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# pH-민감성 삼성분계 공중합체 젤의 합성 및 팽윤 속도론

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# Synthesis and Swelling Kinetics of a Cross-Linked pH-Sensitive Ternary Copolymer Gel System

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**Abstract :** A pH sensitive ternary copolymer gel was synthesized in the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent through radical polymerization of vinyl acetate (VA), acrylic acid (AA) and methyl acrylate (MA) with a weight ratio of 1 : 1.3 : 1. A number of experiments were carried out to determine the swelling behavior of the gel under a variety of pH conditions of the swelling medium. As the pH of the swelling medium was changed from 1.0 to 8.0 at 37 ℃, the gel showed a shift in the pH-dependent swelling behavior from Fickian ($n$=0.3447) to non-Fickian ($n$=0.9125). The resulting swelling parameters were analyzed using graphical and statistical methods. The results showed that the swelling of the gel was controlled by the pH of the medium, i.e. $n=n_0 exp(S_C pH)$, where $n$ is the diffusion exponent, $n_0(=28.9645\times10^{-2})$ is the pre-exponential factor and $S_C(=0.1417)$ is pH sensitivity coefficient. The swelling behavior of the gel was also examined in aliphatic alcohols. The results showed that the rate of swelling increased with increasing number of carbon atoms in the alcoholic molecular chain.

**Keywords :** ternary copolymer, swelling kinetics, pH-sensitive gel, aliphatic alcohols.

## Introduction

Polymer gels may show tendency to swell when they are contacted with water or buffer solutions depending on the type and nature of hydrogel systems as well as the pH of the swelling medium. The swelling kinetics and the degree of swelling of gels are important factors to evaluate pH sensitivity as well as to understand the diffusion mechanism and its control strategies for site-specific drug delivery applications. Based on pH sensitivity, the strategy for site-specific controlled drug delivery can be achieved by various pH-sensitive copolymers in the form of coating agents or in the shape of gel systems.[1-4] In case of coatings, the nature of polymer and the thickness of the coating film are important factors, which can affect the drug release phenomena at a specific site. However, in the case of monoliths, the required rate of drug release at a specific site may be achieved by controlling the degree of crosslinking in the polymer matrix as well as the relative concentration of monomers involved in the formation of polymer network.

On the other hand, the site-specific controlled drug release mechanism based on enzymes can be achieved by using prodrugs, polymeric prodrugs and biodegradable polymers that are degraded mostly by the unique enzymes of the colon.[5-7] Delivery of orally administrated drugs by conventional pharmaceutical formulations can be preferred over parental medication to avoid and control the rapid changes in the blood serum concentrations.[8] The controlled delivery applications of orally administrated protein and peptide drugs are rather difficult due to the sensitivity to gastric acid and the susceptibility to gastrointestinal enzymes.[9]

The site-specific oral delivery of drugs targeted to the colon is desirable to reduce the side effects and to increase pharmacological response for the treatment of various diseases such as colitis, irritable bowel syndrome, crohns disease, colon cancer and local infectious diseases developed at colonic

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site.[10] For a number of local pathologies the direct release of drugs in the colon can improve pharmacotherapy along with reduced potential toxicity and side effects.[11] The polymeric hydrogels can be considered an important device for site-specific controlled drug delivery as they exhibit the response to external stimuli under different physiological conditions, biocompatibility and appropriate drug diffusion phenomena by a pore mechanism due to their water retention ability.[12] For site-specific controlled drug applications, it is important to analyze the swelling behavior as the swelling-controlled release[13] and the degradation-controlled mechanism[14] are closely related to the swelling phenomena of hydrogel systems.

Higher swelling rate of hydrogel systems is one of the significant parameters for drug release applications at the colonic pH. In order to release most of the drug to the desired site, the systemic drug delivery mechanism may be achieved by developing the pH-sensitive polymeric gel systems, which can exhibit low swelling in the acidic pH protecting the encapsulated drug and a relatively high degree of swelling in the alkaline pH medium. In terpolymeric hydrogel system the relative composition of monomers may control the swelling rate of the gel to achieve the required drug delivery mechanism for a specific site. The swelling behaviors of hydrogel systems synthesized using VA/AA, VA/MAA, MA/AA and MA/MAA are reported in literature.[3,4] However, a detailed review of the literature shows no guidelines about the swelling kinetics of a cross-linked pH-sensitive ternary copolymer based on VA-AA-MA gel system.

In the present work, using vinyl acetate (VA), acrylic acid (AA) and methyl acrylate (MA), a cross-linked pH-sensitive ternary copolymeric gel was synthesized in order to study the swelling kinetics at different pH conditions of the swelling media. The swelling mechanism of the pH-sensitive gel system may be affected depending on the type and nature of the swelling media. Therefore, the swelling behavior of the gel was also studied using aliphatic alcohols as swelling media at ambient temperature.

## Experimental

**Materials.** The monomers used were vinyl acetate (VA), acrylic acid (AA) and methyl acrylate (MA). The ethylene glycol dimethacrylate (EGDMA) and benzoyl peroxide were used as crosslinking agent and initiator respectively. The double distilled water was used throughout the studies. The details of the chemicals used are given in Table 1.

**Preparation of the Terpolymeric Hydrogel.** Terpolymeric gel was synthesized in a screw capped tube (1.5 cm internal diameter, 12 cm length) through radical polymerization of vinyl acetate (VA), acrylic acid (AA) and methyl acrylate (MA) with the weight ratio of 1 : 1.3 : 1. Ethylene glycol dimethacrylate (EGDMA) was used as crosslinking agent. Ethanol was used as a solvent and its proportion was 100% (v/v) to the total volume of monomers used. The amount of crosslinking agent and the initiator was 2% (w/v) and 0.1% (w/v) respectively. The air above the solution in the tube was removed with nitrogen and the capped tube was placed in a water bath. The polymerization was carried out at slow heating rate to ensure the uniform formation of polymer as the sudden increase in temperature may cause bubble formation and polymeric cylinder to break. The temperature of 25 ℃ was maintained for 1 hr and then it was slowly raised to 30 ℃ where it was kept constant for 1 hr. Similarly the temperature was raised slowly and kept constant for 1 hr at each interval of

**Table 1. Chemicals Used in Preparation and Swelling of Polymer Gel**

| Sr. No. | Name of chemical | Chemical formula | Mol. Wt. | % Purity | Company |
|---|---|---|---|---|---|
| 1 | Methyl acrylate | $CH_2CHCOOCH_3$ | 86.09 | 99 | MERCK |
| 2 | Vinyl acetate | $CH_2CHOCOCH_3$ | 86.09 | 99 | Fluka |
| 3 | Acrylic acid | $CH_2CHCOOH$ | 72.06 | 99 | Fluka |
| 4 | Ethylene glycol dimethacrylate | $CH_2=C(CH_3)C(O)OCH_2-CH_2OC(O)C(CH_3)=CH_2$ | 198.22 | 100 | Fluka |
| 5 | Benzoyl peroxide | $(C_6H_5CO)_2O_2$ | 242.23 | 100 | MERCK |
| 6 | Sodium acetate | $CH_3COONa \cdot 3H_2O$ | 136.08 | 99 | KANTO CHEMICAL CO. |
| 7 | Acetic acid | $CH_3COOH$ | 60 | 100 | MERCK |
| 8 | Disodium hydrogen phosphate | $Na_2HPO_4$ | 177.99 | 100 | Riedal-De Haën |
| 9 | Citric acid | $C_6H_8O_7$ | 210.14 | 100 | MERCK |
| 10 | Trisodium citrate | $C_6H_5Na_3O_7 \cdot 2H_2O$ | 294.10 | Extra pure | MERCK |
| 11 | Hydrochloric acid | HCl | 36.5 | 37 | MERCK |

5 up to 65 ℃. Then the temperature was raised to 68 ℃. The polymeric column began to build up at this temperature and the synthesis was completed in 3 hrs. A smooth polymeric cylinder was removed from the tube and left over-night for cooling at room temperature. The uniform discs of the polymer gel were cut before washing and drying for swelling study.

**Swelling Study.** Before the swelling study in different buffer solutions, the discs were immersed in deionized water for 24 hrs. After washing with deionized water all the discs were dried in a vacuum oven at 40 ℃ for 30 hrs until the weight of the disc was constant. The swelling experiments were carried out in 100 mL of different buffer solutions at 37 ℃. For pH 1, HCl (0.1 M) buffer was used while for pH 4.0 citric acid-trisodium citrate buffer (0.05 M) was used. Acetic acid-sodium acetate buffer (0.2 M) was used for pH 5.5 while for pH 7.4 phosphate buffer (0.1 M) was used. The buffer solution of pH 8 was prepared by dissolving citric acid (0.0441 g) and disodium hydrogen phosphate (1.6944 g) in 100 mL of deionized water. The pH of these solutions was adjusted by adding small amounts of 0.1 M HCl or 0.1 M NaOH solutions. After certain time intervals the gel disc was taken out from the buffer solution and weighed after removing the excess surface water by blotting with laboratory tissue. The swelling experiments were continued up to 1500 min where the rate of swelling of the disc was not significant and it attained almost a constant weight of the penetrated medium. A number of swelling experiments were also carried out using aliphatic alcohols as swelling medium at ambient temperature.

## Results and Discussion

**Swelling of Gel.** During washing and drying, the change in the appearance of the discs was observed. Appearance of the discs was glassy before washing as shown in Figure 1(a). After washing, the glassy appearance changed to milky as shown in Figure 1(b). The glassy state of the gel again appears after drying in the vacuum oven at 40 ℃. Depending on the composition, the reversible change in the behavior of the gel may be due to the temporary hydrogen bonds between the hydrophilic groups in the side chains and water, thus causing the formation of a hydration shell around the hydrophobic groups of the gel system as reported in similar findings.[15] In the present study, some cracks were observed at the surface of the discs, drying at relatively high temperature up to 50 ℃ for longer time. The formation of such cracks on the gel surface was attributed to the existence of water in two states namely free water and bound water in the gel.[16] The present results indicate that the change in solvent from ethanol to water causes phase separation of the hydrophobic residues. Accordingly, the formation of cracks may be attributed to the resultant shrinkage of the gel, which at relatively high temperature occurs too rapidly to accommodate capillary forces within the gel matrix.

After swelling at different pH conditions, swelling percentage of the gel was calculated using the following relation:

$$\text{Swelling}(\%) = \frac{W_s - W_d}{W_d} \times 100 \quad (1)$$

where $W_s$ is the weight of the swollen gel at time $t$, and $W_d$ is the weight of the dry gel at time 0. The swelling isotherms of the gel system are shown in Figure 2. The results indicate that the percentage swelling increases with time up to a certain value, after which the increase is not significant. The swelling of gels reaches its equilibrium when the rate of swelling is almost equal to zero. Swelling phenomena of gels may be expected to depend on the type and nature of solvents. Therefore, aliphatic alcohols were used to study the swelling behavior of the gel as shown in Figure 3. In the case of aliphatic alcohols, the swelling results show that the rate of swelling increases as the number of carbon atoms decrease

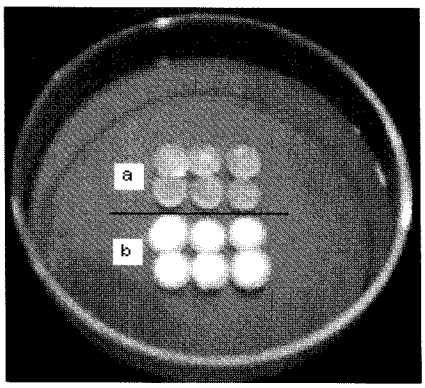


**Figure 1.** Typical swelling characteristic of gel discs before and after washing.

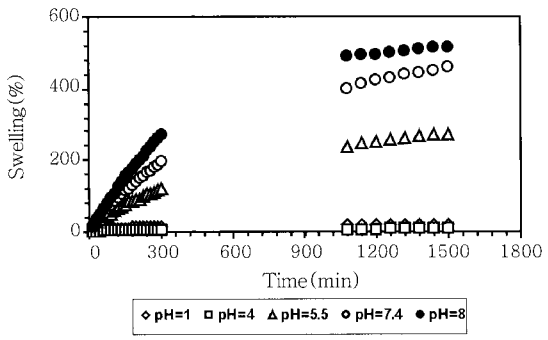


**Figure 2.** Effect of time on swelling(%) of gel for different pH conditions at 37 ℃.

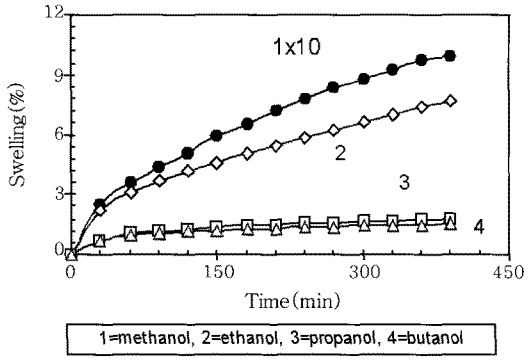


**Figure 3.** Effect of time on swelling(%) of gel in aliphatic alcohols at ambient temperature.

in an aliphatic alcohol.

The swelling behavior of gel systems is an important factor to evaluate pH sensitivity to understand the diffusion mechanism. To normalize the swelling data, the dynamic and equilibrium swelling values were determined gravimetrically using different pH conditions of the swelling media at 37 ℃. The normalized degree of swelling, $Q_t$ was calculated:

$$Q_t = \frac{W_s - W_d}{W_d} = \frac{W_t}{W_d} \tag{2}$$

where $W_s$ is the weight of the swollen disc at time $t$, $W_d$ is the initial weight of the dried disc at $t=0$ and $W_t$ is the weight of the water penetrated into the gel at time $t$. It indicates that the normalized degree of swelling, $Q_t$ is the ratio of water amount penetrated into the gel to the initial weight of the gel sample at time $t$. Similarly, the normalized equilibrium degree of swelling, $Q_e$, was determined:

$$Q_e = \frac{W_\infty - W_d}{W_d} = \frac{W_e}{W_d} \tag{3}$$

where $W_\infty$ is the weight of the swollen gel at time $t_\infty$ when the rate of swelling becomes constant, $W_d$ is the initial weight of the dried disc at $t=0$ and $W_e$ is the weight of the water penetrated into the gel at time $t_\infty$. The normalized equilibrium degree of swelling, $Q_e$ can be defined as the ratio of the water amount penetrated into the gel at time $t_\infty$ to the initial weight of the gel sample at time $t_0$.

**Swelling Mechanism and Kinetics.** The swelling mechanism of hydrogels may depend on pH of swelling media, temperature as well as the nature and composition of reactants involved in the synthesis of polymeric hydrogel systems. Diez-Pena E. *et al.*[17] presented an autocatalytic process mechanism for water penetration into gels on the basis of assumption that the penetration of the first water molecule helps the transport of the next one into the gel network. For the autocatalytic swelling process, let the water transport mechanism into the gel be:

$$H_2O \xrightarrow{k_{non}} H_2O^* \tag{4}$$

$$H_2O + H_2O^* \xrightarrow{k_{aut}} 2H_2O^* \tag{5}$$

where $H_2O$ is the water on the surface of the gel, $H_2O^*$ is the water penetrated into the gel, $k_{aut}$ and $k_{non}$ are the autocatalytic and noncatalytic rate constants respectively. Considering the above Eqs. (4) and (5) it follows that $k_{aut} \gg k_{non}$ when the penetrated water molecule in the polymeric network helps the next one to enter into the gel matrix. Under the autocatalytic process for water penetration into the gel, the differential rate expression can be given:

$$dx/dt = k_{non}(1-x) + k_{aut}\, x(1-x) \tag{6}$$

where $x$ is the fractional swelling, $Q_t/Q_e$. After rearranging and integrating Eq. (6), it follows[18] that:

$$\ln\left[\frac{(k_{non}/k_{aut}) + x}{1-x}\right] = \ln\left[\frac{k_{non}}{k_{aut}}\right] + (k_{non} + k_{aut})\, t \tag{7}$$

The above expression involves two different rate constants and the evaluation of these constants depends on the mechanism involved in the swelling process. The degree of competition among these constants can lead to an appropriate simplification of the autocatalytic process to evaluate these constants. When $k_{aut}$ equally competes with $k_{non}$ and $k_{non} \gg k_{aut}$ is not negligible, the rate constants can be calculated by hit-and-trial method using Eq. (7).

For the case when $k_{non} = k_{aut}$, the Eq. (7) does not hold good to predict any of the individual rate constants for the swelling of gel system, indicating that both of the reactions, Eqs. (4) and (5) go side by side. However, an average rate constant may be calculated using the following Eq. (8):

$$\ln\left[\frac{1+x}{1-x}\right] = 2k_{Av}t \tag{8}$$

where $k_{Av}$ is an average rate constant for the swelling process and the plot of $\ln[(1+x)/(1-x)]$ vs $t$ should yield a straight line with a slope of $2k_{Av}$. At different pH conditions, from the slopes of the plots the average values of the overall

**Table 2. Swelling Kinetic Parameters for Different pH Conditions at 37 ℃**

| pH | $Q_{e\ (exp)}$ ($g_{water}/g_{gel}$) | $(dQ_t/dt)_o \times 10^5$ ($g_{water}/g_{gel}$ s) | $Q_{e\ (cal)}$ ($g_{water}/g_{gel}$) | $k_2 \times 10^5$ ($s^{-1}$) | $R^2$ 2nd-order | $Q_{e\ (cal)}$ ($g_{water}/g_{gel}$) | $^*k_1 \times 10^5$ ($s^{-1}$) | $R^2$ 1st-order | $k_{Av} \times 10^5$ ($s^{-1}$) | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.224 | 2.797 | 0.242 | 0.02087 | 0.9960 | 0.2426 | 22.3 | 0.9334 | 2.50 | 0.9334 |
| 4 | 0.081 | 0.968 | 0.087 | 0.0078 | 0.9962 | 0.0826 | 35.1 | 0.8730 | 2.25 | 0.9011 |
| 5.5 | 2.731 | 11.42 | 3.638 | 1.1587 | 0.9790 | 1.353 | 1.51 | 0.9498 | 2.50 | 0.9662 |
| 7.4 | 4.605 | 15.57 | 6.752 | 2.9239 | 0.9971 | 1.717 | 0.83 | 0.9789 | 2.25 | 0.9876 |
| 8 | 5.162 | 21.35 | 7.267 | 2.4691 | 0.9949 | 2.135 | 1.01 | 0.9731 | 2.75 | 0.9859 |

$^*k_1 = k_{non}$, when $k_{non} >> k_{aut}$.

rate constants were estimated as shown in Table 2. The value of the average rate constant ($k_{Av}$) is found to be $2.50 \times 10^{-5}\ s^{-1}$ with a random variation about 10% for the overall swelling process. This means that the swelling rate is independent of pH of the swelling media, which do not agree with the present case of the swelling process.

For the case when $k_{non} >> k_{aut}$, the oversimplification[17] of Eq. (7) follows that:

$$\ln(1-x) = -k_{non}t \tag{9}$$

The above expression was used to evaluate the noncatalytic rate constant ($k_{non}$). From the slope ($-k_{non}$) of the plot $\ln(1-x)$ vs $t$, the values of the noncatalytic rate constant were calculated as shown in Table 2. The Eq. (9) stands for the first order rate kinetics as well, which indicates that the swelling mechanism of the gel depends on the amount of the sites still available in the gel matrix. The results given in Table 2 show that the value of noncatalytic rate constant ($k_{non}$) increases with the decrease in pH of the swelling medium, indicating an acid catalyzed swelling process. At lower pH, the carbonyl oxygen in the gel chain may get protonated and more polar, thus providing a driving force for water penetration into the gel network. In other words, the value of noncatalytic rate constant decreases due to the suppressed acid catalyzed mechanism as pH of the swelling medium increases more and more.

For the pure autocatalytic mechanism when $k_{aut} >> k_{non}$, Eq. (7) follows that:

$$\ln\left[\frac{x}{1-x}\right] = \ln\left[\frac{k_{non}}{k_{aut}}\right] + k_{aut}t \tag{10}$$

This means that a plot of $\ln(x/1-x)$ vs $t$ should give a straight line with a slope of $k_{aut}$ and an intercept of $\ln(k_{non}/k_{aut})$. The values of the autocatalytic rate constant can be calculated from the slope and the intercept of the plot. For a pure catalytic swelling process, the experimental data were analyzed using Eq. (10). The values of the autocatalytic rate

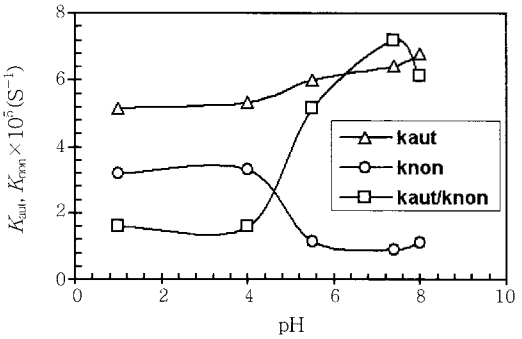


**Figure 4.** Effect of pH of swelling medium on autocatalytic and noncatalytic rate constants.

constant are greater as compared to the noncatalytic ones as shown in Figure 4. The hydrogels with ionic characteristics may show large change during their swelling phenomena, depending on the $pK_a$ of the buffer solutions as well as the $pK_a$ of the hydrogel systems. For *N*-isopropylacrylamide and itaconic acid copolymer hydrogel systems,[15] the results indicated that a relatively high degree of swelling could be achieved by increasing the hydrophilic character of the gel due to an increased degree of ionization above the nominal $pK_a$ values of itaconic acid.

The present results show that the values for both of the types of rate constants are comparable at pH 1 and pH 4. At pH > 4 the noncatalytic rate constant decreases rapidly as compared to the autocatalytic one. The value of rate constant ratio ($k_{aut}/k_{non}$) increases as pH of the swelling medium is increased. Increased value of the rate constant ratio at pH > 4 shows that the autocatalytic swelling mechanism is much more dominant relatively at higher pH of the swelling medium due to the favorable ionization phenomena of carboxyl groups present in the network chains of the gel, depending on the ratio of the swollen sites to the sites still available for swelling in the gel matrix.

The values of second-order rates were estimated using the Robinson-Schott's equation[19-21]:

$$\frac{t}{Q_t} = \frac{1}{t_2 Q_e^2} + \frac{t}{Q_e} \tag{11}$$

Where $k_2$ is a second-order rate constant. For second-order kinetics, a plot of $t/Q_t$ vs $t$ should give a straight line with slope $1/Q_e$ and intercept $1/k_2Q_e^2$. The initial swelling rates can be calculated as it indicates that the intercept $(1/k_2Q_e^2)$ is the reciprocal of the initial swelling rate $(dQ_t/dt)_0$ of the gel. The swelling data were analyzed using the Eq. (11), and the values of initial swelling rate, rate constant $(k_2)$ and the equilibrium degree of swelling were calculated from the best fitting of the experimental data. The values of the initial swelling rate, swelling rate constant, correlation coefficients, experimental and calculated equilibrium degree of swelling are given in Table 2.

The analysis of the results shows that in the case of second order kinetics the calculated values of the equilibrium degree of swelling are found in good agreement with the experimental ones. For first order kinetics the calculated values of equilibrium degree of swelling show a little bit better agreement with the experimental ones only at pH 1 and 4 of the swelling media. However, considering the values of correlation coefficients, the second order kinetics results show a better fit for the overall swelling process as compared to the first order kinetics. The values of the initial swelling rate and second order kinetic rate constant increase with an increase in the pH of the swelling medium, a situation which can be attributed to the fact that for anionic gels the rate of swelling increases as the $pK_a$ of the external solution is increased. The degree of rise in the kinetic rate constants at pH 4 is not much higher, which indicates that the rate of swelling of the gel is appreciable when the $pK_a$ of the buffer components approaches to the $pK_a$ of the gel carboxylic acid. At pH > 4 the results show that the value of the first order rate constant decreases rapidly as compared to the increase in the value of second order rate constant, which is supportive evidence to the pure autocatalytic swelling mechanism relatively at higher pH of the swelling media. The swelling of the ionic gel can be characterized on the basis of the $pK_a$ of the polymeric gel and the $pK_a$ of the buffer medium. For the fast swelling process, the $pK_a$ of the gel should be lower than the $pK_a$ of the contacted buffer so that it may accept protons, resulting in the higher ionization of the carboxyl groups present in the gel network.

As mentioned before, the swelling behavior of pH sensitive gel systems may be changed due to the change in the type and nature of the swelling media. Therefore, the swelling behavior of the gel was also studied using aliphatic alcohols as swelling media at ambient temperature. Using aliphatic alcohols as swelling media, the values of the initial swelling rate, swelling rate constant, correlation coefficients, experimental and calculated equilibrium degree of swelling are given in Table 3.

The analysis of the swelling data shows that for second order kinetics the theoretical values of the equilibrium degree of swelling show a good agreement with the experimental ones. On the other hand, for the first order kinetics the values of the equilibrium swelling do not show a consistency with the experimental ones. The values of correlation coefficients indicate that the second order kinetics show a relatively good fit for the swelling process as compared to the first order kinetics. The values of the initial swelling rate of the gel and kinetic rate constants decrease with increasing the number of carbon atoms in an aliphatic alcohol, a situation which indicates the effect of polarity of the alcoholic molecules on the swelling of the gel. The results show that the swelling of the gel depends on the organic characteristics of an aliphatic alcohol. The polarity of aliphatic alcohols can play a key role in the swelling mechanism of gel systems. The rate of swelling of the gel decreases due to the decrease in the polarity of the alcoholic molecules depending on the number of carbon atoms in the alcoholic molecular chain.

**Swelling Parameters.** The diffusion of water molecules into the polymer and the relaxation of polymer chains in response to the contacted buffer are important factors for swelling controlled drug release systems. In order to expound the swelling phenomena for water penetration $(w_t/w_e)$ less than 60%, the following semi empirical relation was used[22,23]:

$$\frac{w_t}{w_e} = kt^n \tag{12}$$

where $w_t$ is the mass of solvent penetrated into the gel at time $t$, $w_e$ is the amount solvent absorbed at swelling equilibrium, $k$ is the front factor related to the structure of the

**Table 3. Swelling Rate Constants and Normalized Equilibrium Degree of Swelling Using Aliphatic Alcohols**

| Solvent (alcohols) | $Q_{e(exp)}$ ($g_{solvent}/g_{gel}$) | $(dQ_t/dt)_0 \times 10^3$ ($g_{solvent}/g_{gel}$ s) | $Q_{e(cal)}$ ($g_{solvent}/g_{gel}$) | $K_2 \times 10^3$ ($s^{-1}$) | $R^2$ 2nd-order | $Q_{e(cal)}$ ($g_{solvent}/g_{gel}$) | $K_1 \times 10^3$ ($s^{-1}$) | $R^2$ 1st-order |
|---|---|---|---|---|---|---|---|---|
| Methanol | 1.0003 | 0.1223 | 1.4665 | 17.543 | 0.9638 | 0.7776 | 0.1422 | 0.9047 |
| Ethanol | 0.0766 | 0.0112 | 0.1008 | 0.9251 | 0.9578 | 0.0705 | 0.1307 | 0.9220 |
| Propanol | 0.0176 | 0.0052 | 0.0199 | 0.0768 | 0.9948 | 0.0222 | 0.0763 | 0.9577 |
| Butanol | 0.0153 | 0.0051 | 0.0171 | 0.0592 | 0.9939 | 0.0204 | 0.0674 | 0.9236 |

**Table 4. Fitting of Swelling Kinetic Models for Different pH Conditions at 37 ℃**

| pH | $W_t/W_e = k\,t^n$ $W_t/W_e$ up to 300 min | $R^2$ | SE | $W_t/W_e = 1-A_0\,e^{-k1t}$ $W_t/W_e$ > 300 min | $R^2$ | SE |
|---|---|---|---|---|---|---|
| 1 | $W_t/W_e=9.397\times10^{-2}\,t^{0.3447}$ | 0.9990 | ±0.009226 | $W_t/W_e=1-1.5\times10^{3}e^{-8.9\times10-3t}$ | 0.9512 | ±0.286836 |
| 4 | $W_t/W_e=4.663\times10^{-2}\,t^{0.4797}$ | 0.9984 | ±0.015943 | $W_t/W_e=1-0.567\times10^{3}e^{-7.7\times10-3t}$ | 0.9568 | ±0.17831 |
| 5.5 | $W_t/W_e=1.154\times10^{-2}\,t^{0.6363}$ | 0.9976 | ±0.026231 | $W_t/W_e=1-0.289\times10^{3}e^{-7.1\times10-3t}$ | 0.9571 | ±0.209295 |
| 7.4 | $W_t/W_e=0.373\times10^{-2}\,t^{0.8345}$ | 0.9996 | ±0.014708 | $W_t/W_e=1-0.0234\times10^{3}e^{-4.7\times10-3t}$ | 0.9504 | ±0.153575 |
| 8 | $W_t/W_e=0.298\times10^{-2}\,t^{0.9125}$ | 0.9990 | ±0.024346 | $W_t/W_e=1-0.0089\times10^{3}e^{-4.6\times10-3t}$ | 0.9373 | ±0.149982 |

polymeric network, $n$ is the diffusion exponent which indicates the mechanism of absorption. The value of $n$ generally varies from 0 to 1.0. For Fickian kinetics, n=0.5 the swelling is diffusion controlled, where the rate of buffer penetration is the slowest and hence is the rate determining step. When the buffer penetration velocity and the chain relaxation or chain stretching rates are comparable, $n$ is between 0.5 and 1.0 and the kinetics are generally known as non-Fickian, which concerns with ionization of some functional groups present in the gel network. When the buffer penetration rate is much higher than the chain relaxation rate then the penetration of solvent is proportional to the time, i.e., n=1.0. The Eq. (12) can be used for the initial swelling data when the water-penetrated fraction ($W_t/W_e$) is less than 60%, however, for higher penetrated fraction it does not hold good.[24] For swelling fraction more than 60%, the following expression was used[25]:

$$W_t/W_e = 1 - A_0 e^{-k_1 t} \quad (13)$$

To determine the values of diffusion exponent ($n$), front factor ($k$), relaxation rate constant ($k_1$) and the pre-exponential factor ($A_0$), the experimental data were analyzed using Eqs. (12) and (13). Using the values of the swelling parameters, the data were analyzed fitting both of the above-mentioned equations as shown in Table 4. The results indicate that the applicability of these fitted equations is equally good. However, the values of correlation coefficients and standard deviations indicate that the power law, Eq. (12) shows a better fit for the initial swelling ($W_t/W_e$<60%) as compared to the Hopfenberg model, Eq. (13) for the late swelling process ($W_t/W_e$>60%). Fitting the power law at various pH conditions, the agreement between the experimental swelling fractions $(W_t/W_e)_{exp}$ and the calculated $(W_t/W_e)_{cal}$ ones is also tested as shown in Figure 5. The correlation coefficients were found to be 0.9995, 0.9987, 0.9987, 0.9997 and 0.9991 along with the standard error (SE) of ±0.0041, ±0.0085, ±0.0085, ±0.0031 and ±0.0069 from pH 1 to 8, respectively. The values of standard error of estimate indicate that the degree of scatter or the deviation between the true (experimental) and the estimated (calculated) values is very small. Thus, the

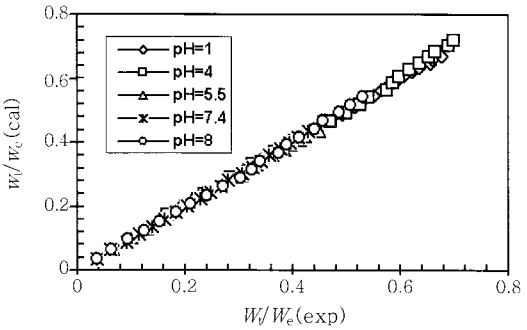


**Figure 5.** Agreement between experimental and calculated swelling fractions of gel at different pH conditions of swelling medium.

results show that the agreement between the experimental swelling fractions $(W_t/W_e)_{exp}$ and the calculated $(W_t/W_e)_{cal}$ ones is fairly good.

According to the results, it has been found that the gel shows a good pH-dependent swelling behavior with transition from Fickian (n=0.3447) to non-Fickian (n=0.9125) as the pH of the swelling media changes from 1.0 to 8.0 at 37 ℃. At highly acidic pH conditions, the swelling behavior of VA-AA-MA gel indicates the presence of unionized carboxylic groups in the gel. However, at higher pH values, the degree of swelling appreciably increases due to the repulsive forces of the fully ionized acidic fraction along the macromolecular chains resulted from the ionization of carboxylic groups in the gel. The swelling behavior of polyampholyte hydrogel, composed of dimethylaminoethyl methacrylate and acrylic acid, was studied and the results showed that the swelling process was Fickian at the isoelectric point (IEP) and non-Fickian when the pH of the media deviated from the isoelectric point.[26] In another study, the swelling kinetic results of NVP grafted chitosan hydrogel system were found to be Fickian with relatively low content of grafted chitosan, however, the swelling behavior was found to be non-Fickian when CHI contents were increased more than 30%.[27] For a thermally cross-linked poly(vinyl alcohol) and poly(acrylic acid) hydrogel systems, the swelling kinetic results were found to be dependent on the mixing ratio as well as pH of the swelling medium.[28]

Regarding the swelling behavior of hydrogel systems, it is worth mentioning that the role of monomer composition can be expected an important parameter. Depending on the dynamic swelling behavior of the gel systems,[15] the analysis of the data showed that an increase in the itaconic acid contents of the gel could result in an increase in the values of diffusion exponent and diffusion coefficient. In the present case, it was found in a separate swelling study that by decreasing the acrylic acid amount from 1.3 to 1 (weight percent ratio) in the ternary copolymer gel system, the swelling rate of the gel was relatively low. The lower swelling rate can be attributed to a relatively higher ratio of hydrophobic to hydrophilic characteristics in the ternary copolymer gel system due to the decrease in the amount of the acid used.

Lisa and Peppas[29] investigated the dynamic and equilibrium swelling behavior of pH-sensitive hydrogel system and the results showed that the swelling kinetics of the gel could be affected by a range of compositional changes in the gel network. The results also indicated that the dynamic swelling behavior was a function of the acidity of the buffered solution. The swelling behavior of poly(acrylic acid) hydrogel systems was studied and the results showed that the cross-linked structure of ionic networks like poly(acrylic acid) copolymers could be affected by the monomer concentration, the pH, and ionic strength during the polymerization.[30]

Jing and Peppas[31] investigated the swelling behavior of temperature-sensitive poly(*N*-isopropylacrylamide) and pH-sensitive poly(methacrylic acid) hydrogel systems. The results showed that these hydrogels exhibited a combined effect of pH and temperature with a specific range of temperature as well as the pH conditions. At different pH conditions and NaCl aqueous solution, the swelling behavior of a cross-linked poly(*N*-vinylpyrrolidone) (PVP) and linear poly(acrylic acid) (PAA) hydrogel system was investigated.[32] The results showed that the semi-IPN hydrogel had excellent pH sensitivity at a pH range from 2.25 to 4.00, while in the presence of the salt the swelling behavior of the gel was not significant.

To determine the pH sensitivity for the swelling behavior of the gel, the values of the diffusion parameter, $n$ were analyzed by graphical and statistical methods. The effect of pH of the swelling medium on the diffusion coefficient is found to be promising with a standard error of 0.04191 and correlation coefficient of 0.9918 as shown in Figure 6. The value of standard error of estimate indicates that the degree of scatter or the deviation between the true (experimental) and the estimated (calculated) values is small. The results indicate that the swelling process is a function of the pH of the swelling media, following a semi empirical model:

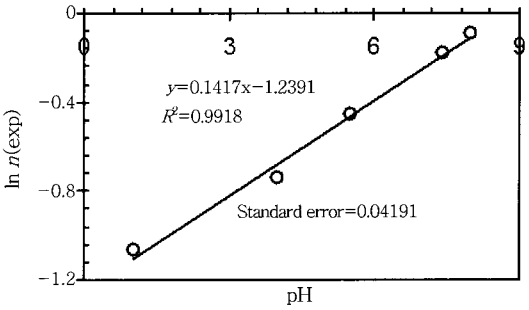


**Figure 6.** Plot between pH of swelling medium and experimental diffusion exponent.

$$n = n_0 \exp(ScpH) \tag{14}$$

where $n$ is diffusion exponent, $n_0$ is pre-exponential factor in the model and $S_C$ is pH sensitivity coefficient of the gel. The pre-exponential factor and pH sensitivity coefficient may provide useful information about the swelling process depending on the nature and type of gel systems as well as swelling conditions. The pre-exponential factor indicates the swelling mechanism of the gel under highly acidic condition of the swelling medium, whereas the pH sensitivity coefficient stands for the swelling capacity and thus the change in the swelling mechanism of the gel with changing pH of the media. Thus, using the values of $n_0$ and $S_C$ from the intercept and the slope of Figure 6 respectively, the Eq. (14) can be written as:

$$n = 0.289645\, e^{0.1417\,pH} \tag{15}$$

To understand the diffusion mechanism of diffusing solvent into the gel, the suggested semi empirical model may be applied at any physiological pH of the medium. The suggested model agrees with some data published in past. For different composition samples, a number of researchers have studied the swelling kinetics depending on just one or two different pH conditions of the swelling medium. However, regarding the modeling aspect, the data for only two different pH conditions cannot be conclusive. The validity of the suggested model has been tested for the similar data reported in literature.[11,15,33] For the swelling of a pH sensitive hydrogel system,[11] the values of diffusion exponents were found to be 0.43, 0.57 and 0.84 at pH 2.0, 4.0 and 7.4, respectively. Similarly, for the swelling of a specific composition hydrogel (PNIPAM/IA 95/5/2) system,[15] the values of diffusion exponent were found to be 0.58, 0.60 and 0.63 at pH 2.2, 4.5 and 6.8, respectively. In another study, for the swelling of a polymer gel (vinyl acetate and methacrylic acid) system,[33] the values of diffusion exponent were found to be 0.64, 0.70 and 0.76 at pH 5.5, 6.5 and 7.0, respectively. Though the

authors did not suggest any models, yet all the above-mentioned data could be analyzed to show an excellent exponential fit for these pH-sensitive hydrogel systems as suggested in the present work.

To test the agreement between the experimental diffusion exponent and the values calculated from the semi empirical model, the graph of $n_{exp}$ versus $n_{cal}$ has been plotted as shown in Figure 7. It has been observed that the agreement between the experimental and calculated values is very good with a correlation coefficient of 0.9948 and standard error of ±0.01927. The data in the scatter diagram shows a positive tendency to cluster around the regression line, which can be attributed to the existence of a good relationship between the variables. The value of the standard error of estimate of $n_{cal}$ on $n_{exp}$ indicates that the degree of scatter of the observed values about the regression line is not significant.

On the other hand, the Fickian ($n < 0.5$) swelling behavior has been found for all the aliphatic alcohols as shown in Table 5. The results show that swelling rate of the polymer gel increases as the number of carbon atoms decreases in the aliphatic chain of the alcohols. In other words, the polarity of the alcoholic O-H bond decreases as the number of carbon atoms increases in the alcoholic molecular chain, thus affecting the swelling kinetics of the gel system. The greater the polarity of the alcoholic solvent, the more is the swelling of the polymer gel. The values of the correlation coefficients indicate that the experimental data fits well to the power law. As shown in Table 5, the results also indicate that the experimental values

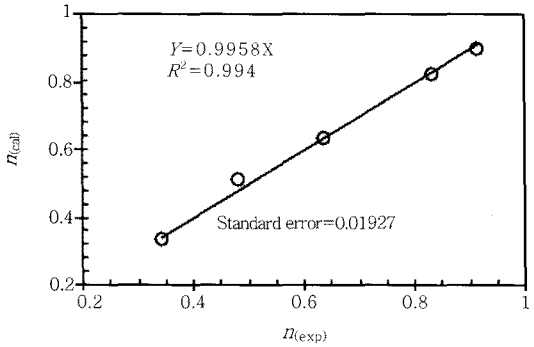


**Figure 7.** Agreement between experimental and calculated diffusion exponents.

**Table 5. Swelling Parameters and Equilibrium Water Contents Using Aliphatic Alcohols**

| Solvent | $n$ | $K\times10^3$ ($s^{-1}$) | $R^2$ | $W_{e(exp)}$ $G_{solvent}$ | $W_{e(cal)}$ $G_{solvent}$ | $R^2$ |
|---|---|---|---|---|---|---|
| Methanol | 0.5392 | 0.659 | 0.9967 | 0.3987 | 0.5446 | 0.9638 |
| Ethanol | 0.4418 | 1.106 | 0.9993 | 0.0293 | 0.0386 | 0.9578 |
| Propanol | 0.3545 | 2.174 | 0.9711 | 0.0073 | 0.0083 | 0.9948 |
| Butanol | 0.2937 | 2.984 | 0.9934 | 0.0064 | 0.0072 | 0.9939 |

of the penetrated alcoholic molecules $(W_e)_{exp}$ are in good agreement with the calculated $(W_e)_{cal}$ values for the swelling process.

**Diffusion Coefficients.** For diffusion into the simple geometric shapes such as spheres, cylinders and discs, the Fick's second law can be used for limiting swelling conditions in water or biological fluids. For short time diffusion, when the swelling fraction is less than 50% the following relation[34] can be used.

$$\frac{W_t}{W_e} = 4\,[D_{St}t/\pi l^2]^{1/2} \tag{16}$$

where $D_{St}$ is the diffusion coefficient for the transport of water into the gel matrix for the swelling fraction ($W_t/W_e$) less than 0.5, $t$ is the time for swelling and $l$ is the thickness of the disc. From the slope of the plot $W_t/W_e$ vs $t^{1/2}$, the values of $D_{St}$ were calculated as shown in Table 6. The average values of the diffusion coefficients were calculated when the swelling fraction was 50% ($W_t/W_e$=0.5):

$$D_{Av} = (0.049\times l^2)/t_{1/2} \tag{17}$$

where $D_{Av}$ is the diffusion coefficient for penetration of water into the gel when the $W_t/W_e$=0.5 and $t_{1/2}$ is the half-swelling time. To determine the diffusivity toward the end of the swelling process, the swelling data can be analyzed by using the late-time approximation[35]:

$$\frac{W_t}{W_e} = 1 - 8\,[8/\pi^2\{\exp(-(\pi^2 D_{Lt}t/4l^2))\}] \tag{18}$$

where $D_{Lt}$ is the diffusion coefficient for late time. For the swelling fraction ($W_t/W_e$) more than 60%, plots for ln ($1 - W_t/W_e$) vs $t$ were drawn to determine the values of $D_{Lt}$ using Eq. (19):

$$D_{Lt}t = -[d(\ln(1-W_t/W_e)/dt)\times l^2/\pi^2] \tag{19}$$

The values of $D_{Lt}$ are shown in Table 6. For short time, it is interesting to note that by the comparison between Eqs. (12) and (16) it follows:

$$kt^n = 4\,[D_{St}/\pi\, l^2]^{1/2}\, t^{1/2} \tag{20}$$

For a complete Fickian diffusion mechanism (n=0.5), the Eq. (20) follows that:

$$D_{Fi} = (\pi\, l^2 k^2)/16 \tag{21}$$

where $D_{Fi}$ is the Fickian diffusion coefficient, which is

**Table 6. Diffusion Coefficients and Equilibrium Water Contents at 37 ℃**

| pH | $D_{St}\times10^5$ ($cm^2s^{-1}$) | $R^2$ | $D_{Av}\times10^5$ ($cm^2s^{-1}$) | $D_{Lt}\times10^5$ ($cm^2s^{-1}$) | $R^2$ | $W_{e(exp)}$ $g_{water}$ | $W_{e(cal)}$ $g_{water}$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 4.27 | 0.9349 | 1.47 | 10.91 | 0.9512 | 0.0915 | 0.0988 | 0.9960 |
| 4 | 4.99 | 0.9962 | 1.69 | 14.12 | 0.9503 | 0.0329 | 0.0352 | 0.9962 |
| 5.5 | 6.11 | 0.9686 | 4.17 | 20.11 | 0.9571 | 1.1011 | 1.4667 | 0.9790 |
| 7.4 | 6.44 | 0.9661 | 4.74 | 26.09 | 0.9504 | 2.0035 | 2.9379 | 0.9971 |
| 8 | 9.33 | 0.9861 | 6.99 | 31.07 | 0.9641 | 2.3779 | 3.3481 | 0.9949 |

independent of time and depends on the value of the front factor when n=0.5. The applicability of Eq. (21) may be tested for a complete Fickian diffusion mechanism.

The values for the diffusion coefficients are given in Table 6 and the results indicate that the diffusion rate increases with an increase in the pH of the swelling medium. At pH 1 and 4, the values of the diffusion coefficients are relatively small, which shows that the swelling phenomena are mostly based on the available interspaces in the gel network rather than the chain relaxation of the gel matrix. However, above pH 4, the increase in the values of the diffusion coefficients is significant, which reflects the chain relaxation controlled mechanism due to relatively greater and favorable $pK_a$ of the buffer solution for the swelling of the gel. The values of late-time diffusion coefficients are found to be relatively higher than the corresponding values of short- and average-time diffusion coefficients. Higher rate of late-time diffusion at pH > 4 indicates the chain stretching mechanism of the gel, which occurs to a greater extent toward the end of swelling process and thus results in relatively fast penetration of water molecules into the polymeric network.

For aliphatic alcohols, the values of the diffusion coefficients were determined as shown in Figure 8. The results show that the diffusion rate increases as the number of carbon atoms decreases in an aliphatic alcohol, which can be attributed to the role of molecular size as well as the organic characteristics of the solvents used for the swelling of the gel system. As mentioned in the previous section, the values of diffusion exponent (n) indicate that the aliphatic alcohols do not show any tendency toward chain relaxation swelling mechanism. However, the values of the diffusion coefficients indicate that the diffusion process is much more faster for aliphatic alcohols than the diffusion rate of water molecules into the gel matrix. Thus, being organic in nature, the gel shows a greater affinity for aliphatic alcohols as compared to the uptake of water molecules.

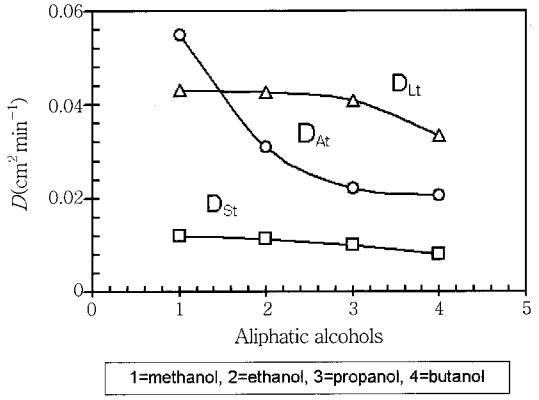


**Figure 8.** Effect of aliphatic alcohols on diffusion coefficients for swelling of gel.

## Conclusions

A pH-sensitive cross-linked ternary copolymer gel was synthesized using the weight ratio 1 : 1.3 : 1 of vinyl acetate (VA), acrylic acid (AA) and methyl acrylate (MA), respectively. In order to achieve the required rate of swelling for site-specific controlled drug delivery applications, the ternary copolymer gel system may be expected to provide a better hydrophobic-hydrophilic balance within the polymer network by controlling relative amount of VA, MA and AA monomers. Thorough washing of the gel resulted in a change from glassy to milky appearance. However, the glassy state of the gel again appears after drying. The reversible change in the behavior of the gel may be due to the temporary hydrogen bonds between the hydrophilic groups in the side chains of the gel and water. The results show that the swelling process of the gel follows the second order kinetics.

The swelling studies of the gel show a fair pH-dependent behavior with transition from Fickian (n=0.3447) to non-Fickian (n=0.9125), as the pH of the swelling medium is changed from 1.0 to 8.0 at 37 ℃. At highly acidic pH conditions, the swelling behavior of the ternary copolymer reflects the presence of unionized carboxylic groups in the gel. However, at higher pH values, the degree of swelling appreciably increases due to the repulsive forces of the fully ionized acidic fraction along the macromolecular chains resulted from the ionization of carboxylic groups in the gel.

Using aliphatic alcohols, the results obtained are indicative of the fact that the swelling rate increases as the number

of carbon atoms decrease in an aliphatic alcohol. The polarity of the alcoholic molecules can play a key role in the degree of swelling of the gels. The rate of swelling of the gel decreases due to the decrease in the polarity of the alcoholic O-H bond due to the positive inductive effect as the number of carbon atoms increase in the alcoholic molecular chain more and more. Despite the fact that the aliphatic alcohols do not show any contributions towards the chain relaxation swelling mechanism, still, the higher rates of diffusion display the significant role of affinity of the gel for the alcoholic molecules than that of water diffusion into the gel.

Analysis of the resultant diffusion exponent data indicates that the diffusion mechanism of water penetration into gel is a function of pH of the swelling media, following a semi-empirical model. The validity of the suggested model has been tested by graphical and statistical methods. For different composition of monomers, it needs further investigations. However, for the present gel system, the analysis of the results reveals that applicability of the suggested model is good and it can estimate the diffusion mechanism at any physiological pH of the swelling media with a standard error or degree of scatter of ±0.01927. In the light of the presented results, the VA-AA-MA ternary copolymer gel system shows appreciable swelling phenolmena at the physiological pH of 7.4.

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