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S. K. Bajpai[a]; Surinderpal Singh Saggu[a]
[a] Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College, Jabalpur (M.P.), India

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Water Uptake Behavior of Poly(methacrylamide-co-N-vinyl-2-pyrrolidone-co-itaconic acid) as pH-Sensitive Hydrogels: Part I

S.K. BAJPAI AND SURINDERPAL SINGH SAGGU

Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College, Jabalpur (M.P.), India

Novel hydrogels composed of the three monomers N-vinyl-2-pyrrolidone, methacrylamide and itaconic acid, have been prepared by free radical aqueous polymerization. The gels demonstrated a sharp pH-dependent swelling. The gel, when transferred from artificial gastric fluid (SGF,pH1.2) to simulated intestinal fluid (SIF, pH 7.4), underwent a sharp swelling transition from 45 ± 4 to 327 ± 12 percent within an hour. The hydrogels also exhibited swelling-deswelling cycles, within a response time of nearly one hour, while maintaining structural integrity. The increase in monomer acid concentration caused an enhancement in water uptake in SIF while the swelling was observed to decrease in SGF with acid content. For an optimum initiator concentration 0.22 mM, the synthesized gel showed the highest water uptake. On increasing the diameter from 0.21 to 0.92 cm, the initial rate of water uptake decreased from 2.50 to 1.15 percent per minute. The Tanaka-Fillmore theory was also verified. The activation energy for the swelling of the sample with 7.54 percent mole fraction of itaconic acid was found to be 19.74 kJmol^{-1}.

Keywords swelling, pH-sensitive, hydrogel, itaconic acid

Introduction

During the last couple of decades tremendous work has been done on different types of polymeric hydrogels. One of these systems is polyelectrolyte polymers which contain relatively ionizable groups at levels ranging from a few mol to 100% of the repeating unit (1–3). Polyelectrolytes may be anionic, cationic or amphillic, and may be synthetic or naturally occurring. These hydrogels undergo controllable volume changes in response to small variations in solution conditions, such as pH, ionic strength, electrical signals, etc. (4–6). These materials are of great importance due to their promising applications in areas such as controllable delivery of medicinal drugs (7–9), artificial muscles (10), sensor systems (11), bioseparations (12), metal ion removal (13), etc.

Application of these hydrogels in gastro-intestinal drug delivery is based on the fact that the pH of the gastric fluid is nearly 1–2, while it becomes nearly 7–8 in the intestine

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Address correspondence to S.K. Bajpai, Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College, Jabalpur (M.P.) 482001, India. E-mail: mnlbpi@rediffmail.com

or colon. As these hydrogels undergo different swelling behavior at these two extreme pH values, they are exploited for delivery of loaded bioactive ingredients at the desired site through swelling-dependent mechanism. The possibility of using a pH-sensitive hydrogel for site-specific delivery depends upon its ability as to how quickly it will swell when transferred from highly acidic gastric fluid to almost neutral intestinal fluid and the extent to which it shall undergo volume change. In this context, the present work describes the water uptake behavior of a novel terpolymeric system, composed of N-vinyl-2-pyrrolidone (NVP), methacrylamide and diprotic itaconic acid in simulating gastric as well as intestinal fluid at physiological temperature. A thorough survey of the literature available reveals that no study has been carried out so for on a ter-polymeric system involving above mentioned monomers. The water soluble methacrylamide monomer, whose hydroxypropyl derivatives is bio-compatible and non-immunogenic (14), has been frequently used to synthesize polymer-drug conjugates for drug-delivery (15, 16). Since methacrylamide is relatively hydrophobic, its combination with the hydrophilic, non-toxic and biocompatible monomer N-vinyl-2-pyrrolidone (16) and with the ionic monomer itaconic acid can result in formation of hydrogel networks with excellent pH-sensitive swelling behavior. In this study, a detailed investigation of water uptake analysis of the proposed hydrogel system has been carried out. However, it is proposed to carry out a detailed investigation of biocompatibility and drug releasing capacity of this hydrogel system in the next part.

Experimental

Materials

The monomers methacrylamide (MAAm) and N-vinyl-2-pyrrolidone (NVP) were obtained from E. Merck (Mumbai, India). Itaconic acid (IA), potassium persulfate (KPS) initiator, N,N′-methylene bisacrylamide (MB) and the catalyst tetramethyl ethylenediamine (TEMED) were obtained from HiMedia (Mumbai, India). The monomer methacrylamide was recrystallized in methanol to remove the inhibitor. Double distilled water was used throughout the investigations.

Synthesis of Terpolymeric Hydrogels

The cylindrical hydrogels were prepared by free-radical (KPS) initiated polymerization of the monomers MAAm, NVP and IA in aqueous media, in the presence of MB crosslinker. In brief, 22.40 mM of NVP, 8.21 mM of MAAm and 2.32 mM of IA were dissolved in distilled water. A pre-calculated amount of crosslinker (MB) was added and the total volume of the reaction mixture was diluted to 5 ml. Finally, 0.07 mM of the initiator KPS and 0.86 mM of catalyst TEMED were added and the solution was poured into PVC straws, each of a diameter of 5.30 mM, and kept in an electric oven (Tempstar, India) at 60°C for a period of 4 h. After the polymerization was over, the resultant opaque gels were cut into small pieces, each 2.54 ± 0.02 cm in length equilibrated with distilled water to remove the unreacted chemicals and then dried in a dust free chamber until the gels attained constant weight. The length, diameter and mass of dry samples were found to be 17.6 ± 0.4 mM, 4.27 ± 0.02 mM and 0.142 ± 0.01 g, respectively.

First, it is worth mentioning that before synthesizing the hydrogels for final studies, we synthesized a number of gels, taking varying amounts of the three monomers and crosslinker. The percent gelation, as determined by mass measurements (17), helped us

to finally select the range of monomer concentrations yielding almost complete gelation (98 $\pm$ 1.6 percent).

The hydrogel samples are denoted as HG(X), where the number in parenthesis denotes the percent mole fraction of itaconic acid with respect to total monomer concentration. For example, the sample, synthesized above will be designated as HG (7.54).

FTIR Spectra Analysis

FTIR spectra of the polymer samples was recorded on Bio Rad WIN FTIR spectrometer (BioRad, Hercules, CA) using KBR pellets.

Water Uptake Studies

A completely dried and pre-weighed hydrogel sample was placed in 500 ml of buffer solution of desired pH at 37°C. The swollen gel was taken out at different 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 gels attained constant weight. The percent water uptake (S_M) was determined using the following expression (18).

$$\%S_M = \frac{M_t - M_o}{M_o} \times 100 \tag{1}$$

where M_t and M_o are the initial mass and mass at different time-intervals, respectively. All the measurements were made with five samples and average values have been reported in the data.

Results and Discussion

FTIR Analysis

The FTIR spectra of the polymer sample is shown in Figure 1. The spectra clearly marks the presence of N-vinyl pyrrolidone and itaconic acid residues, as evident from a broad band appeared at 3220–3600 cm^{-1} (due to H-bonded hydroxyls), methylene group at 2935 cm^{-1} (due to asymmetric stretching i.e., υ_{as} CH_2) and 1663 cm^{-1}(due to asymmetrical stretching of $-COO^-$) and 1428 cm^{-1} (due to symmetrical stretching of $-COO^-$). The spectrum also shows a band of N-H wagging, which appears at 664 cm^{-1}.

Network and Swelling Parameters

The swelling characteristics of a network polymer depends upon the extent of crosslinking. One of the important structural parameters characterizing crosslinked polymer is M_c, the average molar mass between crosslinks, which is directly related to the crosslink density. From the data obtained with swelling experiments, the molar mass M_c between the crosslinks of hydrogels was calculated using the Flory–Rehner equation (19), according to the following simplified form:

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

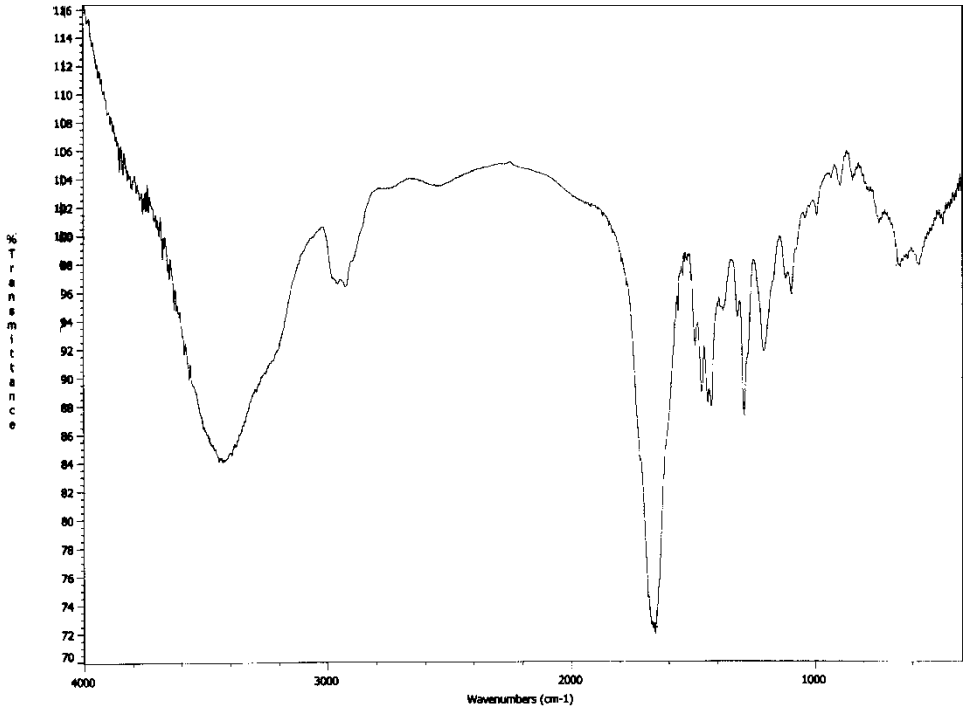

Figure 1. FTIR spectrum of the hydrogel sample.

The volume fraction ϕ of the swollen polymer was calculated using:

$$\phi = \left[1 + \frac{d_p}{d_s}\left(\frac{M_a}{M_b}\right) - \frac{d_p}{d_s}\right]^{-1} \tag{3}$$

In the equations above, d_p and d_s represent the densities of polymer and solvent, M_b and M_a are the mass of the polymer before and after swelling; V_s is the molar volume of solvent used and χ is the Flory–Huggins interaction parameter between solvent and polymer, which was calculated by a reported method (20).

The crosslink density q was calculated as:

$$q = \frac{M_o}{M_c} \tag{4}$$

where M_o is the molar mass of the repeating unit given as:

$$M_o = \frac{m_{vp}M_{vp} + m_{mAAm}M_{mAAm} + m_{IA}M_{IA}}{m_{vp} + m_{mAAm} + m_{IA}} \tag{5}$$

In the equation, m_{vp}, m_{MAAm} and m_{IA} are the mass of VP, MAAm and IA monomers (g) and M_{vp}, M_{MAAm} and M_{IA} are their molar masses, respectively.

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

$$V_e = \frac{d_p N_A}{M_c} \tag{6}$$

where N_A is the Avogadro number.

In addition to the above mentioned structural parameters, the swelling exponent 'n' and gel characteristic constant 'k' were evaluated using Equation (7) (21):

$$\frac{M_t}{M_\infty} = kt^n \tag{7}$$

In order to evaluate these parameters, we synthesized two hydrogel samples, with crosslinker concentrations 12.90×10^{-2} and 32.40×10^{-2} mM in the feed mixture, and studied their water uptake behavior in the phosphate buffer of pH 7.4. It is clear from Figure 2 that the samples prepared with 12.90×10^{-2} and 32.40×10^{-2} mM crosslinker demonstrate water uptake of nearly 1090 ± 21 and 410 ± 11 percent, respectively. This difference may be attributed to the fact that the more crosslinked structure has less free space available for accommodation of solvent molecules. Moreover, due to higher degree of crosslinking, the macromolecular chains undergo relaxation to a less extent, discouraging solvent entrance into the network. Table 1 describes various network and swelling parameters that have been evaluated from the water uptake data displayed in Figure 2. It is clear that the sample prepared with 12.90×10^{-2} mM of MB has a swelling exponent of $n = 0.96$, indicating an anomalous or case II transport. The latter may be attributed to the fact that due to the presence of a fewer number of crosslinks within the swelling network, the chains are sufficiently flexible and undergo appreciable relaxation caused by repulsion among similarly charged $-COO^-$ groups along the polymeric segments at the pH 7.4 of the swelling medium. In this way, the hydrogel sample demonstrates anomalous or totally relaxation controlled swelling. However, the value of n for other samples, being highly crosslinked, is 0.47, which is indicative of the diffusion controlled or Fickian swelling of the polymer. Results of this type are often observed in the case of polyelectrolyte hydrogel networks.

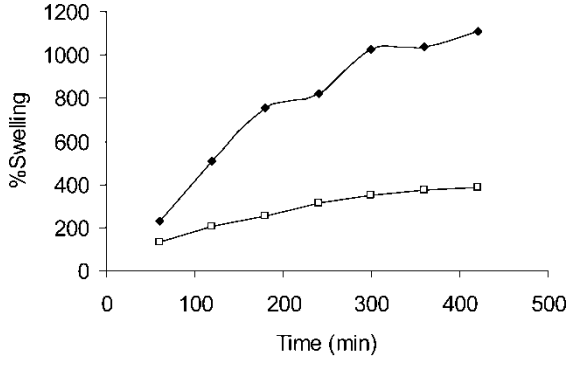

Figure 2. Dynamic uptake of water as a function of time of hydrogel samples HG (7.54) with crosslinking ratio 3.98×10^{-3} (◆) and 9.84×10^{-3} (□) in SIF of pH 7.4 at 37°C.

Table 1
Network and swelling parameters of hydrogel HG (7.54) with varying crosslinking ratios[a]

Sample code	Cross linking ratio[a] $\times 10^3$	Average molar mass between crosslinks $M_c \times 10^{-3}$	Crosslink density $q \times 10^2$	Elastically effective chains $V_e \times 10^{-20}$	Swelling exponent n	Gel characteristic constant $k \times 10^2$
32.4×10^{-2} HG (7.54)	9.84	1.9952	5.81	2.84	0.47	5.1
$12.9x \times 10^{-2}$	3.98	18.8995	0.56	0.36	0.98	3.9

[a]Crosslinking ratio = number of moles of crosslinker/no. of moles of monomer.

Effect of pH on Equilibrium Water Uptake

If the polyelectrolyte hydrogels contain functional groups which can be protonated or ionized (22–23) at a suitable pH, then variation in the pH of the swelling medium causes an appreciable volume phase transition which also forms the basis for the swelling dependent pH-sensitive drug delivery system. The effect of pH on the equilibrium water uptake was investigated for hydrogel samples HG (7.54) and HG (3.01), in the swelling media of varying pH (1–8) and with ionic strength maintained at 0.1M at 37°C. The results, as depicted in Figure 3 clearly indicate that equilibrium water uptake of the two hydrogel samples increases with the pH of the swelling media. The observed findings may be explained on the basis of the fact that as the two pk_a values for itaconic acid are 3.85 and 5.44, respectively (24). The carboxylic acid groups remain almost un-ionized up to pH4.0. With an increase in pH beyond 4.0, the ionization of the first carboxylic acid groups begin, thus producing similarly charged $-COO^-$ groups along the macromolecular chains. With further increase in pH, the other carboxylic groups also ionize thus enhancing the chain relaxation as well as osmotic swelling pressure of the hydrogel system. However after pH 7.0, the two samples approach optimum swelling.

A close look at Figure 3 reveals some interesting facts. For example, the sample HG(3.01) demonstrates relatively higher water uptake than sample HG (7.54), in the pH range 1.0 to 4.0. As mentioned above, the carboxylic acid groups remain almost unionized within the two polymer matrices below pH 4.0. Moreover, these groups provide a compact structure to the hydrogels through H-bonding interactions as has been discussed in detail in our previous work (1). Therefore, as the sample HG (7.54) contains a higher concentration of itaconic acid units, it possesses a greater number of H-bonding interactions within the network, and hence, shows minimum swelling (i.e., nearly 21%). On the other hand, the sample with lower acid content, namely HG (3.01) demonstrates nearly 135 ± 07 percent water uptake.

The shape of the inflation demonstrated by the two samples, in the pH range 4.0 to 7.0, are also quite different. The sample HG (7.54) yields a single step 'S' shaped curve, while the other sample HG (3.01) shows a two-step rise in the water uptake in the above mentioned pH range. This interesting behavior has not been noticed so far and it deserves proper explanation. It has been reported (25) that for biprotic acid, whose two

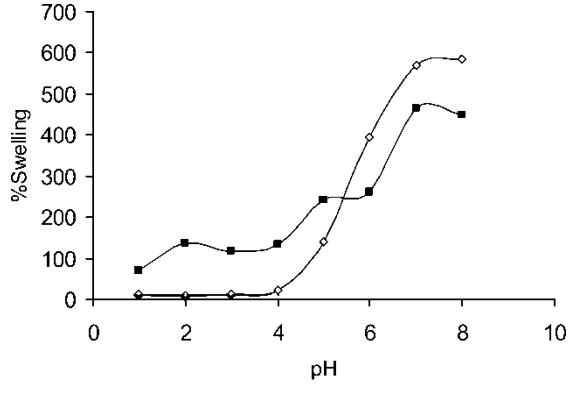

Figure 3. Effect of change in pH of the swelling media on the equilibrium water uptake of the hydrogel samples HG (7.54) (◇) and HG (3.01) (■) at 37°C.

pk_a values do not differ by more than 2 units, the two consecutive swellings usually overlap each other, giving a broad 'S'-shaped curve. As in the present case, the difference between two pk_a values is 1.59, a broad 'S' shaped inflation should have been observed for both the hydrogel samples. However, the occurrence of a two-step inflation for the sample HG (3.01) may possibly be due to the presence of low acid content within the swelling network. Since the number of $-COOH$ groups is relatively smaller, the consecutive enhancements in swelling in the vicinity of two pk_a values(i.e., 3.85 and 5.44) do not overlap each other and hence, result in formation of a 'two-steps' inflation curve. On the other hand, as the sample HG (7.54) contains a higher concentration of carboxylic groups, the two successive swelling-advancements overlap each other as per theoretical predictions.

Swelling in Varying pH Media

The suitability of a pH-sensitive hydrogel for colonic drug delivery is examined by the fact that how quickly the gel expands when transferred from acidic gastric fluid to slightly alkaline environment of a large intestine where it is supposed to deliver the loaded bioactive material. Following the results of gamma scintigraphic-based studies, carried out by Satyanarayan et al. (26), we opted to put hydrogel sample HG (7.54) in the simulated gastric fluid (SGF,pH1.2) for 3 h and then transfer it to artificial intestinal fluid at pH 7.4, studying its water uptake behavior. The results, shown in Figure 4, reveal that the gel exhibits almost negligible swelling (i.e., 45 ± 6 percent) in the first 3 h in acidic medium and it undergoes a drastic increase in its swelling capacity on transferring into SIF of pH 7.4. A close look at Figure 4 also reveals that in the time span of 3 to 6 h, the swelling increases almost in linear fashion, thus indicating a nearly 'zero order' swelling profile. This finding, in the future, may lead as well to a zero-order release profile, which is the most desirable event in the field of drug delivery. It can also be noticed that transition of the hydrogel sample from gastric to intestinal environment results in a nearly 5.6 fold increase in swelling capacity per hour, which is also favorable data for this system to be tested for GI drug delivery. The reasons for the observed increase in the swelling capacity with the change in pH has already been discussed in the previous section.

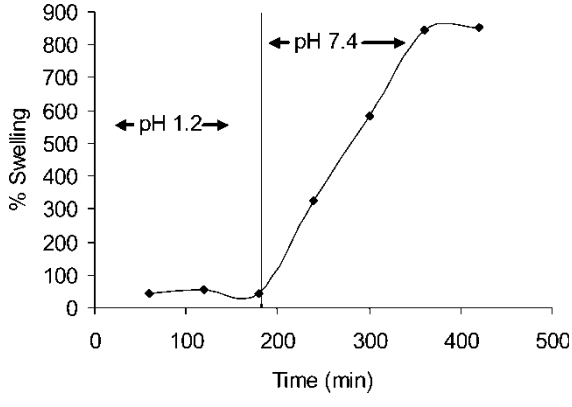

Figure 4. Composite depiction of swelling of hydrogel sample HG (7.54) in the changing pH environment at 37°C.

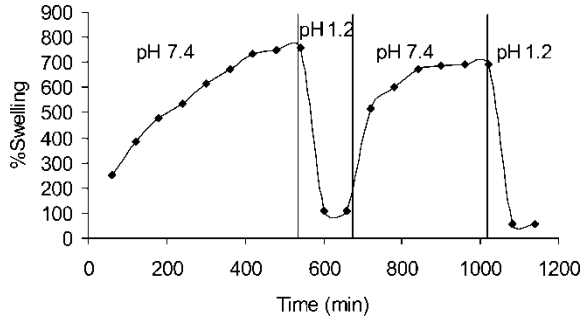

Figure 5. Swelling-deswelling cycles for the hydrogel sample HG (7.54) in the buffer media of pH 7.4 and 1.2 at 37°C.

Finally, Figure 5 depicts the swelling-deswelling cycles for the hydrogel system HG (7.54) at 37°C. The gel demonstrated equilibrium water uptake of nearly 757 ± 16 percent in 6 h in the phosphate buffer of pH 7.4, while it de-swelled to almost 57 ± 7 percent in 1 h in the artificial gastric fluid of pH 1.2. The gel also exhibited similar repeated swelling-deswelling cycles while maintaining structural integrity. The interesting point, to be noted is that it takes nearly 6 h for the hydrogel to swell in phosphate buffer of pH 7.4 while the gel deswells completely in next to one hour when transferred into the artificial gastric fluid of pH 1.2, indicating that the average rate of swelling is very low as compared to the overall de-swelling rate. The faster de-swelling can be attributed to the fact that when the fully swollen gel is put in the acidic medium, the fast moving H^+ ions enter into the swollen network and protonate the charged $-COO^-$ groups, making the gel collapse. One more point to be mentioned here is that after completing one swelling-deswelling cycle when the sample is again put in the SIF of pH 7.4, the gel shows nearly a 7.07 fold increase in the water uptake in 1 hour. It is worthwhile to mention here that while investigating swelling kinetics in the media of varying pH (see Figure 4), the same sample HG (7.54) exhibited nearly 7.21 times swelling in one hour when after staying for 3 h in the gastric fluid of pH 1.2, it was put in the medium of pH 7.4. The main point, to be noted here, is that in Figure 4 the completely dried sample was put for 3 h in SGF of pH 1.2 and then transferred into SIF of pH 7.4 where it swelled to 7.21 times in one hour. On the other hand, in Figure 5, after the sample goes through one complete swelling-deswelling cycle and is put in the SIF of pH 7.4 it swells to nearly 7.07 times in one hour. This close agreement indicates that structural changes during the swelling-deswelling cycle are totally reversible and water uptake values are reproducible.

Effect of IA Content on Swelling

The variation in the amount of itaconic acid present in the polymer network may vary charge density along the macromolecular networks, affecting the chain relaxation process and the swelling capacity of hydrogels. In order to investigate this, we synthesized a number of samples with varying acid content, in the range 0.92 to 3.20 mM and determined their equilibrium water uptake in the simulating gastric fluid of pH 1.2 and in SIF of pH 7.4 at 37°C. The results, as shown in Figure 6, reveal some interesting observations. In the medium of pH 7.4, the equilibrium water uptake increases with an increase in itaconic acid content up to 2.30 mM and then it decreases slightly. This may be explained on the

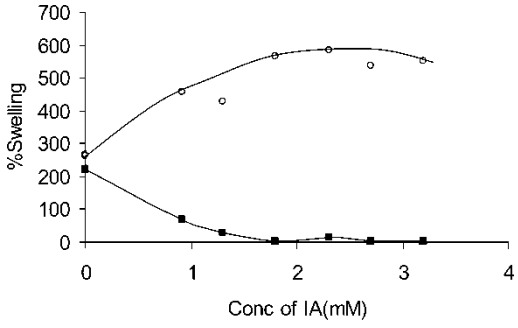

Figure 6. Effect of concentration of itaconic acid in the hydrogel on its equilibrium water uptake in the buffer media of pH 1.2 (■) and pH 7.4 (○) at 37°C.

basis of the fact that initially the increase in acid content causes an increase in the number of −COOH groups along the macromolecular chains. At the pH 7.4 of the invading solvent these groups ionize to yield similarly charged $-COO^-$ groups, causing the polymeric chains to relax due to mutual electrostatic repulsion. As a result, the water uptake value increases. However, a slight decrease in water uptake beyond 2.30 mM concentration of IA may probably be due to the predominant role of unionized itaconic acid within the network. Since IA is a weak acid, a further increase in its concentration beyond 2.30 mM might have increased the number of undissociated carboxylic acid groups within the network, and these groups may bind to the $-CONH_2$ groups of methacrylamide units via H-bonding interactions. This may restrict further relaxation of the polymeric segments and cause a slight decrease in water uptake.

However, in the SIF of pH 1.2, a continuous decrease in the equilibrium water uptake with IA content was observed. The observed decrease may be attributed to the fact that at pH 1.2, the −COOH groups present along the macromolecular chains remain almost in unionized form as pH value of the swelling medium is below the pk_a values of the two carboxylic groups. This imparts non-ionic type character to the gel. In other words, the gels behave as if they were composed of non-ionic constituents. The mutual interactions of these groups via H-bonding interactions impart compactness to the networks. With the increase in the IA content, the number of H-bonding interactions continue to increase, making the gel structure more and more compact. This may be the reason for almost nil swelling observed for the hydrogels beyond 1.80 mM content of IA. Similar observations have also been reported by us for poly(acrylamide-co-maleic acid) hydrogels (27).

Effect of Diameter of Gels on Swelling

According to Tanaka-Fillmore (28), the thickness of the cylindrical device plays a significant role in governing the swelling rate. We synthesized polymer sample HG (7.54) of varying diameter in the range of 0.21 to 0.92 cm and studied their water uptake behavior in SIF at 37°C. The results, as depicted in Figure 7, indicate that the initial swelling rate increases with a decrease in diameter of the samples. This may be due to the fact that with the increase in diameter, the surface area available per g of polymer sample decreases and as the flux is directly proportional to the surface area for the fixed values of the other dependent variables, the swelling rate (i.e., percent mass swelling

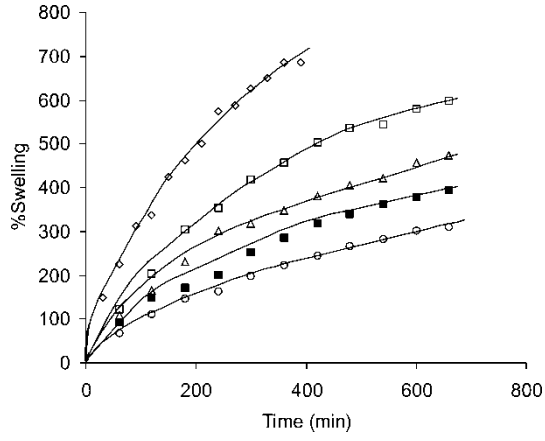

Figure 7. Dynamic uptake of water as a function of time for the hydrogel samples HG (7.54) with varying thickness 2.10 mm (◇), 3.43 mm (□), 5.6 mm (■), 5.92 mm (△) and 9.20 mm (○), in the SIF at 37°C.

per minute) also decreases. Therefore the desired swelling rate (and so probably release rate of encapsulated drug also) can be achieved by picking a device of suitable diameter.

We also evaluated initial and average diffusion coefficients, namely D_i and D_{ave} using the following equations:

$$F = 4\left[\frac{(D_l t/l^2)^{1/2}}{\pi^{1/2}}\right] \tag{8}$$

and

$$D_{av} = \frac{0.049l^2}{t_{1/2}} \tag{9}$$

where l is the diameter of the cylindrical hydrogel and $t_{1/2}$ is the time required for 50% swelling. Table 2 describes values of D_i, D_{ave} and S_{Rate} (i.e., swelling rate) for the various samples studied. Finally, the plot between $t_{1/2}$ values (time required for 50%

Table 2
Initial swelling rate and various diffusion coefficients for the hydrogel samples HG (7.54) having different diameters

Sample code	Diameter of sample(mm)	Initial water uptake rate (% per/minute)	Diffusion coefficient ($cm^2\ min^{-1}$)	
			Initial $D_i \times 10^6$	Average $D_{ave} \times 10^6$
HG (7.54)	2.14	2.50	13.84	17.24
	3.42	1.98	20.42	19.81
	5.90	1.15	27.32	35.51
	9.21	1.68	48.06	53.14

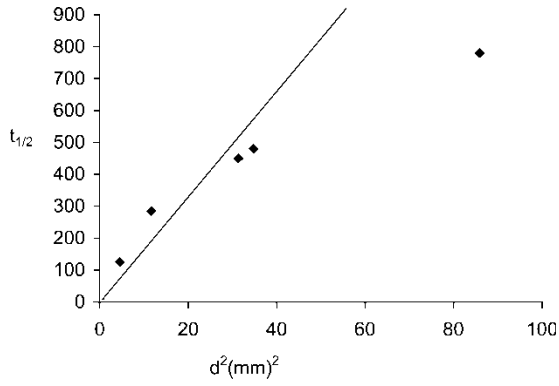

Figure 8. Time required for 50% swelling ($t_{1/2}$) vs. square of the diameter plot for the swelling of the gel sample HG (7.54) in the phosphate buffer medium of pH 7.4 at 37°C.

swelling) and the square of the diameter (mm) yielded a straight line (see Figure 8) which also supports the Tanaka-Fillmore theory.

Effect of Initiator on Water Uptake

Figure 9 shows the effect of the initiator content on water absorbency. The water absorbency increases as the KPS content increases from 3.60×10^{-2} to 14.7×10^{-2} mM, reaching maximum value and then begins to decrease with further increase in the initiator concentration.

The average kinetic chain length (υ) and initiator concentration in free-radical polymerization are related as per the following Equation (10) (29):

$$\upsilon = 1/2k_p(fk_ik_t)^{-1/2}[I]^{-1/2}[M] \tag{10}$$

where k_p, k_i and k_t are the rate constants for propagation,initiation and termination respectively; [I] and [M] are initiator and monomer concentrations and f is efficiency of the

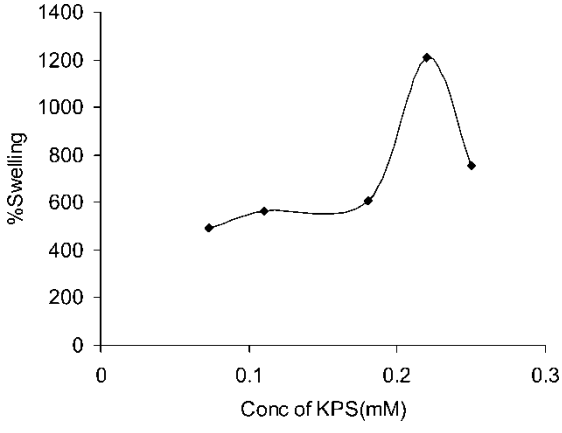

Figure 9. Equilibrium water uptake of hydrogel samples HG (7.54) as a function of initiator concentrations in the feed mixture.

initiator. Now, the increase in the KPS concentration beyond the optimum value of 14.7×10^{-2} mM, may be attributed to the fact that with an increase in the initiator content, the kinetic chain length and hence molecular weight of the resulting polymeric chains decreases. This means, increasing the initiator content leads to small sized polymer molecules. These small sized macromolecular segments occupy less space within the network while relaxing due to repulsion among similarly charged $-COO^-$ groups in the phosphate buffer medium of pH 7.4. This finally results in a decrease in water uptake. On the other hand, when the KPS content is decreased beyond optimum value, the network cannot form efficiently with a smaller number of radicals, resulting in a decrease of water uptake. Similar results have also been reported elsewhere (30).

Effect of Temperature on Water Uptake

The swelling behavior of a hydrogel system is affected, in many ways, by the temperature of the swelling medium. If any constituent of the copolymeric hydrogel possesses lower critical solution temperature (LCST) then usually a sharp volume phase transition occurs (31). Otherwise, the increase in temperature is accompanied by faster diffusion of solvent molecules into the polymer network, due to increased kinetic energy of the molecules. We investigated water uptake behavior of the hydrogel sample HG (7.54) at three temperatures, namely 21, 34, and 55°C in the phosphate buffer medium of pH 7.4. The results, as depicted in the Figure 10, clearly shows that water uptake at different time interval increases with temperature of the swelling medium. This may simply be attributed to the increased kinetic energy of invading solvent molecules.

The activation energy of the swelling process was determined by fitting the experimental data to the Arrhenius equation given below:

$$D = D_o \cdot \exp(-E_D/RT) \tag{11}$$

where E_D is the apparent activation energy for the diffusion process. The activation energy for sample HG (7.54), as determined from the slope of the linear plot (Figure 11) between logarithm of D and $1/T$, was determined to be 19.74 $kJmol^{-1}$. Here, it is worth mentioning that the average activation energy value available in the literature for a non-ionic hydrogel

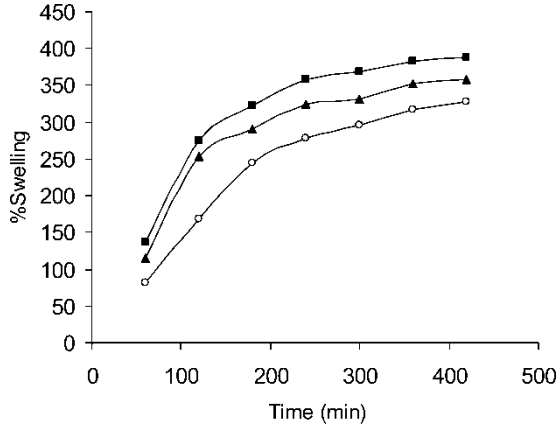

Figure 10. Dynamic uptake of water as a function of time for the hydrogel sample HG (7.54) in the swelling medium of pH 7.4 at 21°C (◇), 34°C (▲) and 55°C (■).

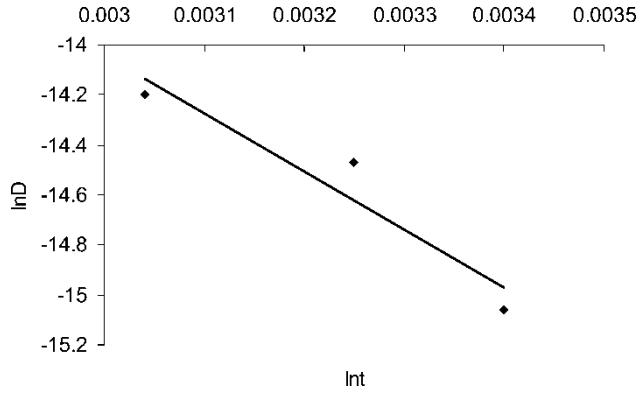

Figure 11. Arrhenius plot for the determination of activation energy for the swelling process of the sample HG (7.54) in SIF.

is nearly 8.3 $kJmol^{-1}$ (32), while in the present case, a higher value has been obtained. The higher activation energy value for the polyelectrolyte 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 (33). Higher values of activation energies for ionic hydrogels have also been previously reported (34).

Effect of Gel Composition on Swelling

As stated in the 'Iintroduction' section, the idea behind selecting MAAm and NVP monomers was that variation in the relative amounts of these two in the feed mixture could be a parameter to control the water uptake behavior of resulting hydrogels. To investigate this, we synthesized two samples, with VP to MAAm molar ratios 0.67:1 and 1.53:1 and studied their water absorbency in the SIF at 37°C. The results, as depicted in Figure 12, clearly shows that the hydrogel with higher NVP content exhibits greater water absorbency. This may be attributed to the more hydrophilic nature of the

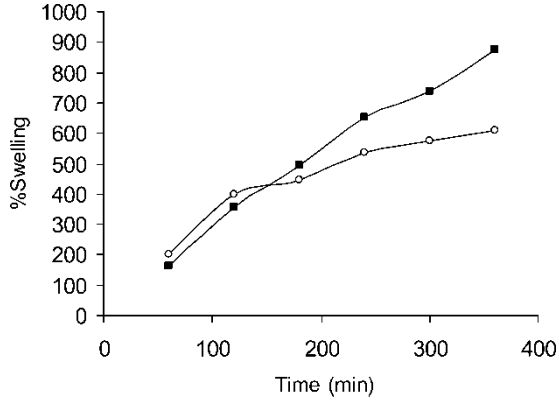

Figure 12. Dynamic uptake of water as a function of time for the hydrogel samples with varying molar ratio of NVP to MAAm 1.53:1 (■) and 0.67:1 (○) in the medium of pH 7.4 at 37°C.

monomer NVP imparting more hydrophilicity to the resulting hydrogel. This suggests that water uptake behavior of this terpolymeric hydrogel system can be regulated by varying the relative concentrations of the three monomers.

Conclusions

On the basis of various results obtained in this study, it can be concluded that terpolymeric systems composed of methacrylamide, N-vinyl-2-pyrrolidone and itaconic acid show excellent pH-responsive swelling behavior when transferred from SGF to SIF, showing nearly a 7.2 fold increase in one hour. The gel also shows swelling-deswelling behavior while maintaining structural integrity. The water absorbency can be controlled by varying amounts of monomers and initiator in the feed mixture and diameter of the gels. The activation energy of the sample HG(7.54) is found to be nearly 19.74 $kJmol^{-1}$. The overall outcome of this study is that it has the potential to be explored for the GI drug delivery of protein/peptide drugs, subject to the condition that a detailed investigation is made.

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References

1. Bajpai, S.K. and Dubey, S. (2004) *Iran. Polym. J*. 13 (3): 189–203.
2. Mohan, Y.M., Murthy, P.S.K., Reddy, M.M., and Raju, K.M. (2005) *J. Macromol. Sci., Pure and Appl. Chem.*, 42: 1227–1245.
3. Elliott, J.E., Macdonald, M., Nie, J., and Bowman, C.N. (2004) *Polymer*, 45: 1503–1510.
4. Caykara, T., Bozkaya, U., and Kantoglu, O. (2003) *J. Polym. Sci. Part B: Polym. Phys.*, 41: 1656–1664.
5. Kim, S.J., Lee, C.K., Lee, Y.M., Kim, I.V., and Kim, S.I. (2003) *React. Funct. Polym.*, 55: 291–298.
6. Kim, B., Flamme, K.L., and Peppas, N.A. (2003) *J. Appl. Polym. Sci.*, 89: 1606–1613.
7. Kim, B. and Peppas, N.A. (2003) *Biomedical. Microdevices*, 5 (4): 333–341.
8. Bajpai, S.K. and Dubey, S. (2004) *Polym. Int.*, 53: 2178–2187.
9. Bajpai, S.K., Saxena, S., and Dubey, S. (2006) *Polym Int.*, 55 (1): 12–18.
10. Suzuki, M. (1986) *Biorheology.*, 23: 274.
11. Mamada, A., Tanaka, T., Kungwatchakun, D., and Irie, M. (1990) *Macromolecules*, 23: 157.
12. Galave, I.V. and Mattiasson, B. (1999) *Trends Biotechnol*, 17: 335–340.
13. Bajpai, S.K. and Jhonson, S. (2005) *React. Funct. Polymers*, 62: 271–283.
14. Rihova, B., Beles, M., Vetvicka, V., Ulbrich, K., Strohalm, J., and Duncan, R. (1989) *Biomaterials*, 10: 335–342.
15. Sakuma, S., Lu, Z.R., Pecharova, B., Kopeckovra, P., and Kopeck, J. (2002) *J. Bioact. Comp. Polym.*, 17: 305–319.
16. Sariri, R. and Tighe, B. (1996) *Iran. Polym. J.*, 5 (4): 259.
17. Guven, O. and Sen, M. (1991) *Polymer*, 32: 2491–2485.
18. Guven, O. and Sen, M. (2002) *Eur. Polym. J*, 38: 751–757.
19. Flory, P.J. (1953) *Principals of Polymer Chemistry*; Cornell University: Ithaca, NewYork.
20. Aithal, U.S., Aminabhavi, T.M., and Cassidy, P.E. (1990) *J. Membr. Sci.*, 50: 225.
21. Saryadin, D. and Karadag, E. (1995) *Tr. J. Chem.*, 19: 179.
22. Gan, L.H., Deen, G.R., Gan, Y.Y., and Tam, K.C. (2001) *Eur. Polym. J.*, 37: 1413.

23. Flory, P.J. and Rehner, J.J. (1943) *J. Chem. Phys*, 11: 521.
24. Weast, R.C. (1972) *Handbook of Chemistry and Physics*; 53rd ed.; The Chemical Rubber Co.: Ohio.
25. Sen, M. and Guven, O. (1998) *Polymer*, 39: 1165.
26. Krishnaiah, V.S.R., Satynarayana, S., RamaPrasad, Y.V., and Narsimha Rao, S. (1998) *J. Cont. Release*, 55: 245.
27. Bajpai, S.K. and Jhonson, S. (2006) *J. Appl. Polym. Sci.*, 100 (4): 2759–2769.
28. Tanaka, T. and Fillmore, D.J. (1979) *J. Chem. Phys.*, 70: 5151–5159.
29. Allcock, H.R. and Frederick, W.L. (1981) *Contemporary Polymer Chemistry*; Prentice Hall: Englewood Cliffs, NJ.
30. Li, A., Wang, A., and Chen, J. (2004) *J. Appl. Polym. Sci.*, 92: 1596–1603.
31. Tanaka, T., Hocker, L.O., and Benedec, G.B. (1973) *J. Chem. Phys*, 59: 5151.
32. Vazquez, B. and Roman, J.S. (1997) *Macromolecules*, 30: 8440.
33. Rathna, G.V.N., Mohan Rao, D.V., and Chatterjee, P.R. (1996) *J. Macromol. Sci., Pure and Appl. Chem.*, A33: 1199.
34. Bajpai, S.K. and Sonkusley, J. (2002) *J. Appl. Polym. Sci.*, 83: 1717–1729.