# Poly(methacrylamide-*co*-acrylic acid) Hydrogels for Gastrointestinal Delivery of Theophylline. I. Swelling Characterization

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**ABSTRACT:** pH sensitive copolymeric hydrogels have been synthesized by free-radical polymerization of methacrylamide and acrylic acid in aqueous medium. The gels were characterized by FTIR spectroscopy, thermogravimetric analysis, and swelling measurements. To determine the suitability of theses hydrogels for gastrointestinal oral delivery of model drug theophylline, their swelling behavior was investigated as a function of pH and various structural parameters such as the average molecular weight between crosslinks, crosslink density, and mesh size were calculated. Likewise initial, average and late time diffusion coefficients were also evaluated in simulating intestinal fluid of pH 6.8 at 37°C. The gel underwent sharp volume phase transition in the vicinity of pH 5.8. The mesh sizes of the hydrogel were between 8.4 and 9.2 Å in the collapsed state (pH range 1–2; SGF) and between 514 and 524 Å in the swollen state (pH range 7–8; SIF). The experimental data was found to fit well to Beren-Hopfenberg equation thus suggesting that later part of swelling was chain relaxation controlled. The activation energy, as determined from Arrhenius equation was found to be 13.71 kJ $mol^{-1}$. Likewise, enthalpy of mixing was also evaluated using Gibbs-Helmholtz equation. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 101: 2995–3008, 2006

**Key words:** hydrogels; pH-sensitive swelling; acrylic acid; methacrylamide

## INTRODUCTION

Hydrogels are crosslinked polymer networks that can expand substantially and retain large amount of water without being dissolved.[1] These are able to respond to external stimuli such as pH,[2] temperature,[3] ionic strength,[4] antigen,[5] light and electric field,[6] etc. They find a number of applications including pharmaceuticals,[7,8] biomedicine,[9] bioengineering,[10] agriculture,[11] food industry,[12] etc.

In the last decades, the design of polymeric hydrogels for biomedical applications has been extensively investigated, thus leading to new concepts in the treatment of human diseases. In recent years, colon-targeted drug delivery systems have been the focus point of formulation laboratories because the colon is considered as a suitable site for both conventional and labile drugs,[13] and it is also a suitable site for some special diseases such as ulcerative colitis, chron's diseases, bowel cancer, some infections, and constipation, which require local drug delivery.[14] Site-specific delivery systems offer many advantages compared to conventional dosage forms, including improved efficiency, reduced toxicity, improved patient compliance, and cost effective therapeutic treatment.[15] Various approaches have been used for colon-targeted drug delivery, which include pH-dependent swelling controlled systems,[16] delayed-release delivery systems,[17] intestinal pressure-controlled colon delivery capsules,[18] and enzymatically degradable systems that utilize various enzymes produced by intestinal flora.[19]

Although numerous reports have already been published on the swelling behavior of pH sensitive hydrogels but a thorough survey of the literature reveals that copolymeric system involving methacrylamide and acrylic acid has not been taken into consideration for gastrointestinal drug delivery. Methacrylamide is a water-soluble monomer that has thermosensitivity,[20] biocompatibility,[21] and is used to prepare drug-release devices by attacking hydrophobic monomers to hydrophilic matrices.[22] Its hydroxyethyl derivative is nonimmunogenic[23] and has been frequently used to synthesize polymer–drug conjugates for drug delivery and autonomous control of flow in microfluidic devices.[24–27] Similarly, polyacrylic acid is known to be a good mucoadhesive and may increase the transit time of formulation.[32] The polymers, composed of acrylic acid, have the ability to absorb a large amount of water and are used in many applications including ion exchange resins, personal hygiene products, membranes for hemodialysis, ultrafiltration, and controlled

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release devices.[28–31] The major objectives of the proposed study involve synthesis of pH-sensitive poly(methacrylamide-*co*-acrylic acid) hydrogels and their characterization with special reference to pH-dependent swelling behavior so that the gels could be used for the oral delivery of model drug theophylline along the GI tract.

## EXPERIMENTAL

### Materials

The monomers methacrylamide (MAAm; BDH, Poole, UK) and acrylic acid (AAc; Research Lab, Pune, India), the crosslinker *N,N*′methylenebisacrylamide (MB; Research Lab, India), the initiator potassium persulphate (KPS; Merck, Mumbai, India) were of analytical grade. The monomer MAAm was distilled in methanol to remove the inhibitor, while AAc was vacuum distilled at 47°C/7 mmHg. Double-distilled water was used throughout the investigations.

### Synthesis of hydrogels

The cylindrical hydrogels were prepared by carrying out free radical polymerization of AAc and MAAm in aqueous medium using MB as a crosslinker and KPS as an initiator. The control sample was synthesized by dissolving 1.0 mL of AAc, 1.0 g of MAAm, and 0.05 g of crosslinker MB in distilled water to give a clear solution with a total volume of 5.0 mL. Finally, 0.03 g of KPS was added and the reaction mixture was poured into straws, each of a 5.3 mm diameter, and kept in an electric oven (Tempstar, India) at 70°C for a period of 2 h. After the polymerization was over, the transparent gels were taken out of straws, cut into small pieces each of a length of 2.04 ± 0.02 cm in length, equilibrated in distilled water to remove the unreacted salts, then dried in a dust-free chamber until they attained constant weight. The length, diameter, and mass of samples were found to be 18.4 ± 0.3, 4.32 ± 0.02, and 0.165 ± 0.01 g, respectively. However, variation in mass did not affect the accuracy of the results as the calculations were made for 1 g of the polymer. The samples shall be denoted by HG(x) where "x" denotes the % mol fraction of acrylic acid in the sample.

### Characterization of polymeric hydrogel

#### IR spectral analysis

The hydrogel prepared as described above was characterized by recording FTIR spectra on Fourier Transformed Infrared spectrophotometer in the Indian Institute of Technology (IIT), Kanpur, India.

#### Thermal analysis

TGA was performed in the Indian Institute of Chemical Technology (IICT), Hyderabad, India, using a thermogravimetric analyzer (Mettler, Toledo GmbH, Switzerland). About 7.03 mg of powdered sample of hydrogel HG(56.17) was placed in ceramic crucibles and analyzed over the temperature range 25°C to 1000°C at the rate of 20°C $min^{-1}$ under the dry flow of $N_2$ at the rate of 30 mL/min.

#### Swelling studies

The completely dried preweighed hydrogel sample was placed in 500 mL of buffer solution of desired pH at 37°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 until the attainment of the equilibrium. The percentage of mass swelling ($S_M$) was determined using the following expression:[33]

$$\%S_M = [(M_t - M_o)/M_o] \times 100 \quad (1)$$

where $M_o$ and $M_t$ are the initial mass and mass at different time intervals, respectively. All the experiments were carried out with five samples and the average values have been reported in the data.

## RESULTS AND DISCUSSION

### Characterization of hydrogels

#### Thermogravimetric analysis

Figure 1 depicts the thermogram obtained for the sample HG[56.17]. The value of $T_{id}$ (initial decomposition temperature), $T_{df}$ (final decomposition temperature), and $T_{max}$ (temperature of maximum rate of weight loss) were found to be 220, 700, and 380°C, respectively. Because the proposed hydrogel system is to be used for colon-targeted drug delivery at body temperature, that is, at 37°C, the polymer is totally stable at this temperature.

#### IR spectral analysis

The IR spectra (see Fig. 2) clearly shows a broad band in (3300–3550) $cm^{-1}$, which is due to hydrogen bonded $\upsilon$ OH from carboxylic group and $\upsilon$ NH from amide group and the C═O stretching vibration at 1650 $cm^{-1}$ is due to carboxylic group of acrylic acid and —$CONH_2$ group of methacrylamide. Asymmetrical and symmetrical stretching of C—H is found at 2954 and 2613 $cm^{-1}$, respectively. The IR spectra also shows a broad band at 2179 $cm^{-1}$, which is due to the presence of the —C—N group of the crosslinking

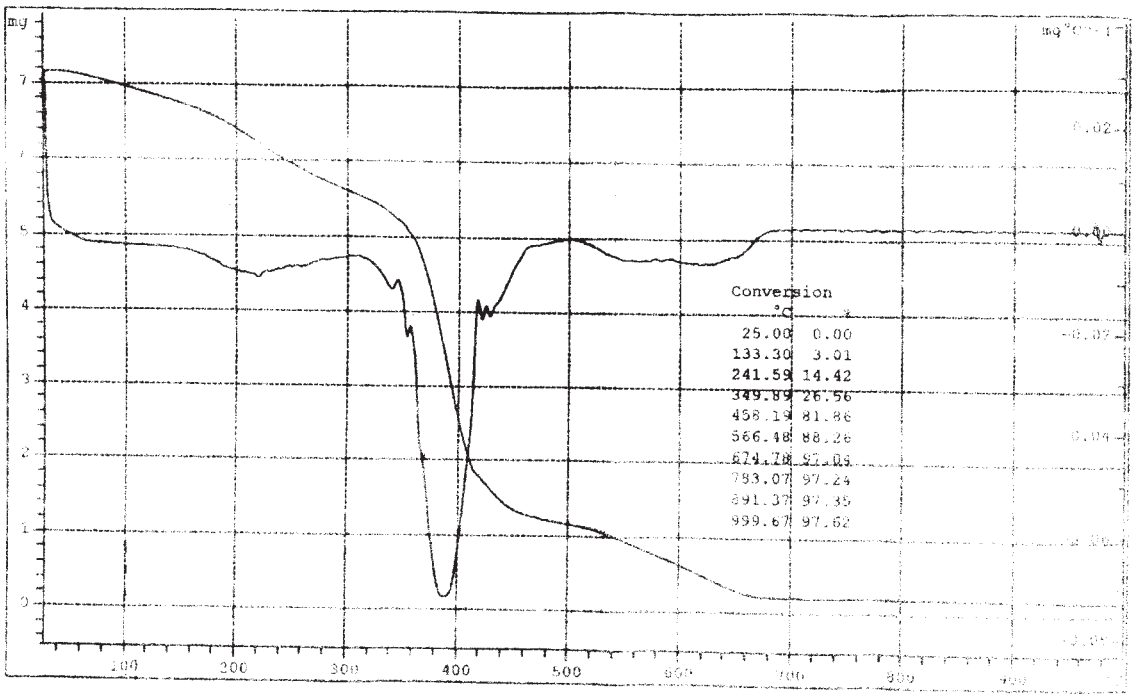


**Figure 1** Thermogravimetric analysis of the poly(methacrylamide-*co*-acrylic acid) copolymeric hydrogel.

agent (*N,N′*methylene bisacrylamide) and polymethacrylamide.

### Swelling parameters/network parameters

The swelling behavior of a polymer network depends upon a number of factors like hydrophilic–hydrophobic interactions in the network and degree of crosslinking of the network.[34] One of the important structural parameters characterizing crosslinked polymer is $M_c$, the average molecular mass between the crosslinks, which is directly related to the crosslinks density. The Florry-Rehner equation,[35] used to calculate the mass $M_c$ between crosslinks, can be given as:

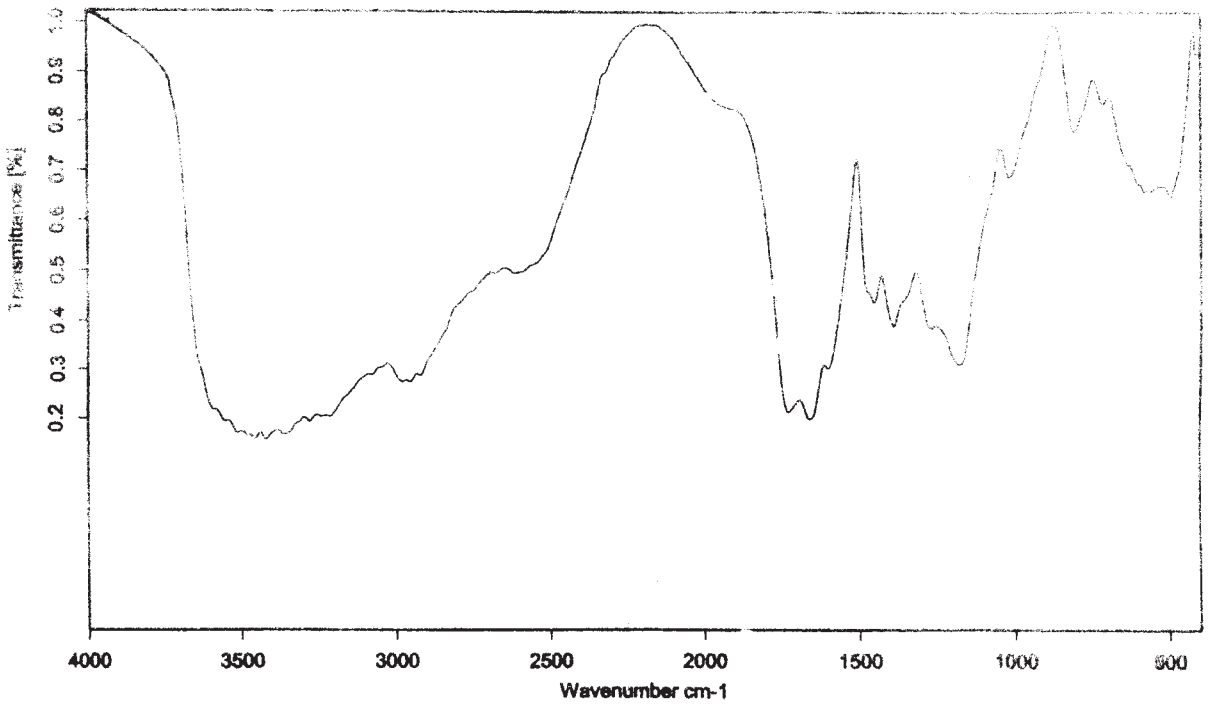


**Figure 2** FTIR spectra of the hydrogel sample.

$$M_c = -d_p V_s \phi^{1/3}[\ln(1-\phi) + \phi + \chi\phi^2]^{-1} \quad (2)$$

The volume fraction $\phi$ of the swollen polymer was calculated using the equation

$$\phi = [1 + d_p/d_s(M_a/M_b) - d_p/d_s]^{-1} \quad (3)$$

In the above equation, $d_p$ and $d_s$ represent the densities of polymer and solvent, respectively; $M_a$ and $M_b$ are the mass of hydrogels before and after swelling, $V_s$ is the molar volume of the solvent used for swelling studies, and $\chi$ is the Flory-Huggins interaction parameters between solvent and polymer, which was calculated by a method described elsewhere.[36]

The crosslinks density $q$ was calculated as

$$q = M_o/M_c \quad (4)$$

where $M_o$ is the molar mass of repeating unit, given as

$$M_o = [m_{\mathrm{AAc}}M_{\mathrm{AAc}} + m_{\mathrm{MAAm}}M_{\mathrm{MAAm}}]/[m_{\mathrm{AAc}} + m_{\mathrm{MAAm}}] \quad (5)$$

Here, $m_{\mathrm{AAc}}$ and $m_{\mathrm{MAAm}}$ are the mass of AAc and MAAm monomers (g) and $M_{\mathrm{AAc}}$ and $M_{\mathrm{MAAm}}$ are their molar mass, respectively.

Some other authors define a crosslinking density as the number of elastically effective chains, totally induced in a perfect network per unit volume given as

$$V_e = d_p N_A/M_c \quad (6)$$

where $N_A$ is the Avogadro number.

One more important parameter of networks is pore size or mesh size ($\xi$), which was calculated as below.

From the molecular weight between crosslinks (i.e., $M_c$), the number of links between two crosslinks $n$ was calculated

$$n = \frac{2M_c}{M_o} \quad (7)$$

where $M_o$ is the molecular weight of the repeating unit. The value of the root-mean-squared end-to-end distance of the polymer chain in the freely jointed state was calculated using eq. (8):

$$(\bar{r}^{\,2})^{1/2} = l\sqrt{n} \quad (8)$$

where $l$ is the carbon–carbon bond length (1.54 Å). The root-mean-squared end-to-end distance of the polymer chain in the unperturbed state was

$$(\overline{r_o^2})^{1/2} = \sqrt{C_n}(\overline{r^2})^{1/2} \quad (9)$$

where $C_n$ is the Flory characteristic ratio or rigididity factor of the polymer. Finally, the mesh size of the polymer network $\xi$ was determined by the following equation

$$\xi = \phi^{-1/3}(\overline{r_o^2})^{1/2} \quad (10)$$

To evaluate above parameters three hydrogels samples, with varying crosslinking ratio in the range $7.27 \times 10^{-3}$ to $16.98 \times 10^{-3}$, they were allowed to swell in phosphate buffer of pH 6.8 and their mass measurement was done at different time intervals until the attainment of maximum swelling. The results, as depicted in Figure 3, clearly indicate that as the crosslinking ratio increases, the amount of water absorbed at different time intervals decreases. This may be attributed to the fact that with the increase in the crosslinking ratio, the number of crosslinks per unit volume also increases, which finally causes a decrease in the free space available between crosslinks, thus providing less space for accommodation of water molecules in the network.

Table I describes the various network parameters calculated for the hydrogel samples having different crosslinking ratios. It is clear that as the crosslink density of the network increases, the value of $M_c$ decreases. Moreover, the number of elastically effective chains increases because it varies inversely with $M_c$.

### Kinetic analysis of water transport from polymer

When a glassy polymer is placed in a solvent, the solvent diffuses into the polymer matrix, thus causing it to swell. Swelling of hydrogels involves larger scale segmental motion ultimately resulting in an increased distance of separation between macromolecular chains.[37]

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

$$M_t/M_\infty = kt^n \quad (11)$$

where $M_t$ and $M_\infty$ denote the amount of solvent that diffused into the polymer matrix at time $t$ and at equilibrium, respectively; and $k$ is a characteristic constant of the hydrogel, $n$ is a swelling exponent describing the mode of penetrant transport mechanism. For a cylindrical gel, $n = 0.45$–$0.50$ corresponds to Fickian-type diffusion process, while $0.5 < n < 1.0$ indicates non-Fickian or anomalous transport, and $n = 1$ implies case II (relaxation controlled) transport.

The constants $n$ and $k$ were calculated from the slopes and intercepts of the plots of ln ($M_t/M_\infty$) versus ln $t$ from the experimental data shown in Figure 4, and have been given in the Table II. It is clear that the swelling exponent $n$ for the samples with varying

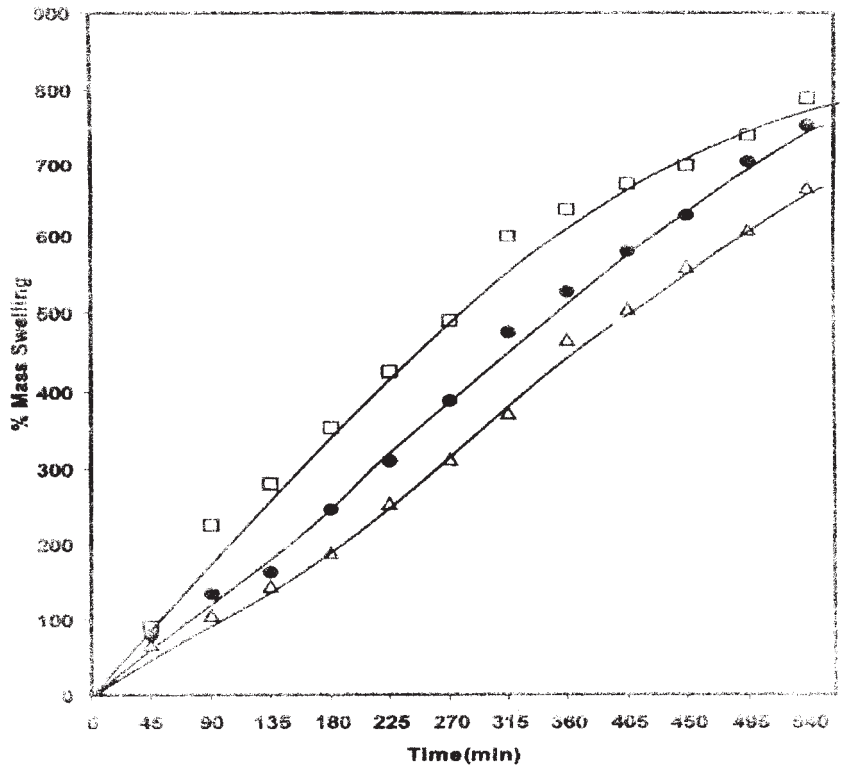


**Figure 3** Dynamic uptake of water as a function of time for the hydrogel sample HG(56.17) with crosslinking ratio 7.27 $\times 10^{-3}$ (□), 12.13 $\times 10^{-3}$ (●), and 16.98 $\times 10^{-3}$ (△) in distilled water at 30°C.

crosslinking ratio lies between 0.80 to 1.00, thus suggesting that gels exhibit not only anomalous or non-Fickian-type diffusion but also case II transport. This can be attributed to the fact that as the pH of the swelling medium is 6.8, the —COOH groups attached along the macromolecular chains ionize completely to give fixed —$COO^-$ groups along the polymeric chains and free $H^+$ ions within the gel phase. Because the free $H^+$ ions remain inside the gel to neutralize the fixed charges on the network chains, their higher concentration within the gel phase makes the osmotic swelling pressure [$\pi_{ion} = RT \Sigma (C_i^g - C_i^s)$, where $C_i^g$ and $C_i^s$ are molar concentrations of mobile ions in the gel and in the solution phase, respectively] appreciably high, thus resulting into extensive swelling of the hydrogel. In addition to this, the electrostatic repulsion among similarly charged —$COO^-$ groups also causes an extensive chain relaxation process within the network. These two factors, namely osmotic swelling pressure and chain relaxation process, being comparable, are thus responsible for the gels to exhibit a non-Fickian type of swelling behavior.

Ficks first and second laws of diffusion (1855) adequately describe the most diffusion process. For cylindrical-shaped hydrogels, the integral diffusion at short times, the main result is

$$F = 4[(Dt/l^2)^{1/2}]/\pi^{1/2} \quad (12)$$

where $F$ is the fractional release ($M_t/M$), $D$ is diffusion coefficient. In eq. (12), the slope of the linear plot between $F$ and $t^{1/2}$ yields diffusion coefficient $D$. However, it is not unusual to observed that $F$ is nonlinear with $t^{1/2}$.[38] This non-Fickian behavior is often

**TABLE I**
**Network Parameters of Hydrogel Sample HG[56.17] Containing Varying Amounts of Crosslinker MB**

| Crosslinking ratio $\times 10^3$ | Average molar mass between crosslinks $M_c$ $\times 10^{-4}$ | Crosslink density $q$ $\times 10^4$ | Elastically effective chains $V_e$ $\times 10^{-18}$ | Mesh size (Å) | |
|---|---|---|---|---|---|
| | | | | Dry gel | Swollen gel |
| 7.27 | 9.81 | 7.75 | 6.44 | 247.25 | 631.58 |
| 12.13 | 6.98 | 10.89 | 9.05 | 208.56 | 510.58 |
| 16.98 | 3.67 | 20.68 | 17.18 | 151.23 | 342.62 |

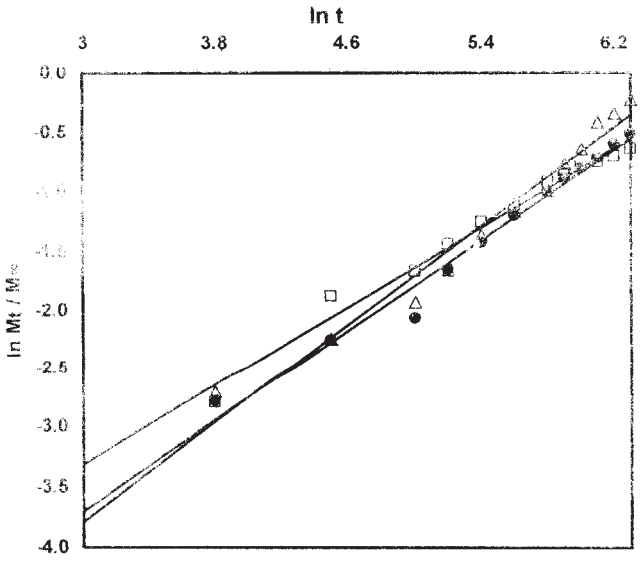


**Figure 4** Evaluation of swelling exponent and gel characteristic constants for the hydrogel sample HG(56.17) with crosslinking ratio $7.27 \times 10^{-3}$ (□), $12.13 \times 10^{-3}$ (●), and $16.98 \times 10^{-3}$ (△) in distilled water at 30°C.

found for diffusion into glassy polymers below their $T_g$. Therefore, initial diffusion coefficient $D_i$ was also evaluated from the initial linear portion of the plot.

The average diffusion coefficient $D_{ave}$ may also be calculated for 50% of the equilibrium swelling by putting $M_t/M_\infty = 0.5$ in the above expression, which finally yields

$$D_{ave} = 0.049l^2/t_{1/2} \tag{13}$$

Diffusion coefficients were also calculated using the late time approximation as described by Peppas.[39]

$$M_t/M_\infty = 1 - [8/\pi^2\{\exp(-\pi^2 Dt/4l^2\}] \tag{14}$$

A plot between ln $(1 - M_t/M_\infty)$ and $t$ was used for evaluation of $D_L$. The plots as shown in Figure 5 yielded a distinct break in slopes as is indeed found experimentally in both Fickian and non-Fickian diffusion. Similar type of observations have also been reported previously.[40] Finally, the late-time diffusion coefficient $D_L$ was calculated from the slope of the line after the break, using the simplified form of eq. (14).

$$D_L = -(\text{Slope} \times l^2/\pi^2) \tag{15}$$

All the three diffusion coefficients for the samples with different crosslinking ratios have been given in Table II. A close look at the table reveals that for all the samples studied the late-time diffusion coefficients $D_L$ are nearly five times more than the initial diffusion coefficients $D_i$, which suggest that diffusion in the fully swollen relaxed polymer is faster than in the initial state when diffusion is associated with stress relaxation. Smith et al.[38] reported almost similar results in the case of non-Fickian diffusion of water in melamine formaldehyde resins.

The previously discussed model, although adequately describing a major protection of swelling behavior, fails to give an accurate analysis above $M_t/M_\infty = 0.60$. To obtain a better model for fractional water uptake more than 0.6, we assumed that for longer periods the penetrant sorption was mainly dominated by relaxation of the polymer chains, and therefore, the Borens-Hopfenberg differential equation[41] could be written as follows:

$$dM_t/d_t = k_1(M_\infty - M_t) \tag{16}$$

where $k_1$ is the relaxation rate constant. The integration of eq. (16) leads to

$$M_t/M_\infty = [1 - A\exp(-k_1 t)] \tag{17}$$

where $A$ is a constant. The constants $A$ and $k_1$ were calculated from the slopes and intercepts of plot of ln $(1 - M_t/M_\infty)$ versus time $t$ at times later than those corresponding to $M_t/M_\infty = 0.60$. The values of $A$ and $k_1$ are also listed in Table II.

**TABLE II**
**Swelling Parameters and Various Diffusion Coefficients of the Hydrogel Sample HG[56.17] Containing Varying Amounts of Crosslinker MB, in the Medium of Phosphate Buffer of pH 6.8 at 37°C**

| Crosslinking ratio $\times 10^3$ | Swelling exponent "n" | Gel characteristic constant $k \times 10^3$ | Diffusion Coefficients ($cm^2\ min^{-1}$) | | | Constants for Hopfenberg equation | |
|---|---|---|---|---|---|---|---|
| | | | Initial $D_i \times 10^7$ | Average $D_{ave} \times 10^5$ | Late-time $D_L \times 10^6$ | A | $k_1 \times 10^3$ ($min^{-1}$) |
| 7.27 | 0.83 | 33.72 | 7.69 | 1.53 | 4.40 | 0.87 | 1.11 |
| 12.13 | 0.95 | 22.51 | 6.51 | 1.92 | 8.81 | 1.21 | 2.22 |
| 16.98 | 0.99 | 20.40 | 6.37 | 2.84 | 16.96 | 3.93 | 4.27 |

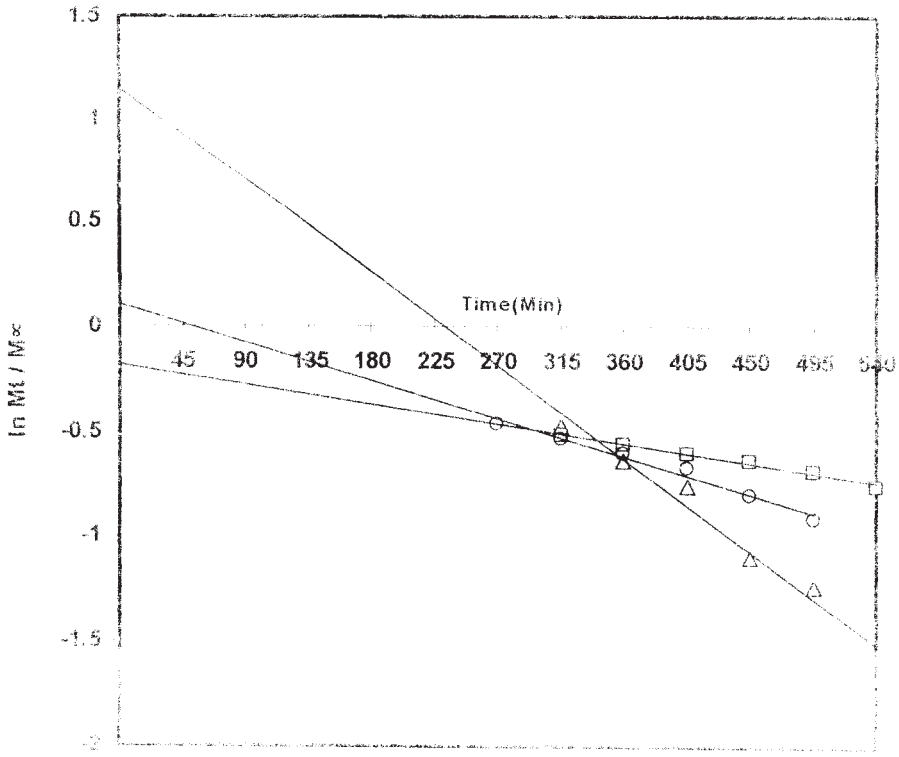


**Figure 5** Evaluation of late time diffusion coefficient, constant $K_1$ and A of Beren-Hopfenberg equation for the hydrogel samples HG(56.17) with crosslinking ratio $7.27 \times 10^{-3}$ (□), $12.13 \times 10^{-3}$ (○), and $16.98 \times 10^{-3}$ (△) in distilled water at 37°C.

### pH sensitive property

The pH of the swelling medium plays an important role in influencing swelling behavior of hydrogels. If the hydrogel contains some ionizable groups, which can dissociate or get protonated at some suitable pH of the swelling media, then the degree of swelling of hydrogels undergoe appreciable change with external pH. Figure 6 depicts the dynamic uptake of water by the sample HG(56.17) in the buffer media of pH 1.2, 4.0, and 6.8, with ionic strength of 0.1*M* at 37°C. The gel exhibits minimum swelling in the medium of pH 1.2, and as the pH becomes 6.8, the degree of swelling at different time intervals increases. The values of swelling exponent $n$, as determined from double logarithmic plots, was found to be 0.46, 0.50, and 0.99 for the media of pH 1.2, 4.0, and 6.8, respectively. These values suggest that gel demonstrates almost Fickian-type swelling behavior in the medium of pH 1.2 and 4.0, while it shows anomalous or non-Fickian behavior when allowed to swell in the media of pH 6.8. This can be attributed to the fact that when the gel is allowed to swell in the media of pH 1.2, the —COOH groups present within the network remain almost nonionized, thus imparting almost nonpolyelectrolyte type behavior to the gel. Moreover, there exits strong H-bonding interactions between —COOH groups of acrylic acid and —$CONH_2$ groups of methacrylamide, which are present within the network, thus resulting in a compact structure that does not permit much movement of polymeric segments within the hydrogel.

However, in the medium of pH 6.8, 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 ionization also causes an increase in ion osmotic pressure. These two factors are thus responsible for a higher degree of swelling in the medium of pH 6.8.

When a dosage form is taken orally, first it goes into the stomach, and after residing there for a definite time, it passes on to the small intestine and finally to the colon. Thus, the dosage form is exposed to media of varying pH during its journey from the mouth to the colon along the GI tract. To mimic this transition, we exposed the hydrogel to media of varying pH and the transit times in various parts of the GI tract were opted from the results of Satyanarayana et al.,[42] who after carrying out gamma scintigraphic studies on guar gum tablets using 99mTc-DTPA as a tracer in human volunteers reported a mean gastric emptying time of 1.08 ± 0.11 h, and the mean colonic arrival time of 2.83 ± 0.33 h. Hence, it means that the small intestinal transit time is likely to be 1.75 ± 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

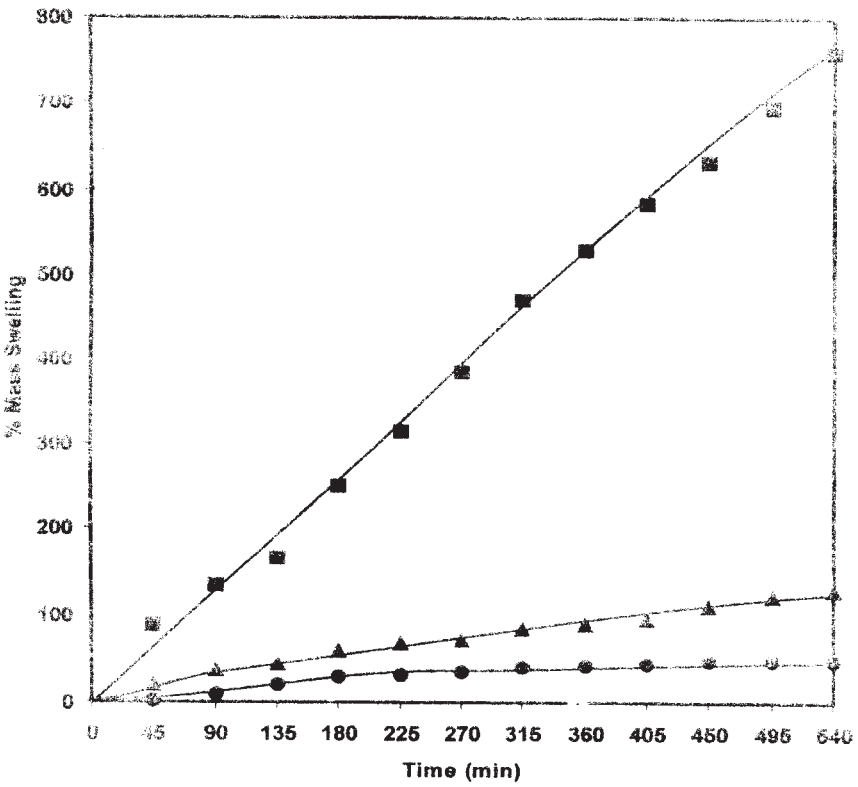


**Figure 6** Dynamic uptake of water as a function of time for the samples HG(56.17) in the media of pH 1.2 (●), 4.0 (▲), and 6.8 (■) with ionic strength 0.1*M* at 30°C.

of 3 h at pH 1.2 and then the next 9 h in the medium of pH 6.8, thus mimicking the transition of formulation from the stomach to the colon. The results, as depicted in Figure 7, indicates that, out of a total swelling of 615% in the first 12 h, the hydrogel swelled to only 15% in first 3 h in the medium of pH 1.2, then

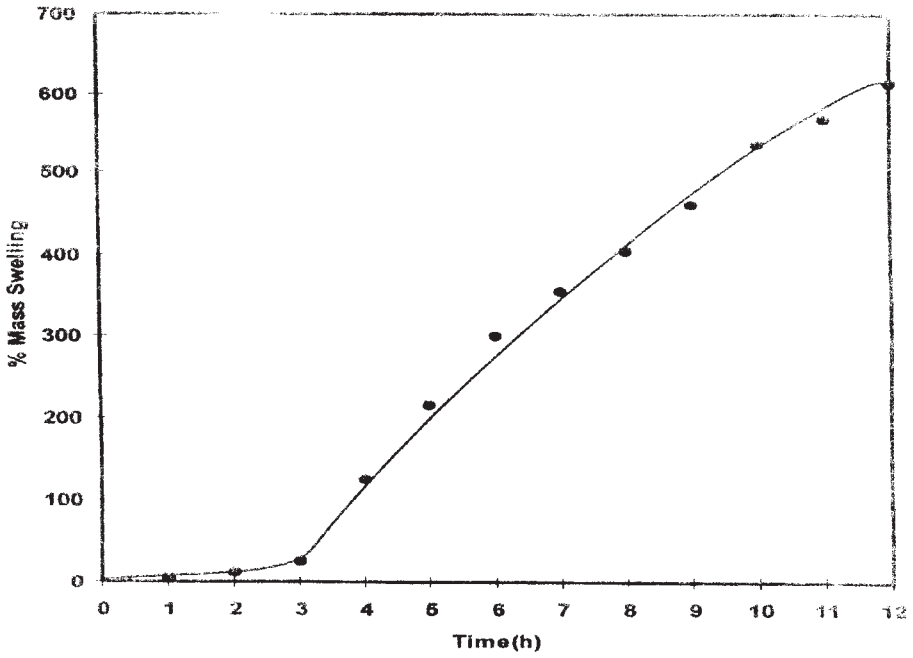


**Figure 7** Composite depiction of swelling of hydrogel HG(56.17) in the environment of changing pH with ionic strength I = 0.1*M* at 37°C.

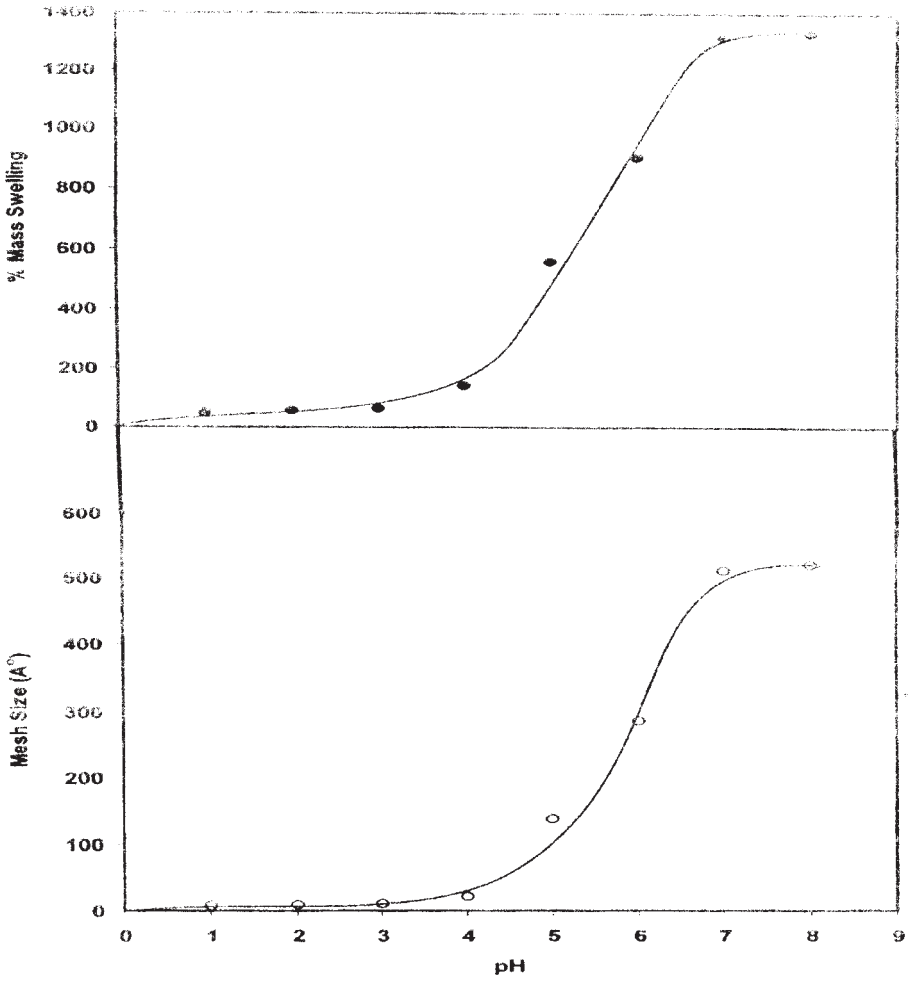


**Figure 8** Effect of pH of the hydrogel samples HG(56.17) in percentage swelling (●) and mesh size (○) with ionic strength 0.1*M* at 37°C.

600% in the rest of the 9 h in the buffer medium of pH 6.8. This suggests that the proposed hydrogel, if loaded with a suitable drug (which is, of course, the next part of our study), should also release the encapsulated drug in almost a similar way. Therefore, the device has the potential to be used for the colon-targeted drug delivery.

Finally, to study the effect of pH of the swelling media on the mesh size of the hydrogel, the equilibrium water uptake of sample HG(56.17) was also measured by placing the hydrogel samples in the media of varying pH, ranging from 1 to 8, as depicted in Figure 8. It is clear that there are drastic changes in the equilibrium of water uptake of the hydrogel at a pH of about 5.8, which is approximately the $pK_a$ of polyacrylic acid. Below pH 5.8, the polymer sample was in a relatively collapsed state. Above pH 5.8, the sample swelled to 10–13 times the initial dry weight. This sharp transition between the swollen and collapsed states indicates that the system gives good response to the environmental pH changes; this behavior is favorable towards an on–off mechanism of drug release. The observed effect may be attributed to the fact that in the media of low pH, the carboxylic groups remain almost unionized, thus producing a compact structure through H-bonding interactions. In addition to this, the osmotic swelling pressure and chain relaxation process are also not operative, thus contributing towards minimum swelling. However, when the pH of the swelling media exceeds a pH value 5.8 the carboxylic groups attached along with the macromolecular chains get ionized, thus yielding —$COO^-$ groups that are attached along with polymeric chains. Therefore, the chain relaxation process begins to operate, along with osmotic swelling pressure, and these two factors result in higher degree of swelling of the polymer matrix.

We also calculated the mesh sizes of the hydrogels swelled at different pH, and the values thus obtained have been plotted as a function of pH of the medium in Figure 8. As can be seen, the mesh size increases with the increase in pH of the swelling medium. The hydrogel attains maximum mesh size, in the range 514–524 Å in the pH range of 7–8 (simulating intesti-

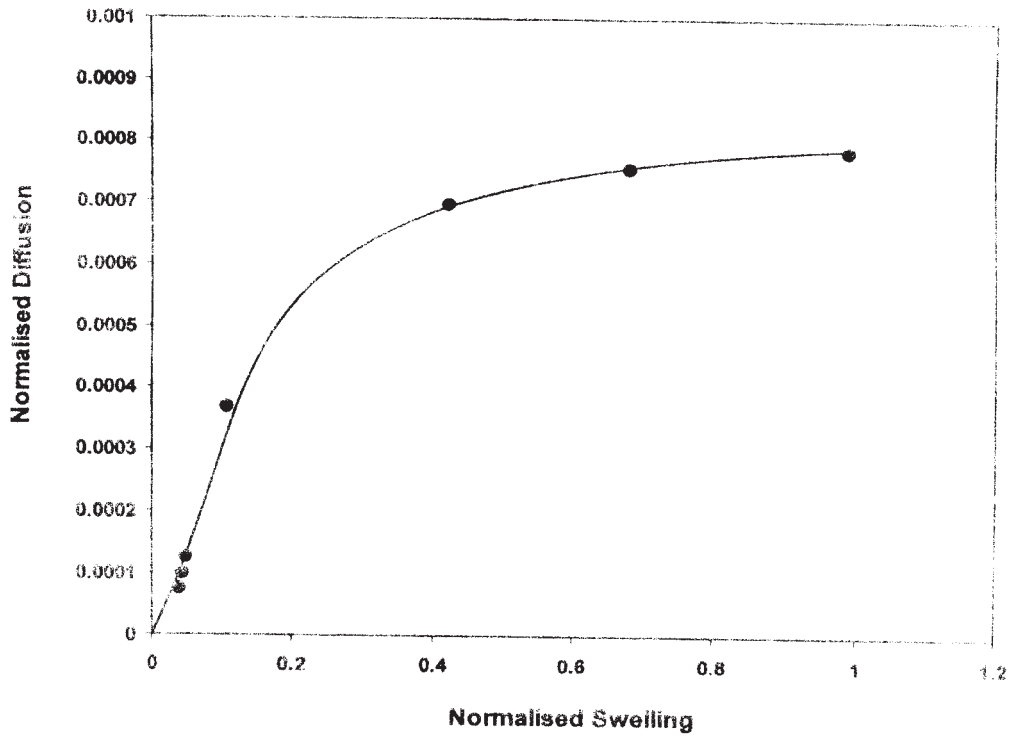


**Figure 9** Normalized percent water uptake of hydrogel HG(56.17) versus normalized theophylline diffusion coefficients in the media of varying pH. The diffusion coefficients have been normalized with respect to diffusion coefficient of theophylline in water and percent water uptake values have been normalized with respect to water uptake at pH 8.0.

nal fluid) while the minimum mesh size was found in the range of 8.4–9.2 Å in the highly acidic medium (gastric fluid, pH 1–2). Therefore, incorporated drug theophylline (hydrodynamics radius 3.5 Å) could easily diffuse out of the drug-loaded hydrogel in the medium of colonic pH (i.e., 7.4). Although the size of the theophylline is also smaller than the mesh size of the gel in the collapsed state (i.e., 8.4–9.2 Å in the simulating gastric fluid), it seems that the entrapped drug might diffuse out in the lower pH also, but this difference is, of course, very small and the entanglements of the network could also prevent theophylline molecules from diffusing out in the collapsed state (this study shall be carried out in the next part of this communication).

We also determined the diffusion coefficient $D$, of a solute of radius $r$, which can be related to the mesh size by the following relation[43]

$$D \cong \left(1 - \frac{r}{\xi}\right) e^{[-Y/(Q-1)]} \tag{18}$$

Here, $Y$ is a constant taken to be equal to 1 for most polymeric systems, and $Q$ is volume swelling ratio. The diffusion coefficient of theophylline was calculated for the swollen and collapsed state of the hydrogel HG[56.17] and the ratio $D_{\text{swollen}}/D_{\text{collapsed}}$ was found to be approximately 10. This indicates that the diffusion of the drug shall be greatly enhanced by the swelling process.

Finally, the theophylline diffusion coefficients through hydrogel sample HG(56.17) under various equilibrium swelling conditions are depicted in Figure 9. The values of the diffusion coefficients were calculated from eq. (18) given the mesh size of the gel at a certain pH. The diffusion coefficient was normalized with respect to the diffusion coefficient of theophylline in water (i.e., $117.6 \times 10^{-7}$ cm$^2$ min$^{-1}$). The percent water uptake was also normalized with respect to water uptake at pH 8.0. It is evident that in the collapsed state the theophylline diffusion coefficients were very small. As the mesh size increased, the normalized diffusion coefficients also increased asymptotically. Similar results have also been reported elsewhere.[44]

### Effect of temperature

Many polymers having N-substituted acrylamide can undergo a thermally induced reversible transition in aqueous media[45] at a temperature known as lower critical solution temperature (LCST) or cloud point. If the polymer constituent present in the hydrogel possesses a LCST, then a sharp volume phase transition is expected to occur across the LCST.[46] The effect of temperature on water uptake of sample HG[56.17]

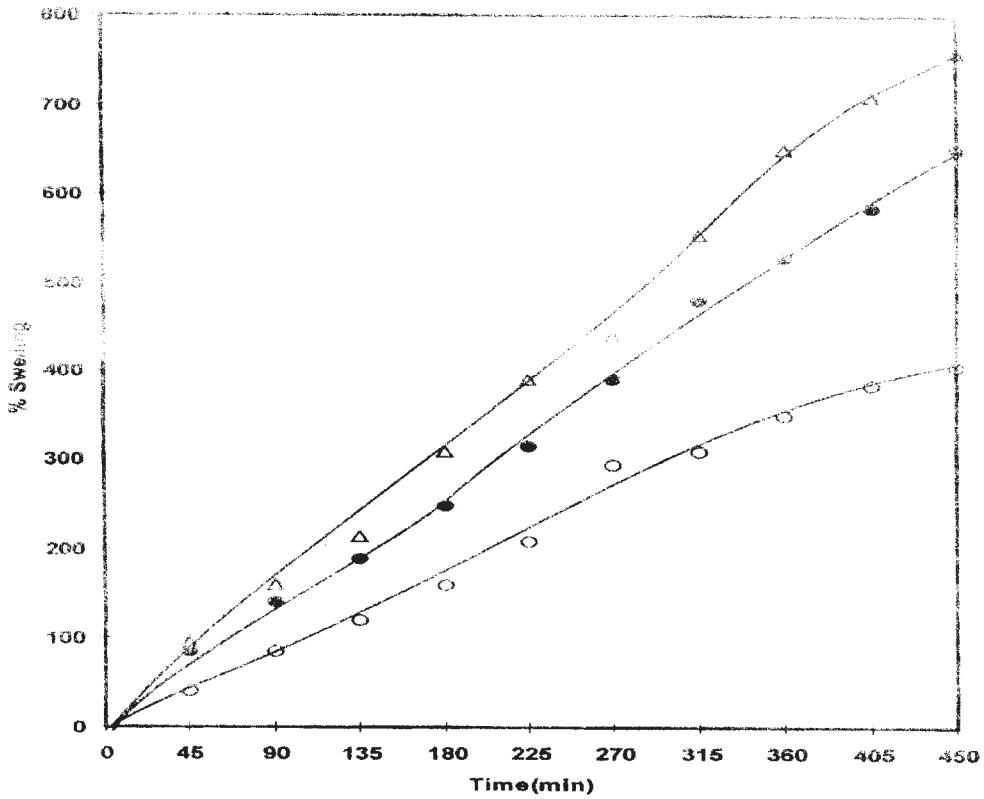


**Figure 10** Dynamic uptake of water as a function of time for the hydrogel sample HG(56.17) in the swelling media of pH 6.8 with I = 0.1*M* at 25°C (○), 35°C (●), and 45°C (△).

was studied in the temperature range 25–45°C in the buffer of pH 6.8 having ionic strength of 0.1*M*. Figure 10 clearly suggests that the increase in the temperature causes an increase in the swelling, which may be attributed to the fact that a rise in temperature causes an increase in penetration rate of solvent into the gel matrix. The activation energy of the swelling process was determined by fitting the experimental data to Arrehenius equation given below:[47]

$$D = D_o \exp(-E_D/RT) \tag{19}$$

where $E_D$ is the apparent activation energy for diffusion process. The activation energy, as determined from the slope of linear plot (see Fig. 11) between the logarithm of $D$ and $1/T$, was found to be 13.71 kJ $mol^{-1}$. Here, it is to be noted that we also synthesized a nonionic hydrogel sample, composed of methacrylamide, and determined its activation energy; the value of activation energy for the nonionic hydrogel came out to be 11.38 kJ $mol^{-1}$. The higher value of the activation energy for the acid containing the hydrogel 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.[48] Similar higher values of activation energy for itaconic and acrylic acid containing hydrogels have also been reported previously.[49,50]

The enthalpy of mixing, $\Delta H_{mix}$ between dry polymer and an infinite amount of water was determined for the sample HG[56.17] and HG[39.31] by measuring

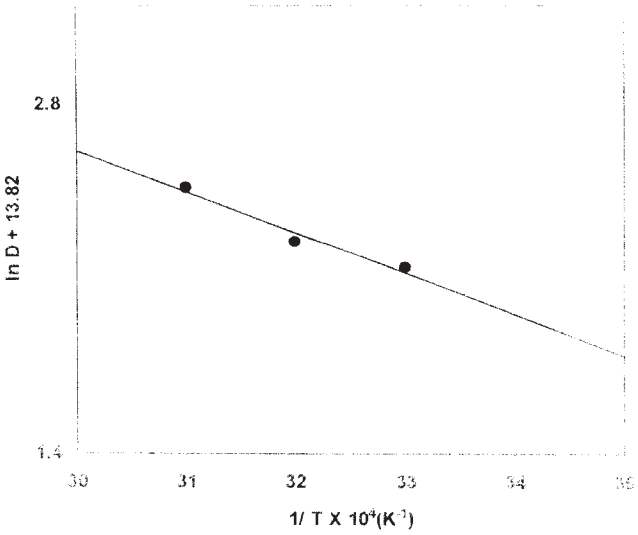


**Figure 11** Arrhenius plots for determination of activation energy of the swelling process for the sample HG(56.17).

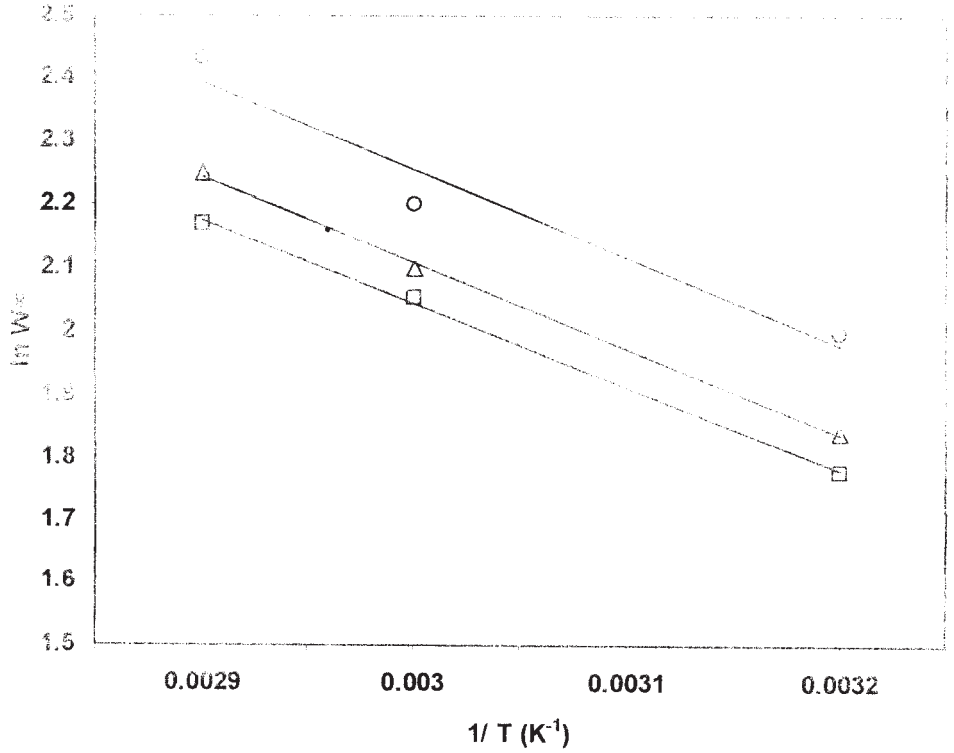


**Figure 12** Plot of ln $M_\infty$ versus $1/T$ for evaluation of enthalpy of mixing for the water uptake of samples HG[79.28] (○), HG[56.17] (△), and HG[39.31] (□).

their water uptake in the temperature range of 25–45°C, using the following Gibbs-Helmholtz equation:

$$d\ln M_\infty / d\ln(1/T) = -\Delta H_{\text{mix}}/R \qquad (20)$$

where $R$ is the gas constant and $T$ is the temperature on an absolute scale. On plotting ln $M_\infty$ values against $1/T$ for the hydrogel sample with % mol fraction of acrylic acid of 79, 56, and 39, we obtained straight lines with the slope (Fig. 12). It is clear that all three straight lineS have nearly the same slope, thus suggesting that slope is independent of composition within the experimental errors. The average value of $\Delta H_{\text{mix}}$ was found to be 11.1 kJ mol$^{-1}$. Similar results have also been reported elsewhere.[47]

### Effect of acid content on swelling

Amount of acrylic acid, present within the hydrogel affects the equilibrium water uptake. Figure 13 depicts the equilibrium mass swelling of hydrogel as a function of the number of moles of acrylic acid, and it is very clear that in the swelling medium of pH 6.8, the equilibrium water uptake continuous to increase with the content of the acid monomer. This observed behavior might be explained as follows.

When the hydrogels with increasing number of moles of acrylic acid are placed in the swelling media of pH 6.8, 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 results in an increase in the equilibrium water uptake of the polymer matrices. Similar observations have also been reported elsewhere.[49] A close look at Figure 13 reveals that in the medium of pH 6.8, when the AAc content is sufficiently low (i.e., 2.25 m*M*), the charges are shielded by counterions present in the buffer, and this results in a 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 4.50 and 15.00 m*M*) the charge density is so high that the counterions are not sufficient to provide proper shielding; therefore, the chain relaxation of polymeric segments takes place to a greater extent, thus causing a large increase in the degree of swelling.

We also studied this effect in the media of pH 1.2, and the results have been depicted in Figure 13. It is clear that in the lower pH, the equilibrium water uptake decreases with an increase in acid content in the gel. The observed decrease is simply due to the fact that at low pH, carboxylic groups present in the polymer network do not ionize, thus imparting nonionic character to the hydrogel. Moreover, in the me-

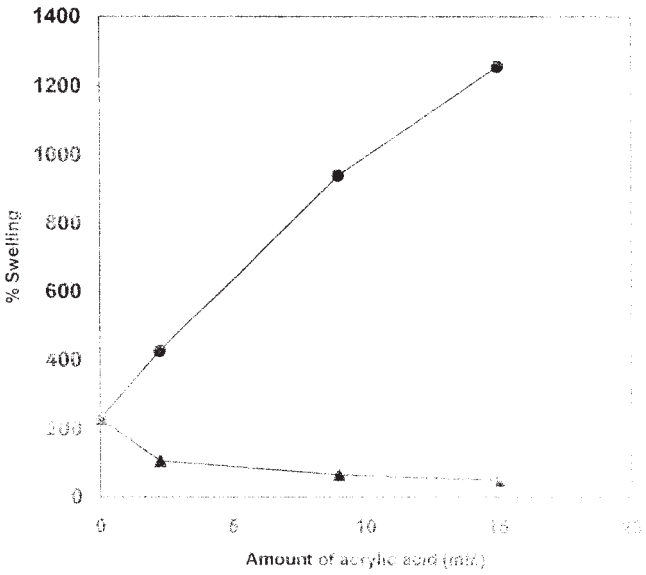


**Figure 13** Equilibrium water uptake as a function of acrylic acid content in the hydrogels in the media of pH 1.2 (▲) and pH 6.8 (●) with ionic strength 0.1*M* at 37°C.

dium of lower pH, H-bonding interactions are also present, thus making the gel structure compact. This accounts for lower water uptake of the gels.

Table III depicts the mesh size, crosslink density, and molar mass between the crosslinks for the hydrogel samples having an acid content of 2.25, 9.00, and 15.00 m*M* in the simulating gastric fluid of pH 1.2 and intestinal fluid of pH 6.8 at 37°C. It is clear that the change in mesh size is very small (1.2–16.7 Å) in the collapsed state at pH 1.2 and to a great extent (93.0–342.6 Å) in the swollen states at pH 6.8, and mesh size increased nearly 6–40 times during the swelling process. This suggests, therefore, that the diffusion of solute through the polymer network would be greatly enhanced by swelling process. It is also indicated by the data that as the acid content in the feed monomers increases, the mesh size decreases at pH 1.2, while it increases at pH 6.8. This may be attributed to the fact that at pH 1.2, the unionized carboxylic groups form hydrogen bonds within the polymer network, thus resulting in lower mesh size, while in the medium of pH 6.8, the ionization of —COOH groups yield $—COO^-$ charges along the macromolecular chains, which causes extensive chain relaxation due to repulsion among similarly charged groups. This accounts for larger mesh sizes in the swollen state.

Similarly, with the increase in acid content, the value of $M_c$ decreases in the medium of pH 1.2, which may be attributed to the fact that there is increase in number of hydrogen bonding interactions with acid content. This also accounts for smaller $M_c$ values in the pH 1.2. However, the gels behave differently in the swollen state (i.e., in the medium of pH 6.8). The value of $M_c$ increases with an increase in acid content, which was already expected. Moreover, it can be seen that values of $M_c$ in the medium of pH 6.8 are extremely greater than those in the medium of pH 1.2. This may be attributed to the fact that at pH 1.2, there are a large number of H-bonding interaction within the network. On the other hand, in the medium of pH 6.8, the H-bonding interactions are totally absent, and polymeric chains are fully relaxed, thus contributing to higher $M_c$ values in the swollen state.

## CONCLUSIONS

From the results obtained in above study, it can be concluded that poly(methacrylamide-*co*-acrylic acid) hydrogels undergo a sharp volume phase transition with the change in pH of the swelling medium from an acid to an alkaline one. The drastic change occurs near pH 5.8. The mesh sizes of the hydrogels also increase from nearly 5.4 to 514 Å as pH changes from 1.0 to 8.0, thus suggesting that diffusion of the entrapped drug will be greatly enhanced with a change in pH of the medium. The amount of initiator also influences the water uptake of hydrogels. The activation energy, as determined from the Arrhenius plot, is found to be 13.71 kJ $mol^{-1}$. The experimental data is well fitted to the Beren-Hopfenberg equation, thus suggesting that the later part is governed by a chain relaxation process. Finally, the hydrogels seems to have potential to be used for gastrointestinal drug delivery of theophylline through oral administration.

**TABLE III**
**Values of Molecular Weight between Crosslinks, Crosslink Density, and Mesh Size for Samples with Different Acid Content in the Medium of pH 1.2 and 6.8 at 37°C**

| Amount of acrylic acid (mM) | Average molar mass between crosslinks $M_c$ | | Crosslink density $q \times 10^3$ | | Mesh size (Å) | |
|---|---|---|---|---|---|---|
| | pH 1.2 | pH 6.8 | pH 1.2 | pH 6.8 | pH 1.2 | pH 6.8 |
| 2.25 | 271.95 | 4545.35 | 279.85 | 16.74 | 16.67 | 93.01 |
| 9.00 | 123.58 | 30839.72 | 615.82 | 2.46 | 10.41 | 304.04 |
| 15.00 | 84.05 | 63776.46 | 905.45 | 1.19 | 8.30 | 342.62 |

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