 8-45°C, as depicted in the Figure 9. The various swelling parameters, described in Table 3, clearly suggest that as the temperature of the swelling media increases the diffusion coefficient also increases which may simply be attributed to the fact that a rise in temperature causes an increase in the penetration rate of solvent into the gel matrix. The activation energy, as determined from the Arrhenius equation \(D = D_0 \exp \left(-\frac{E_D}{RT}\right)\) with the

![Figure 9. Dynamic uptake of water as a function of time for the hydrogel sample HG (41) in the swelling media of pH 7.4 with I = 0.1 M at 8°C (△), 25°C (●), 35°C (■) and 45°C (○).](image)

| Temperature (°C) | Swelling parameters |
|-----------------|--|---|---|---|---|
|                 | \(S_M\) (%) | \(n\) | \(k\times10^3\) | \(D\times10^6\) (cm\(^2\) min\(^{-1}\)) | \(D\times10^5\) (cm\(^2\) min\(^{-1}\)) |
| 8               | 1248          | 0.75 | 32.7          | 8.8          | 2.03          |
| 25              | 2033          | 0.87 | 32.7          | 11.76        | 9.66          |
| 35              | 2400          | 0.80 | 20.3          | 20.35        | 15.71         |
| 45              | 2483          | 0.83 | 19.2          | 19.2         | 27.16         |
help of the logarithmic plot (Figure 10) was found to be 15.52 kJ mol$^{-1}$. Here it is to be noted that we also synthesized non-ionic hydrogel sample, composed of acrylamide and methacrylamide, and determined its activation energy. The values of $E_D$ came out to be 11.22 kJ mol$^{-1}$. The higher value of activation energy for acid containing gel 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 [32]. Similar higher values of activation energy for itaconic acid containing gels have also been reported previously [26].

Oscillatory Swelling Behaviour

The oscillatory swelling experiments were conducted to investigate whether the response to the environmental pH was reversible and to examine how fast the hydrogel could respond to the external stimuli. In fact, the proposed hydrogel system is expected to respond to the change in pH of the swelling media in a similar way as by a dosage form, which undergoes a pH-change when administered orally, in passing from gastric fluid (where, pH is 1-2) to intestinal fluid (where pH is 7-8) during its transit along the gastrointestinal tract. Thus, in order to have information about the possible mode of action of the proposed system along the GI tract, the swelling-deswelling behaviour was studied by placing the sample HG (41) in the medium of pH 7.4 till the attainment of equilibrium and then allowing it to deswell in the media of pH 1.0. It is clear from the Figure 11 that the gel took almost 13 h to swell to maximum (i.e., 2066 %) while it required almost 9 h to deswell completely (i.e., 183 %). The deswollen gel was again allowed to undergo further swelling-deswelling cycles. We carried out five such cycles and found that the gel maintained its shape as well as mechanical strength throughout the studies. However, only two such cycles have been depicted in the Figure 11. A close look at the Figure reveals some interesting results. The hydrogel takes almost 13 h to attain the equilibrium swelling while the time required to deswell to minimum is nearly 9 h. This result is just contradictory to our previous findings according to which co-polymeric gels of acrylamide and maleic/itaconic acid were observed to require more time for complete deswelling as compared to the time required for swelling [33-34]. Moreover, the initial deswelling-rate is very fast i.e., in the first hour the equilibrium mass swelling decreases from 2066% to 708%. In other words, the equilibrium swelling decreases by nearly 65% in the first hour when the swollen gel is placed in the medium of pH 1.0. The above experimental findings may be explained as below:

When the completely dried hydrogel sample is placed in the swelling medium of pH 7.4, the solvent
diffuses into the outer surface of the gel through the micropores, resulting in the plasticization of macromolecular chains. At the same time, the carboxylic groups, attached along the polymer backbone, undergo ionization to yield -COO⁻ groups (since the pH of the swelling medium is more than the pKₐ value of acrylic acid inside the gel matrix). This results in the formation of a charged hydrated layer through which the counter ions along with the solvent molecules embed into the interior dry core region and allow the gel to swell. In this way, the dry core slowly disappears and the gel matrix continuous to swell. The swelling is further enhanced due to relaxation (or unfolding) of macromolecular chains owing to the repulsion among similarly charged -COO⁻ groups which also promotes the swelling process.

When the fully hydrated gel is placed in the medium of pH 1.0, H⁺ ions present in the external solution, diffuse into the gel matrix through water-filled macropores which have been existing in the fully hydrated gel. These H⁺ ions protonate the -COO⁻ groups to yield uncharged -COOH groups which ultimately results in folding of the macromolecular chains as the repulsive forces no longer exist, thus letting the solvent molecules to come out of the polymer matrix as shown in Scheme I.

This may probably be the reason for the sudden collapsing of the gel along with greater extent of deswelling (i.e., almost by 65%). Later on, the uncharged collapsed gel structure becomes much more compact due to H-bonding interactions between the -COOH and -CONH₂ groups as described in previous sections. Hence, more solvent diffuses out of the gel, although with extremely slow rate as it is clear from the Figure 11.

Here, it is worth mentioning that after carrying out two swelling-deswelling cycles there appeared slight turbidity in the alkaline solution which, at first moment, was thought to be due to possible dissolution of the polymeric matrix. However, as the hydrogel is covalently bonded structures, the chances of its dissolution are almost nil. The observed turbidity might be due to presence of some impurities which were retained within the gels, and later on appeared as insoluble salt (probably as phosphate) thus making the swelling medium a little turbid. Although the gels were washed with distilled water, but not washed by equilibration of the freshly prepared gels in distilled water and hence it is probable that some impurities might have retained within the polymer matrix.

**Effect of Sample Thickness**

According to the Tanaka-Fillmore theory [35], the thickness of the cylindrical hydrogel plays a significant role in affecting its swelling behaviour. In order to study the effect of thickness of the hydrogel sample on the dynamic uptake of water, the sample HG (41) with varying diameter in the range 1.46 to 4.24 mm were synthesized and their dynamic uptake of water was studied in the swelling media of pH 7.4 at 30°C. The results, as depicted in the Figure 12, clearly suggest that as the diameter of the hydrogel sample increases, the percent mass swelling at different time-intervals decreases. This may be attributed to the fact that with the increase in the diameter, the surface area available per g of the matrix decreases and as the flux is directly proportional to the surface area for the fixed values of the other dependent variables, the swelling-rate (i.e., percent mass swelling per minute) also decreases. Therefore, it is clear that the desired swelling rate (and hence drug-release rate if the drug is loaded into the hydrogel matrix) can be obtained by taking the sample of suitable diameter. Therefore, in order to use the proposed hydrogel system for colon targeted drug delivery (which is to be studied in detail in next part of this arti-

![Figure 12. Dynamic uptake of water as a function of time for the hydrogel HG (41) with varying thickness 1.46 mm (○), 2.13 mm (●), 3.87 mm (■) and 4.24 mm (△) in the medium of pH 7.4 with I = 0.1 M at 30°C.](https://example.com/figure12.png)
cle), it is necessary that the hydrogel sample should exhibit minimum degree of swelling prior to its entry to the colon and hence hydrogel with large diameter shall be the most suitable for this purpose.

Finally the plot between $t_{1/2}$ values (i.e., time required for 50% swelling) and the square of the diameter (mm) yielded a straight line (Figure 13) which also supports the Tanaka-Fillmore theory.

**Effect of Gel Composition**

The nature of constituent monomers involved in a copolymeric gel plays an effective role in governing the swelling capacity of the gel [36]. In the present study, two hydrogels having molar ratio of acrylamide to methacrylamide 1:4 and 4:1, but having the same concentration of acrylic acid, were synthesized and their swelling dynamics was studied in the phosphate buffer of pH 7.4. The results, as depicted in the Figure 14, clearly indicate that hydrogel having AAm to MAm ratio 4:1 exhibit greater water uptake as compared to the sample with the ratio 1:4. This indicates that as the concentration of methacrylamide in the gel increases, the swelling capacity decreases. This may probably be due to two reasons. First is that the presence of methyl group in the methacrylamide imparts some hydrophobic character to the monomer as compared to the other monomer acrylamide. Secondly, the methyl group of methacrylamide may offer some steric hindrance towards the diffusion of solvent as has been observed in some cases [7,37]. Thus, the hydrogel having greater concentration of methacrylamide demonstrates a little hydrophobic character and hence exhibits smaller uptake of water as compared to the gel with smaller concentration of methacrylamide. One more explanation for the observed finding is the fact that monomer acrylamide is more hydrophilic, and hence its presence in greater proportion makes the gel more hydrophilic, thus resulting in greater uptake of water. In this way, relative concentrations of monomers in the ter-pol meric system influence its dynamics swelling behaviour.

**CONCLUSION**

From the detailed study of swelling behaviour of poly (acrylamide-co-methacrylamide-co-acrylic acid) hydrogel system, it is concluded that the hydrogel exhibits a fair pH-dependent swelling behaviour and undergoes transition from Fickian to non-Fickian swelling behaviour with the change in pH of the swelling media from 1.0 to 8.0. The swelling capacity of the hydrogel system studied also depends upon valency of counter ions present in the solution, and amount of monomer acid within the gel matrix. The
The cylindrical hydrogel also demonstrates a number of swelling-deswelling cycles when put in the swelling media of pH 7.4 and 1.0, respectively. The gel retains its shape throughout the studies. Finally, the swelling rate of the cylindrical hydrogel can be controlled by varying the diameter of the hydrogel as well as the relative concentrations of the monomers AAm, and MAm, in the hydrogels.

Thus, the proposed hydrogel system bears the potential to be used for the oral delivery of drugs along the gastrointestinal (GI) tract. It will keep the encapsulated drugs almost protected in the highly acidic environment of the stomach by exhibiting minimum swelling and will release most of the drug in the media of pH 7.4 (i.e., pH of the fluid at the colon) by exhibiting maximum swelling. Therefore, the diseases of colon such as colon cancer, may be curable through oral administration of anticancer drug encapsulated in the proposed system in the form of nanoparticles, pallets, discs or other suitable forms. For example, antisense oligonucleotides have proved to be efficient drugs for colon-specific delivery in the treatment of cancer.

Although acrylamide, a repeat unit in the proposed ter-copolymeric system, is reported to be a lethal neurotoxin and has been found to cause cancer in the laboratory animals, but studies carried out by some researchers [38-39] reveal that acrylamide is not released from polyacrylamide during degradation. In fact, there seems to be a clear-cut difference of opinion over the breakdown products of polyacrylamide. Moreover, the PAAm degrades extremely slowly (less than 10 % in 28 days) while the total gastrointestinal transit time for an oral formulation is not more than 24 h. Hence, the system studied by us, is expected to get disposed off along with other waste materials from the body without producing toxic effect.

ACKNOWLEDGEMENTS

Authors are thankful to Dr. S.S. Ghai, Head of the Chemistry Department, for providing facilities.

REFERENCES


