

## Effect of Cross Linker Concentration on Swelling Kinetics of a Synthesized Ternary Co-Polymer System

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**Summary:** Using equal volumes of three monomers (acrylic acid, vinyl acetate and methyl acrylate), ternary co-polymers were synthesized with different concentrations of cross linker, ethylene glycol dimethacrylate (EGDMA). Benzoylperoxide was used as an initiator (concentration of 1% w/v) for the synthesis of hydrogel systems. A number of experiments were carried out to illustrate the swelling behavior of the gel with different concentrations of cross linker. The analysis of swelling data shows that the swelling phenomena is function of concentration of the cross linker used. Graphical and statistical analysis of diffusion exponents shows that the diffusion mechanism for water penetration into the synthesized gel system is controlled by concentration of the cross linker, i.e.  $n = n_0^{CC}$ , where  $n$  is diffusion exponent,  $n_0 (=0.6548)$  is pre-exponential factor,  $C_L (= -0.0345)$  is cross linker concentration sensitivity coefficient of the gel.

**Keywords:** Terpolymeric hydrogel, acrylic acid, vinyl acetate, methyl acrylate, cross linker sensitive swelling model, cross linker concentration coefficient.

### Introduction

Much interest has been devoted in recent years to the synthesis and development of various hydrogel systems exhibiting controlled volume change in response to changes in environmental conditions. All these efforts have led researchers to better understand for controlling the stimuli responsiveness of hydrogel systems and also to predict their equilibrium swelling phenomena under different conditions. Predictability of equilibrium swelling ratio, which is the ratio of volume of swollen gel to the volume of the dry gel for a particular hydrogel system, is important in the design calculations and utilization of these materials in specific applications.

A hydrogel is a multi-component system consisting of a hydrophilic polymer swollen with water. Because of the relatively high water content of these hydrogels, they have found with widely spread applications in biomedical, pharmaceutical, food and environmental fields. The higher water content imparts them high biocompatibility and makes them very well tolerated when implanted in vivo studies. Consequently, they are used in variety of biomedical applications such as drug delivery systems, wound dressings, contact lenses, soft tissue substitution and catheters [1, 2].

Incorporation of a multitude of comonomers with specific functional groups into hydrogel systems lead to a number of novel applications in a variety of areas including solute recovery, affinity separation and environmentally

sensitive membranes [3]. Hydrogels can be tailor synthesized to possess some responsive moieties showing selectivity of proteins [4, 5], enzymes [6], bio-molecules [7], dyes [8], pigments or some anions or cations [9].

Numerous attempts have been made to develop theoretical models to explain swelling behavior of different hydrogel systems. The widely used of these theories is the classic swelling theory developed by Flory Rehner [10], which describes the swelling behavior of gels where cross links are introduced in dry stage and assumed to be tetra functional. The effect of presence of solvent during network formation at equilibrium swelling behavior of gels was also considered by Flory [11], Wall and Flory [12] and elaborated by Dusek and Prins [13]. Peppas and Merrill [14] also derived an equation which is applicable to systems where solvent is present during the cross linking process.

Hydrogels are cross linked hydrophilic polymers capable of imbibing large volumes of water and yet are insoluble due to their network structures, crystalline regions or entanglements. The hydrophilic characteristics of these materials is mainly attributed due to the presence of hydrophilic functional groups such as -OH, -COOH, -CONH<sub>2</sub>, -CONH and -SO<sub>3</sub>H along the polymer chain net work [15-17].

Yoshida *et al.* [18] synthesized thermo and pH responsive acryloyl-1-proline ether ester copolymers with methacryloylglycine (MA-Gly) and

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methacrylic acid as a novel bio-functional gel for application in colon delivery systems. Nakamae *et al.* [19] synthesized phosphate group containing methacryloyloxyethyl dihydrogen phosphate/N-isopropyl acrylamide copolymeric charged enzymes. The results indicated that the negatively charged phosphate groups bind ionically to positively charged lysozyme. They also recommended that this type of pH sensitive hydrogel systems may be ideal and useful for drug delivery applications to the small intestine, while avoiding release in the stomach.

Environmental sensitivity or control of swelling ability of polymer electrolyte hydrogels under a variety of external conditions make them ideal adsorbents for removal and adsorption of some water soluble agents such as proteins, biomolecules, metallic impurities and dyes. Novel applications of hydrogels in bio-separation or as clever artificial systems have been widely presented in the literature [20]. The hydrogels based on poly-electrolyte structure and synthesized via irradiation of aqueous solutions of acrylamide and N-vinyl-2-pyrrolidone with small quantities of maleic or itaconic acids have been regarded as systems with potential mobilization, chelating and adsorptive properties for various bio-applications. The capacity of these gels to adsorb bovine serum albumen (BSA) was investigated by using the gels with varying compositions of maleic acid [21] and itaconic acid moieties [4].

The swelling kinetics and the degree of swelling of hydrogel systems are important informative factors to evaluate pH sensitivity as well as to understand the diffusion mechanism for site-specific controlled drug delivery applications. Using constant amount of ethylene glycol dimethacrylate (EGDMA) as a cross linking agent the ternary copolymeric pH-sensitive gel was synthesized for studying the swelling behavior of the gel at different pH conditions of the swelling media [22]. The swelling results of the gel showed a fair pH-dependent swelling behavior shifting from Fickian to non-Fickian as the pH of the swelling medium changed from 1.0 to 8.0 at 37°C. It was found that the diffusion mechanism for water penetration into the gel matrix was controlled by pH of the swelling medium. At specific concentration of cross linking agent, the graphical and statistical analysis results also showed that the swelling mechanism of the gel system was an exponential function of the pH of the swelling medium [22]. However, the concentration of cross linking agent may affect the swelling behavior of hydrogel systems. Therefore, for studying the effect of concentration of cross linking agent, ternary systems composed of acrylic acid, vinyl acetate and

methacrylate (AA/VA/MA) were synthesized under different concentrations of ethylene glycol dimethacrylate (EGDMA) as a cross linking agent in the present work.

## Results and Discussion

### *Gelation Contents and Swelling of Gel*

To find the gelation content of the terpolymeric hydrogel the following relation was used:

$$\text{Gelation content (\%)} = (w_d / w_i) \times 100 \quad (1)$$

where  $w_d$  is the weight of the washed and dried hydrogel and  $w_i$  is the initial weight of the hydrogel without washing with deionized water. The gelation contents were found to vary from 74 to 83%. This indicates that the degree of gelation depends on the process conditions as well as the amount of the cross linking agent used. On the other hand, it indicates that the unreacted materials or non-crosslinked parts of the hydrogels were varied from 26 to 17% respectively. The variation in the gelation contents of hydrogels may also be affected by the rate of change in temperature as well as the time given to the polymerization process at specific temperatures. However, in the present case it is expected that the gelation contents of the synthesized hydrogels are affected due to the change in the concentration of the cross linking agent as the rate of change in temperature has been controlled by equal intervals of time during the whole process of synthesis. The literature also indicates that the addition of EGDMA content may increase the crosslink density in hydrogels and the increased crosslink density may result in higher polymerization and more stabilization of hydrogel systems [23-25]. It has been indicated by CHEN and GUAN [24] that the degree of polymerization increases with the increase in the concentration of cross-linkers. It is also indicated that multi-armed cross-linkers may enhance the cross-linking density of the gel. Being a tetra-functional cross-linking agent, EGDMA has been widely used as a cross-linking agent due to its multiple functional tendencies [25], and it may also increase the percentage gelation of hydrogel systems [24]. Literature also indicates that the amount of EGDMA may affect the particle size of copolymers and higher amount of EGDMA results in bigger particle size of copolymer hydrogel systems [26].

In the present work, it has been observed that the sample having a relatively high amount of

EGDMA shows greater milky appearance and lower transparency, a situation which may be attributed to the light scattering phenomena. The higher percentage of EGDMA may facilitate the greater amount of monomers in the gel system, thus increasing the particle size of the ternary copolymer. This larger size of the molecule may be responsible for greater light scattering and thus milky appearance in the system. Moreover, the increase of percentage gelation and cross-linking density with the increase in cross-linking agent in MA-VA-AA hydrogel system can be explained by the chain transfer agent properties of EGDMA and formation of intermolecular cross-links during the cross-linking of the system.

#### Swelling Behavior of Hydrogel Systems

During washing, some reversible changes were observed in the hydrogels. Before washing, the hydrogels were almost transparent and after washing the gels turned milky as shown in Fig.1 (a) and (b) respectively. The milky appearance after washing, can be expected due to the formation of hydrogen bonding between water molecules and hydrophilic parts of the polymeric gels [22]. This hydrogen bonding may have constructed a hydration shell around the hydrophobic parts of the hydrogels which gave a milky appearance to the discs [27]. The glassy state of the gels again appeared on drying. The equilibrium degree of swelling was found after about 25 hrs of swelling of the gel in the buffer solution of pH 8.0.



Fig. 1 (a): The gel disc before washing in distilled water.



Fig. 1 (b): The gel disc after washing in distilled water.

#### Dynamic and Equilibrium Swelling

The swelling behavior of hydrogel systems is an important factor to understand the diffusion mechanisms regarding site-specific drug delivery applications. To normalize the swelling data, the dynamic and equilibrium swelling values were determined gravimetrically using pH of 8.0 of the swelling media at 37°C. The normalized degree of swelling,  $Q_t$  was calculated:

$$Q_t = \frac{w_s - w_d}{w_d} = \frac{w_t}{w_d} \quad (2)$$

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 shows 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:

$$Q_e = \frac{w_\infty - w_d}{w_d} = \frac{w_e}{w_d} \quad (3)$$

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,  $Q_e$  may be defined as the ratio of water amount transported into the gel matrix at time  $t_\infty$  to the initial weight of the gel sample at time  $t_0$ .

*Morphology*

The morphology of the tercopolymer hydrogel system was studied by SEM as shown in Figs. 2 (a and b). By comparison with the morphologies of the dry gel and swollen gel, the hydrogel system shows two different features regarding the degree of porosity. Before swelling, it is observed that the dried gel shows some sort of macro pores indicating the surface morphology with higher swelling capacity of the hydrogel system as shown in Fig. 2(a). The morphology of the gel swollen at equilibrium degree of swelling in the buffer solution of pH 8 is shown in Fig. 2 (b). At equilibrium degree of swelling of the gel, lesser degree of porosity is seen and the macro pores have been changed into very thin micro pores due to almost complete swelling of the gel penetration of water at 37 °C.

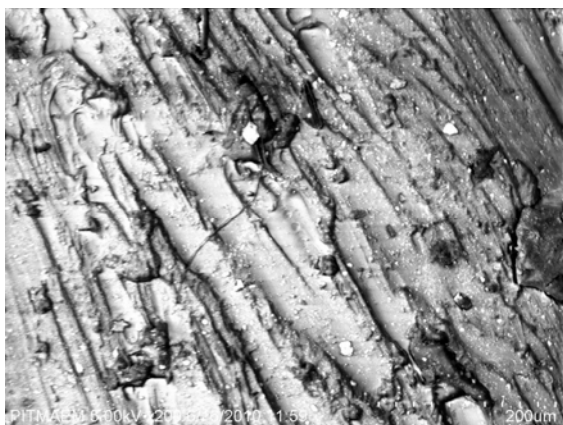


Fig. 2(a): SEM micrograph of the gel before swelling.

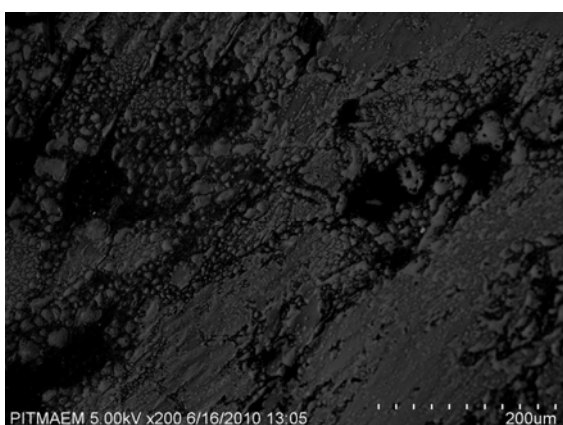


Fig. 2 (b): SEM micrograph of the gel at equilibrium swelling.

*Swelling Mechanism and Kinetics*

The mechanism of swelling of hydrogels may depend on concentration of cross linking agent, pH of swelling media, temperature as well as the nature and composition of reactants involved in the preparation of polymeric hydrogel systems. At different concentrations of cross linking agent (EGDMA), the swelling curves are shown in Fig. 3. Using the values of the normalized degree of swelling at any time  $t$  ( $Q_t$ ) and the normalized equilibrium degree of swelling at  $t_e$  ( $Q_e$ ), it is possible to analyze the kinetic order of the swelling process [28]. For first order kinetics the following equation may be used:

$$\frac{Q_t}{Q_e} = 1 - e^{-kt}$$

or

$$[\ln(Q_e - Q_t / Q_e)] = e^{-kt} \quad (4)$$

For first-order kinetics, a plot of  $[\ln(Q_e - Q_t / Q_e)] = e^{-kt}$  vs  $t$  should be linear with a slope of  $-k$ . However, for second-order kinetics [29] the following equation can be used:

$$\frac{t}{Q_t} = \frac{1}{kQ_e^2} + \frac{t}{Q_e} \quad (5)$$

For second-order kinetics, a plot of  $\frac{t}{Q_t}$  vs  $t$  should be linear with a slope of  $\frac{1}{Q_e}$  and an intercept of  $\frac{1}{kQ_e^2}$ . The Eqs. (4) and (5) were used to analyze the order of the swelling process as shown in Fig. 4 (a) and (b) respectively. By comparing the fits of first-order kinetic (Fig. 4 (a)) and second-order kinetic (Fig. 4 (b)) models to the experimental data, it was observed that the second order model describes the swelling behavior better than the first-order kinetic model.

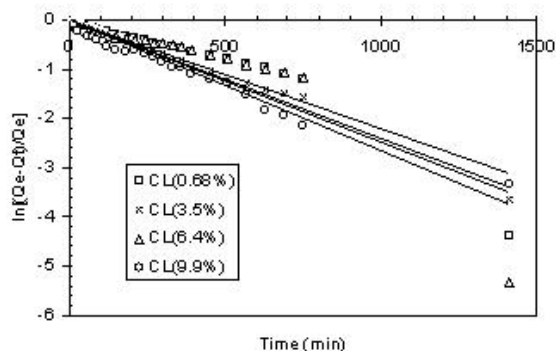


Fig. 4 (a): Plot for first-order kinetics.

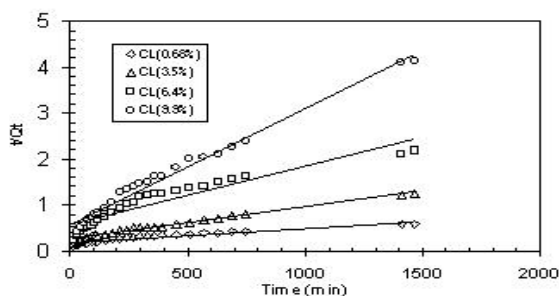


Fig. 4 (b): Plot for second-order kinetics.

Swelling Parameters

The diffusion of water molecules into polymer hydrogel systems and the relaxation of polymer chains in response to the contacted buffer are significant factors for swelling controlled drug delivery applications. Using different concentrations of cross linking agent (EGDMA), the swelling curves (Fig. 3) show the decrease in water penetration capacity with increase in concentrations of the cross linking agent is increased. In order to illustrate the swelling mechanism for water penetration, the following semi empirical relation may be used [30,31]:

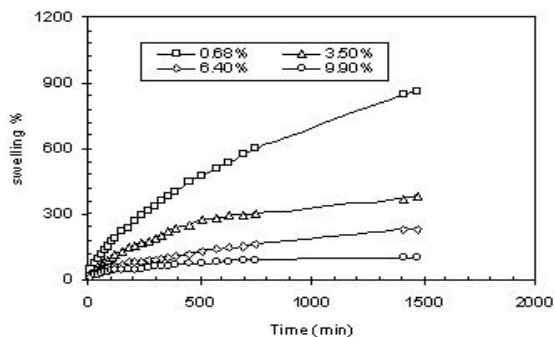


Fig. 3: Effect of time on swelling (%) of gel with different concentrations of cross linker.

$$\frac{w_t}{w_e} = kt^n \tag{6}$$

where  $w_t$  is the amount of water penetrated into the gel at time  $t$ ,  $w_e$  is the amount of water absorbed at swelling equilibrium,  $k$  is the front factor related to the structure of the polymeric network,  $n$  is the diffusion exponent which can indicate the mechanism of swelling phenomena. The value of  $n$  may vary from 0 to 1.0. For Fickian kinetics,  $n=0.5$  the swelling is generally known as diffusion controlled, where the rate of water penetration is the slowest and hence is the rate determining step. When the water

penetration velocity and the chain relaxation or chain stretching rates are comparable,  $n$  is generally found between 0.5 and 1.0 and the kinetics are generally known as non-Fickian, which is generally concerned with ionization of some functional groups present in the gel network. When the water penetration rate is much higher than the chain relaxation rate then the penetration of water is proportional to the time, i.e.,  $n=1.0$ .

To determine the values of diffusion exponent ( $n$ ) and front factor ( $k$ ), the experimental data were analyzed using Eq. (6) as shown in Fig. 5. From the slopes and intercepts of the straight lines, the values of diffusion exponent ( $n$ ) and swelling rate constant or front factor ( $k$ ) were calculated and are given in Table-2. The results show that during swelling, the gel having relatively low concentration of EGDMA indicates higher values of diffusion exponent ( $n$ ) and swelling rate constant ( $k$ ). It is interesting to note that when the concentration of the cross linking agent is increased from 0.68 to 9.9%, the values of diffusion exponent ( $n$ ) decrease as well as the values of swelling rate constant ( $k$ ) decrease in a similar manner as shown in Table-2. This situation may be attributed to the fact that the diffusion exponent is function of swelling rate constant and the swelling conditions. According to the results, it has been found that the gel shows a good cross linker concentration-dependent swelling behavior with transition from non-Fickian ( $n=0.6507$ ) to Fickian ( $n=0.473$ ) as the concentration of the cross linking agent changes from 0.68 to 9.9% at 37°C. The present results are supported by the literature [23] that the amount of EGDMA content can increase the crosslink density in hydrogel systems and the higher crosslink density may result in more stabilization of the gel network. During the swelling process, it was also observed that the discs having relatively low concentration of EGDMA were de-shaped at their boundaries, which could be attributed to the faster rate of swelling at boundaries than in the middle portion.

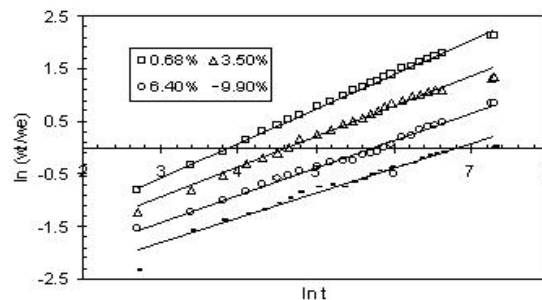


Fig. 5: Plot between  $\ln t$  and  $\ln(w_t/w_e)$  to find swelling kinetic parameters.

To determine the cross linker concentration 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 concentration of the cross linking agent on the diffusion coefficient is found to be promising with a coefficient of determination of 0.9808 as shown in Fig. 6. Graphical and statistical analysis of diffusion exponents show that the diffusion mechanism for water penetration into the gel system is controlled by the concentration of the cross linker agent, following an exponential relation:

$$n = n_o e^{C_L C_c} \quad (7)$$

where  $n$  is diffusion exponent,  $n_o$  is pre-exponential factor,  $C_L$  is cross linker concentration sensitivity coefficient of the gel. The pre-exponential factor and cross linker concentration sensitivity coefficient can provide some useful information about the swelling process depending on the nature and type of hydrogel systems as well as on the swelling conditions. The pre-exponential factor indicates the swelling mechanism of the gel under highly low cross linking density (without cross linker) of the hydrogel system, whereas the cross linker concentration sensitivity coefficient stands for the swelling capacity and thus the change in the swelling mechanism of the gel with changing concentration of the cross linking agent. Thus, using the values of  $n_o$  and  $C_L$  from the intercept and the slope of Fig. 6 respectively, the Eq. (7) can be written as:

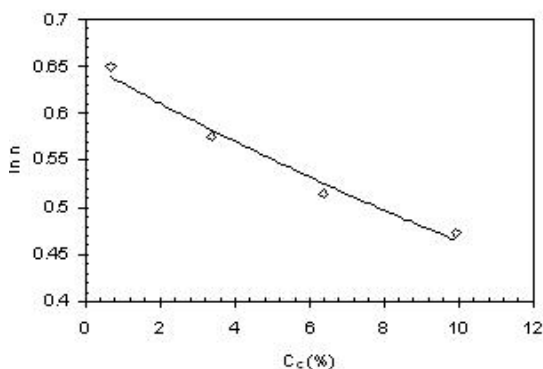


Fig. 6: Plot between the concentrations of cross linker and diffusion exponent.

$$n = 0.6548 e^{-0.0345 C_L} \quad (8)$$

To understand the diffusion mechanism of diffusing solvent into the gel matrix, the suggested exponential relation may be applied for any concentration of the cross linking agent used for the synthesis of the hydrogel system. For the applicability of the suggested equation, it is necessary to check the agreement between the experimental diffusion exponent values and those of the values calculated by using the above equation.

To test the agreement between the experimental diffusion exponent and the values calculated from the suggested exponential relation, the graph of  $n_{exp}$  versus  $n_{cal}$  was plotted as shown in Fig. 7. It is observed that the agreement between the experimental and calculated values is good with correlation coefficient of 0.9837, coefficient of determination of 0.9677 and standard error of estimate of 0.01697. The data points in the scatter diagram indicate a positive tendency to cluster around the regression line, which can be attributed to the fact that there is a good relationship between the variables. The value of the standard deviation of regression or standard error of estimate of  $n_{cal}$  on  $n_{exp}$  shows that the degree of scatter of the observed values about the regression line is not significant.

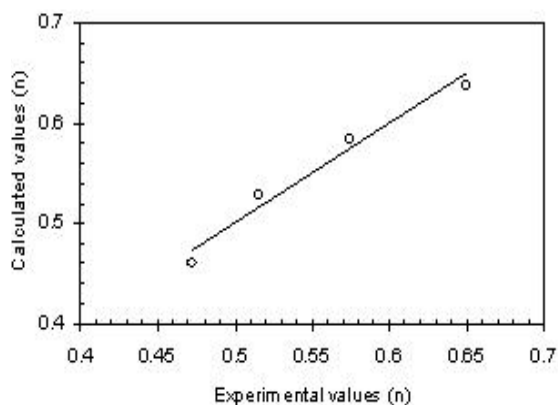


Fig. 7: Agreement between experimental and calculated diffusion exponents.

For further testing the applicability of the suggested relation, the relative mean square of errors may also be analyzed statistically. Using the statistical analysis for the experimental as well as calculated data, a relative mean square of errors of 0.021881 was calculated by Eq. (9):

$$ER = \left[ \frac{1}{N} \sum_{i=1}^N \frac{(n_{cal} - n_{exp})^2}{(n_{cal})^2} \right]^{1/2} \quad (9)$$

The value of relative mean square of errors indicates that, in such probabilistic models, such a value of the random errors is not significant.

### Experimental

#### Materials

The monomers used were vinyl acetate (VA), methyl acrylate (MA) and acrylic acid (AA). 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 purities and other details of the chemicals used are given in Table-1, 2.

#### Preparation of the Terpolymeric Hydrogel

The equal volumes of the three monomers (AA/VA/MA) were mixed to make a solution taking 2 mL of each component. Different concentrations of EGDMA (0.68%, 3.5%, 6.4%, 9.9% mol%) were added into the samples. The benzoyl peroxide was added to the every solution as an initiator with the concentration of 1% (w/v). Monomer solutions thus prepared were placed into the capped glass tubes of 1 cm internal diameter. The terpolymeric gels were synthesized through radical polymerization. Ethanol was used as solvent with its proportion of 100% (v/v) to the total volume of monomers used. The oxygen above the solution in the tubes was removed with dissolved nitrogen and the capped tubes were placed in the water bath. The polymerization was carried out at slow heating rate to ensure the uniform formation and to prevent the polymeric cylinder to break. The temperature of 30°C was maintained for 1 hour. Then the temperature of the polymer was increased by 5 °C

after 1 hour regularly until the final temperature of 65 °C was attained. At the temperature of 68 °C, the polymeric column began to build up and ultimately, the synthesis was completed within 3 hours at 68 °C as shown in Fig. 8. The smooth polymeric cylinders were removed from the tubes and left overnight for cooling at room temperature. Hydrogels obtained in long cylindrical shapes were cut into pieces of 3-4 mm thickness and stored for later evaluation.

#### Gelatin Content

For finding the gelation content, the gel discs were weighed and immersed in deionized water for 24 hrs to remove the unreacted material or non-crosslinked parts of the hydrogel. After washing properly with deionized water all the discs were dried in a vacuum oven at 40°C for 30 hrs until the weight of the disc was constant.

#### Swelling Study of Gel

For swelling experiments, the buffer solutions of pH 8 were 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. The swelling experiments were carried out in 100 ml of buffer solutions at 37°C. Swollen gels were removed from the buffer solutions at regular intervals, were dried superficially with filter paper, weighed and placed in the same bath. The measurements were continued until a constant weight was reached for each sample. A number of swelling experiments were carried out using various hydrogels synthesized with different concentrations of EGDMA (0.68%, 3.5%, 6.4%, 9.9% mol%).

Table-1: Swelling kinetic parameters for different concentrations of cross linker at 37 °C.

Cross Linking Agent Concentration (%)	Diffusion Exponent(n)	Swelling Constant or Front Factor (k) Sec <sup>-1</sup>	Coefficient of Determination (R <sup>2</sup> )
0.68	0.6507	0.081033	0.9884
3.37	0.575	0.069439	0.9875
6.4	0.515	0.051457	0.9935
9.9	0.473	0.039305	0.9636

Table-2: The purities and the details of the chemicals used in the synthesis and swelling kinetics.

Sr.No.	Name of Chemical	Chemical formula	Mol. Wt.	% Purity	Company
1	Methyl Acrylate	CH <sub>2</sub> CHCOOCH <sub>3</sub>	86.09	99	MERCK
2	Vinyl acetate	CH <sub>2</sub> CHOCOCH <sub>3</sub>	86.09	99	Fluka
3	Acrylic acid	CH <sub>2</sub> CHCOOH	72.06	99	Fluka
4	Ethylene Glycol dimethacrylate	CH <sub>2</sub> =C(CH <sub>3</sub> )C(O)OCH <sub>2</sub> -CH <sub>2</sub> OC(O)C(CH <sub>3</sub> )=CH <sub>2</sub>	198.22	100	Fluka
5	Acetic acid	CH <sub>3</sub> COOH	60	100	MERCK
6	Disodium hydrogen phosphate	Na <sub>2</sub> HPO <sub>4</sub>	177.99	100	Riedal-De Haën
7	Citric acid	C <sub>6</sub> H <sub>8</sub> O <sub>7</sub>	210.14	100	MERCK
8	Trisodium citrate	C <sub>6</sub> H <sub>5</sub> Na <sub>3</sub> O <sub>7</sub> ·2H <sub>2</sub> O	294.10	Extra pure	MERCK
9	Hydrochloric acid	HCl	36.5	37	MERCK

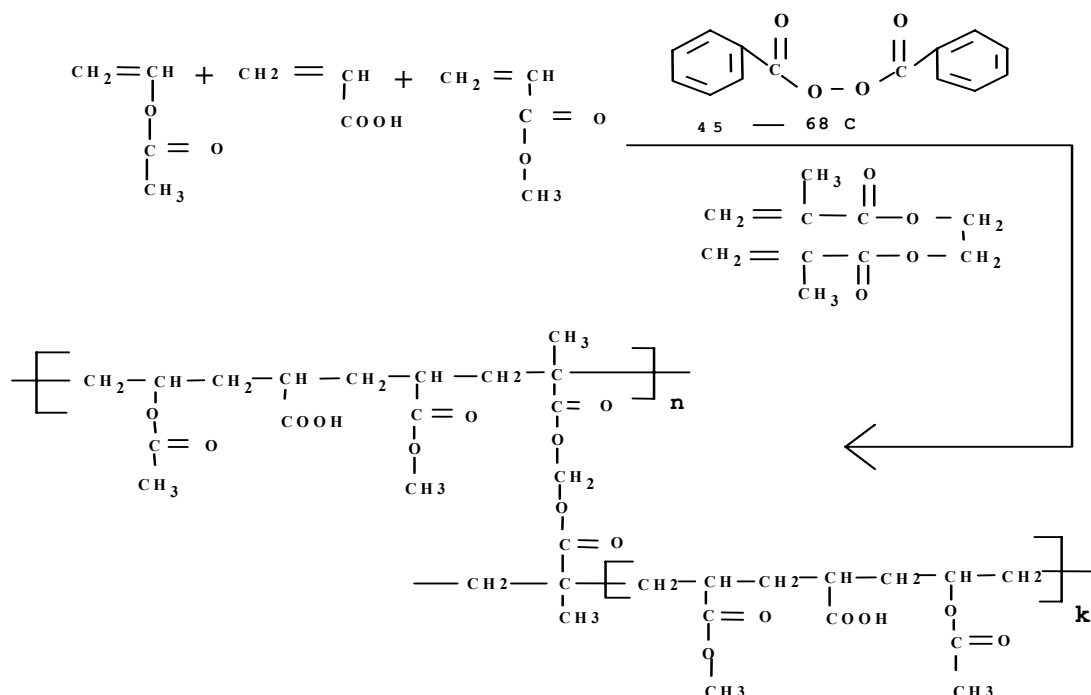


Fig. 8: Expected reaction between methyl acrylate vinyl acetate and acrylic acid using benzoyl peroxide as an initiator in the presence of ethylene glycol dimethacrylate (EGDMA) as cross linking agent.

## Conclusions

Using acrylic acid (AA), vinyl acetate (VA) and methyl acrylate (MA), a cross linker concentration sensitive terpolymeric hydrogel was synthesized. The swelling studies is found that the hydrogel shows a good cross linker concentration-dependent swelling behavior with transition from non-Fickian ( $n=0.6507$ ) to Fickian ( $n=0.473$ ) as the concentration of the cross linking agent changes from 0.68 to 9.9% at 37°C. At higher concentration of the cross linking agent, the swelling behavior of AA-VA-MA hydrogel indicates the presence of unionized carboxylic groups in the hydrogel matrix. However, at lower concentration of the cross linking agent, 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 hydrogel net work.

Analysis of the resultant diffusion exponent data by graphical and statistical methods shows that the diffusion mechanism of water penetration into hydrogel is a function of cross linker concentration, following the exponential relation. The applicability of the suggested relation shows that the agreement between the experimental and calculated values is

good with correlation coefficient of 0.9837, coefficient of determination of 0.9677 and standard error of estimate of 0.01697. In the light of the presented results, it shows that this type of hydrogels may be considered for drug delivery applications in the starting part of small intestine where pH is alkaline due to the inclusion of bile in the intestinal juice.

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