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Swelling Behavior of Poly(2-hydroxyethyl Methacrylate-co-acrylic Acid-co-ammonium Acrylate) Hydrogels

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The purpose of this study was to prepare a series of pH-sensitive hydrogels from 2-hydroxyethyl methacrylate (HEMA), acrylic acid (AA), and ammonium acrylate, NH_4Ac, which was obtained by neutralization of AA with ammonium hydroxide. Hydrogels were prepared by free radical copolymerization in aqueous solution in the presence of redox initiators, $Na_2S_2O_8/Na_2S_2O_5$, and crosslinker, ethylene glycol dimethacrylate, EGDMA. The copolymers were synthesized by varying AA, EGDMA, and NH_4OH concentrations. The effect of pH, temperature, ionic strength, concentration of crosslinker, and AA content on the swelling behavior of the copolymeric gels were investigated. Equilibrium swelling studies, in the pH range of 2−8, were performed to determine the polymer mesh size (ξ), 14.17−127.6 Å, molecular weight between crosslinks (M_c), 324−10229 g/mol, and crosslinking density (q), 0.012−0.366, by using the Flory-Rehner equation. Copolymeric gels exhibited reversible change in their swelling behaviors in response to cycling pH. The diffusional exponent values (n) of the synthesized hydrogels were found in the range of 0.77−0.80, indicating a non-Fickian diffusion mechanism. FT-IR spectral analysis was also performed in order to confirm the formation of copolymer from the bands that appeared as a result of functional groups. It was concluded that these hydrogels demonstrated a sharp change in their water absorbency and mesh size of the networks with a change in the pH of the swelling media, suggesting their strong candidature for being used as oral drug delivery systems and ion-exchangers for removal of metal ions from aqueous media, owing to the carboxylate groups within the polymeric network.

Keywords: hydrogel; pH-sensitive hydrogels; acrylic acid; 2-hydroxyethyl methacrylate; molecular weigth between crosslinks; mesh size

1 Introduction

Hydrogels exhibiting pH-dependent swelling behavior contain either acidic or basic functional groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize, developing fixed charges on the gel (1). As a result of the electrostatic repulsions, the uptake of solvent into the network is increased (1).

Crosslinked polymeric networks are used for a variety of applications such as contact lenses, wound dressings, absorbents, monolithic drug delivery systems, membrane materials and chromatographic packing materials (2). For those purposes, acrylate-based acidic (acrylic acid, AA) and its sodium salt comonomers of 2-hydroxyethyl methacrylate (HEMA) based copolymers are widely synthesized by a crosslinking copolymerization process. For example, Ende and Peppas reported (3) the transport of ionizable drugs and proteins in crosslinked poly(acrylic acid-co-hydroxyethyl methacrylate) hydrogels. Poly(sodium acrylate-co-hydroxyethyl methacrylate) hydrogel was synthesized by inverse suspension polymerization as an superabsorbent polymeric material (4). A series of 2-hydroxyethyl methacrylate-co-acrylic acid-co-sodium acrylate copolymeric gels were prepared using N,N′-methylene bisacrylamide (NMBA) as the crosslinking agent for the purpose of drug release by Lee et al. (5). Acrylamide and sodium acrylate containing hydrogels were also used for the removal of diavalent toxic ions from aqueous solutions (6). In order to be used as drug delivery device, pH-thermoreversible hydrogels were also synthesized from N-isopropylacrylamide (NIPAAm), acrylic acid neutralized 50 mol% by sodium hydroxide, and N,N′-methylene bisacrylamide (NMBA) (7).

Poly(2-hydroxyethyl methacrylate) is a synthetic hydrogel, which possesses high mechanical strength and resistance to significant chemical and microbial degradation (8). Much attention has been paid to improving the chemical and physical properties of PHEMA. For example, incorporation of a ionic comonomer, such as acrylic acid and ammonium acrylate, into PHEMA hydrogels significantly changes swelling properties and promotes a gain in pH-sensitivity. Polymer networks containing ionic moities show a sudden

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or gradual change in their dynamic and equilibrium properties in response to the pH and ionic strength (9). Because of the charge repulsion in the ionic hydrogels, they can absorb a large amount of water (9).

In this study, in order to improve the water sorption characteristics and physical properties HEMA-based hydrogels, acrylate-based acidic (acrylic acid, AA) and its ammonium salt, ammonium acrylate, comonomers of 2-hydroxyethyl methacrylate (HEMA) were used to synthesize poly(HEMA-co-AA-co-NH_4Ac) hydrogel by a crosslinking copolymerization process in the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinker. To date, there is no study having the same composition in the literature. Temperature, ionic strength, pH and crosslinker content influence on the swelling behavior of newly synthesized poly(HEMA-co-AA-co-NH_4Ac) hydrogels have been studied and water uptake data have been analyzed with the help of a kinetic model. In addition, various network parameters including molecular weight between crosslinks (M_c), mesh size (ξ), and crosslinking density (q) have also been evaluated.

These novel pH-sensitive acrylate-based hydrogels can be effectively used in oral drug delivery systems and metal ion removal from aqueous media via an ion-exchange mechanism.

2 Experimental

2.1 Materials

Acrylic acid (AA) and 2-hydroxyethyl methacrylate (HEMA) monomers were obtained from Sigma-Aldrich (Steinheim, Germany). Sodium metabisulfite ($Na_2S_2O_5$) and sodium persulfate ($Na_2S_2O_8$) (Sigma-Aldrich, Steinheim, Germany) were used as redox initiators. Ethylene glycol dimethacrylate (EGDMA) (Sigma-Aldrich, Steinheim, Germany) was used as received. Ammonium acrylate, NH_4Ac, was synthesized by partially neutralizing acrylic acid with ammonium hydroxide. Ammonia, n-heptane, H_3PO_4, KH_2PO_4, K_2HPO_4, HCl and NaOH were purchased from Merck.

2.2 Synthesis of Hydrogels

Cylindrical shaped hydrogels were prepared by performing free radical crosslinking copolymerization of HEMA, AA, and NH_4Ac monomers, using EGDMA as the crosslinking agent and $Na_2S_2O_5$ and $Na_2S_2O_8$ as the redox initiator system. Three different poly(HEMA-co-AA-co-NH_4Ac) hydrogel samples were synthesized by changing the amount of AA, EGDMA, and neutralization percent of AA. In the synthesis of Sample 1, 1.03×10^{-2} mol HEMA, 3.65×10^{-3} mol AA, and 2.64×10^{-4} mol EGDMA were combined in a pyrex test tube and mixed in a Vortex mixer. A solution of 4.21×10^{-5} mol $Na_2S_2O_5$ and 3.36×10^{-5} mol $Na_2S_2O_8$ in 1.6 ml of 2.0 M NH_4OH solution, was combined with the monomer mixture, which neutralized the AA monomer in the molar ratio of 87% and initiated the polymerization reaction. Finally, the resultant mixture in the pyrex tube was immediately mixed in a Vortex mixer.

In the preparation of Sample 2, 1.03×10^{-2} mol HEMA, 5.47×10^{-3} mol AA and $2.64\text{x}10^{-4}$ mol EGDMA were put into a pyrex test tube. A mixture of 4.21×10^{-5} mol $Na_2S_2O_5$ and 3.36×10^{-5} mol $Na_2S_2O_8$, dissolved in 2.0 ml of 2.0 M NH_4OH solution, was immediately added into the monomer mixture. In this case, the degree of neutralization of AA was 73.1%.

Another experiment was designed to determine the influence of the crosslinking agent amount on hydrogel properties. The HEMA, AA, and initiator moles were held constant, corresponding to the amounts used in Sample 2 preparation, while the number of moles of EGDMA added to the monomer mixture was varied to produce hydrogels containing less dense crosslinks. Sample 3 was prepared by using 1.03×10^{-2} mol HEMA, 5.47×10^{-3} mol AA and 1.32×10^{-4} mol EGDMA monomer mixture and the same amount of redox initiator system, as in Samples 1 and 2, was dissolved in 2.0 ml of 2.0 M NH_4OH solution.

Polymerization reactions were carried out at room temparature for 1 day in the pyrex test tubes. After polymerization was completed, cylindrical gels were cut into discs 0.3 mm thick and 11 mm in diameter and then immersed into distilled water for 2 days to remove the residual unreacted monomers, crosslinking agent, and initiator before drying in an oven for one day at 37°C.

2.3 FT-IR Analysis

The synthesized copolymers were characterzed by FT-IR. For example, the spectrum of copolymer (Sample 2) was recorded using a KBr pellet and a Bruker Vector 22 FT-IR with OPUS spectroscopic software [version 2.0 (France)] over the range of 4000 cm^{-1} − 400 cm^{-1}. Since all of the three samples contain the same functional groups, the FT-IR spectrum of Sample 2 was selected as the representative one.

2.4 Swelling Studies

Swelling properties of the hydrogel samples, in the form of disc, were explored by placing the dried samples into 50.0 ml phosphate buffer solution, pH 7.4, at 37°C with ionic strengths of 0.05 and 0.15 M, respectively. Ionic strengths of the swelling media were maintained at the desired values with the addition of NaCl. Swelling studies were also conducted at temperatures of 10, 20, 37, and 50°C, respectively, until swelling equilibrium was attained. All the swelling studies were carried out in an incubator operating in the temperature range of −10 to 80°C (Nüve ES 110, Ankara, Turkey). In addition, effect of pH cycling on the swelling behavior of synthesized hydrogels was investigated by changing pH from 8.0 to 4.0 and same cycle was repeated several times at 37°C. pH measurements were performed using an Orion Model 720A with a combined

electrode (Beverly, MA 01915, USA). Furthermore, swelling studies of the hydrogels were also carried out for the determination of molecular weight between crosslinks at pH values of 2.0, 3.0, 5.0, 7.0, and 8.0 (I = 0.1 M) at 37°C, respectively.

At certain time intervals, discs were taken out of the solutions, and the swollen weight of each disc at time t (W_s) was determined after removing the surface water by blotting with filter paper, and then weighed. Swelling percent, S%, was calculated using the following expression:

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

Where W_d is the dry weight of disc.

3 Results and Discussion

3.1 FT-IR Analysis of the Polymer Samples

The FT-IR spectrum of Sample 2, (Figure 1) represents the peaks corresponding to the functional groups attached to the monomeric units of polymer chain. The broad band appeared near the 3600–3150 cm^{-1} region belongs to the ammonium salt of acrylic acid (N-H stretching vibration) and HEMA monomer (O-H stretching vibration) in the copolymer. The peaks observed at 2924 and 2853 cm^{-1} correspond to O-H, due to acrylic acid dimer, and aliphatic C-H stretching vibrations, respectively. In addition, the peak appeared at 1733 cm^{-1} (C═O stretching vibration) is due to the carbonyl group of ester bond. The peak observed at 1633 cm^{-1} (C═O stretching vibration) is due to acrylic acid. Furthermore, two peaks observed at 1575 and 1402 cm^{-1} (asymmetric and symmetric C-O stretching vibrations) confirm the presence of carboxylate anion. Since there are ester bonds in both EGDMA and HEMA monomers, a C-C(═O)-O asymmetric stretching vibration peak s appeared at 1164 cm^{-1}. These FT-IR spectral observations indicated that all of the monomeric units, HEMA, AA, EGDMA and NH_4Ac, were incorporated into the copolymer backbone.

3.2 Network Parameters of Hydrogels

3.2.1 Determination of Molecular Weight between Crosslinks, M_c

A crosslinked polymer, when placed in a good solvent, rather than dissolving completely, will absorb a portion of the solvent and subsequently swells (10). Since swelling is a simple and low-cost technique to characterize polymer networks, network parameters of the hydrogels were determined by using their equilibrium swelling values. One of the important parameters characterizing a crosslinked

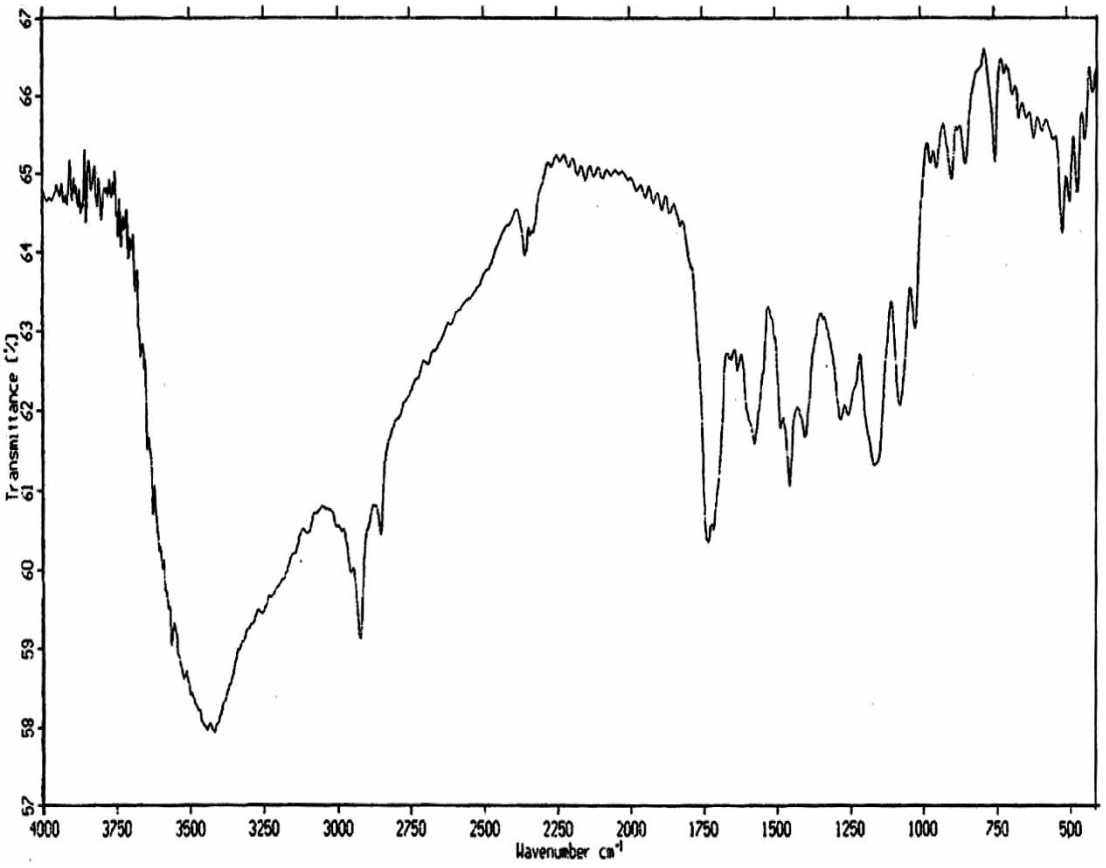

Fig. 1. FT-IR spectrum of Sample 2.

hydrogel is the molecular weight between crosslinks, M_c. The following well-known Flory-Rehner equation can be used to calculate M_c value (11):

$$M_c = -d_p V_s(\upsilon_{2,s}^{1/3} - \upsilon_{2,s}/_2)[\ln(1-\upsilon_{2,s}) + \upsilon_{2,s} + \chi\upsilon_{2,s}^2]^{-1} \quad (2)$$

The volume fraction, $\upsilon_{2,s}$, of the swollen polymer is calculated using the following equation:

$$\upsilon_{2,s} = \left[1 + \frac{d_p}{d_s}\left(\frac{M_a}{M_b'} - 1\right)\right]^{-1} \quad (3)$$

In this equation, d_p and d_s (1 g/ml) are the densities of the polymer and solvent, respectively. The density of the polymers were determined by a pycnometer using n-heptane as a non-solvent. M_b and M_a are the masses of the polymer before and after swelling; V_s is the molar volume of the solvent (18.0 ml/mol) and χ is the Flory-Huggins polymer-solvent interaction parameter (12). The values of χ for the HEMA and AA were taken from the literature (13, 14) and the weighed average of these values were used in the calculation of M_c. Equilibrium swelling results of poly(HEMA-co-AA-co-NH_4Ac) hydrogels, named as Sample1, 2, and 3 were used to determine M_c values at various pH media (pH 2.0–8.0 and I = 0.1 M) at 37°C. Experimental M_c values were calculated using Equation (2) developed by Flory and Rehner and were listed in Table 1 for hydrogels of varying compositions and crosslinking ratios.

Table 1 presents the fact that values of M_c increased with decreasing crosslinking ratio and volume fraction of the swollen hydrogel. In addition, the effect of the external medium pH on the M_c values of hydrogels were also investigated and it was seen that as the external medium pH was raised, M_c values increased significantly. For example, M_c value of the Sample 3 reached 10229 g/mol from 565 g/mol when the pH was changed from 2.0 to 8.0. This relatively high change in M_c value can be attributed to the fact that as the pH of the swelling medium changes from pH 2.0 to 8.0, the -$COONH_4$ and COOH groups attached to the polymer chains ionize completely to give charged carboxylate, -COO^-, groups and NH_4^+ counter ions within the hydrogel. Because free counter ions remain inside the hydrogel to neuralize the fixed charges on the polymer chain, this high ion concentration inside the hydrogel results in high osmotic pressure and in turn high swelling percent. Furthermore, carboxylate groups repel each other due to electrostatic repulsive forces, which causes the relaxation of the polymer network.

It was also determined that M_c value changed depending upon on the composition of the polymeric sample. Mole percents of ionizable monomer, AA, based on the total monomer, for Samples 1, 2, and 3 were 26.16, 34.7, and 34.7%, respectively. Due to higher concentration of ionizable group, Sample 2 swelled to a greater extent than Sample 1 and owing to this high extent of swelling, its M_c value was found as 4571 g/mol as compared to 2610 g/mol for Sample 1. When Samples 2 and 3 were compared, it was seen that Sample 3 had a significantly greater M_c value than Sample 2, which can be attributed to the lower crosslinking ratio.

3.2.2 Determination of Crosslinking Density, q, and Mesh Size, ξ

Another significant parameter characterizing crosslinked polymers is the crosslinking density, q, and can be find

Table 1. Network parameters determined from equilibrium swelling studies of hydrogels at various pH media at 37°C (I = 0.1 M)

	Sample no.	Crosslinking ratio[a] × 10^2	Volume fraction of the swollen polymer, $\upsilon_{2,s}$	Molecular weight between crosslinks, M_c (g/mol)	Crosslink density, q	Mesh size, ξ (Å)
pH 2.0	1	1.90	0.533	502	0.243	14.17
	2	1.68	0.519	530	0.238	14.50
	3	0.84	0.510	565	0.210	15.50
pH 3.0	1	1.90	0.484	1352	0.090	24.00
	2	1.68	0.400	1520	0.070	29.00
	3	0.84	0.140	3672	0.032	60.90
pH 5.0	1	1.90	0.201	1843	0.066	37.70
	2	1.68	0.150	3396	0.035	57.10
	3	0.84	0.090	7003	0.017	97.70
pH 7.0	1	1.90	0.153	2610	0.047	49.10
	2	1.68	0.121	4571	0.026	71.20
	3	0.84	0.072	9939	0.012	125.10
pH 8.0	1	1.90	0.148	2720	0.045	50.70
	2	1.68	0.110	5250	0.023	79.00
	3	0.84	0.070	10229	0.012	127.60

[a]Crosslinking ratio = number of moles of crosslinker/number of moles of monomers.

using the following equation:

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

where M_r is the molar mass of the repeat unit and is defined as

$$M_r = \frac{m_{HEMA}M_{HEMA} + m_{AA}M_{AA} + m_{NH4AC}M_{NH4Ac}}{m_{HEMA} + m_{AA} + m_{NH4AC}} \tag{5}$$

Here, m_{HEMA}, m_{AA}, and m_{NH4Ac} are the masses of the monomers HEMA, AA and NH_4Ac, respectively. In addition, M_{HEMA}, M_{AA}, and M_{NH4Ac} are the molar masses of HEMA, AA, and NH_4Ac, respectively.

The mesh size, ξ, which is a term that describes the available space for solute transport within the polymer network, is also an important paramater in analyzing crosslinked polymers and calculated according to Equation (6), which is described in more detail by Canal and Peppas (15):

$$\xi = \upsilon_{2,s}^{-1/3}\left(\frac{2M_c}{M_r}\right)^{1/2} C_n^{1/2}\ell \tag{6}$$

Here, M_r is the molecular weight of the repeating unit; ℓ, the C-C bond length of 1.54 Å; and C_n, the characteristic ratio, is the weighed average of the C_n values of HEMA, 6.9 (3), and AA, 6.7 (14).

ξ and q values of the Samples 1, 2, and 3 are presented in Table 1 as a function of pH and sample composition. Results indicated that as the pH of the swelling medium increased from pH 2.0 to 8.0, ξ value for Sample 3 increased from 15.5 to127.6 Å and q value decreased from 0.21 to 0.012. Thus, while the pH of the external medium increased, hydrogels swelled to a greater extent and the space avilable between the crosslinks became larger. The data also showed that the crosslinking density decreased with increasing external medium pH, indicating that there is more space between the crosslinks and the hydrogel is less dense.

3.3 Dynamic and Equilibrium Swelling Studies

Swelling studies were performed to investigate the influence of external conditions, such as pH, temperature and ionic strength, and hydrogel composition on the dynamic and equilibrium swelling properties of pH-sensitive poly(HEMA-co-AA-co-NH_4Ac) hydrogels,.

3.4 Effect of pH

pH-sensitive hydrogels play a significant role in controlled oral drug delivery systems. These hydrogels can be prepared by the incorporation of weakly acidic monomer such as carboxylic acids. While those kinds of delivery systems show a low swelling degree in acidic medium of the stomach, their swelling degree increases as they passdown the gastrointestinal tract due to an increase in the pH. Thus, a pH-sensitive drug delivery system protects the drug from the acidity of the stomach and releases the drug in the small intestine or colon depending upon the composition of the hydrogel. To be used as a drug delivery system, pH-sensitivity of the hydrogel is of great importance. In this study, pH-sensitivity of the poly(HEMA-co-AA-co-NH_4Ac) hydrogels was investigated by varying the pH of the swelling medium in the range of 2.0-8.0. Equilibrium swelling results were depicted in Figure 2, which reveals that equilibrium swelling percent increases as a function of pH for all the three samples. Figure 2 shows that swelling percents of Samples 1 and 2 remained constant between pH 2.0 to 3.0; however, there was a sharp increase in the swelling values of both samples at pH 5.0 which is above the pK_a value, 4.7, of the AA. This is because the ionization of the polymeric networks containing carboxylic acid groups takes place as the pH of the external medium increases (7). In addition, ammonium carboxylate in the polymeric backbone dissociates at this pH value and electrostatic repulsion among the similarly charged -COO^- groups and osmotic pressure inside the hydrogel increase, resulting in a sharp increase in the swelling degree of the hydrogels.

Apart from the Samples 1 and 2, a dramatic increase in the equilibrium swelling percent value of Sample 3 was obtained. When the pH was changed from 2.0 to 3.0, swelling percent value reached 479% from 74%. This unusual swelling behavior at pH 3.0 can be attributed to the low content of crosslinker used in Sample 3 compared to the Samples 1 and 2. However, this effect was not significant after pH 7.0 since it reached equilibrium state. These results proved the pH-sensitivity of the prepared hydrogel samples.

3.5 Effect of Ionic Strength

Swelling properties of Samples 1, 2 and 3 were investigated as a function of time in two different pH 7.4 solutions with ionic strengths of 0.05 and 0.15 M, respectively. Figure 3

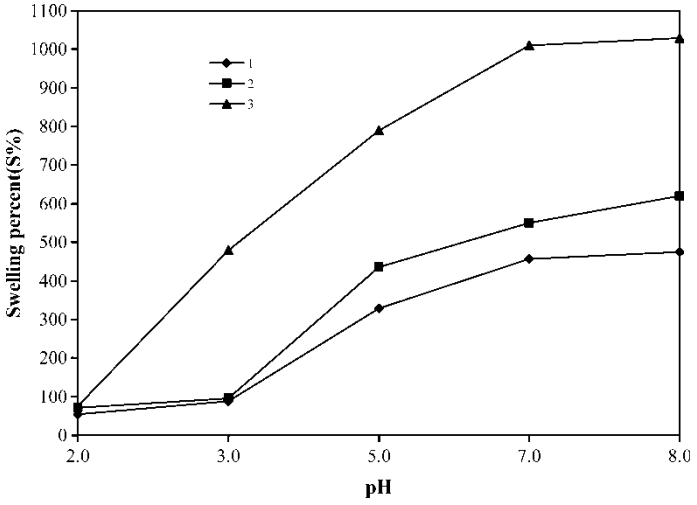

Fig. 2. Equilibrium swelling behavior of hydrogels at various pH media containing phosphate buffers with ionic strength of I = 0.1 M at 37°C.

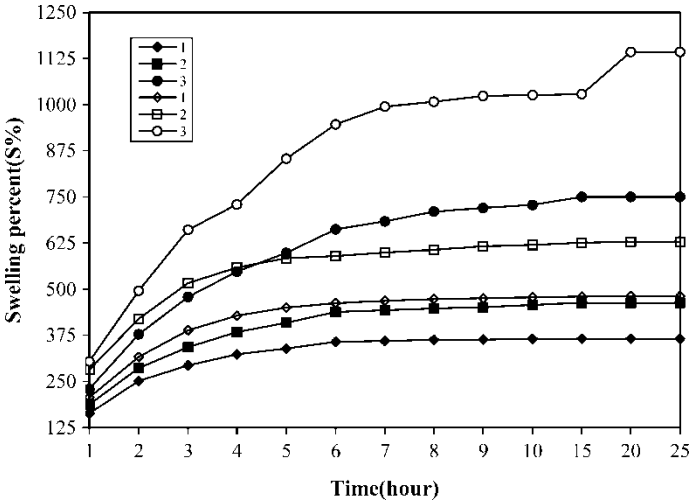

Fig. 3. Effect of ionic strength on the swelling behavior of hydrogels in pH 7.4 phosphate buffer solution at 37°C (open and closed symbols represent I = 0.05 M and I = 0.15 M, respectively).

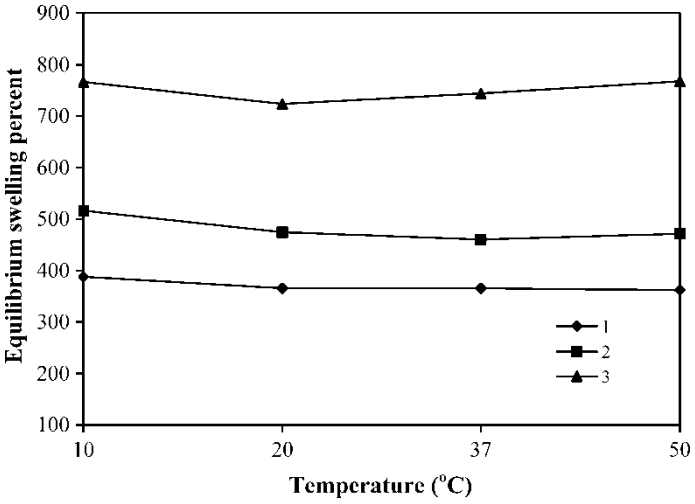

Fig. 4. Equilibrium swelling properties of hydrogels as a function of temperature in pH 7.4 phosphate buffer solution with ionic strength of 0.15 M.

demonstrates that as the ionic strength increased from 0.05 (open symbols) to 0.15 M (closed symbols), the swelling percent of the hydrogels decreased because the difference in the concentration of mobile ions between the hydrogel and the solution was reduced. As a result of this, osmotic swelling pressure reduced, resulting in lower swelling percent values. Apart from Samples 1 and 2, there was a substantial decrease in equilibrium swelling percent, reduced from 1150 to 750%, for the Sample 3. According to the Donnan osmotic pressure equilibrium, an increase in concentration of the movable counter ions of a solution leads to a decrease in the osmotic pressure within the hydrogel, causing the hydrogel to shrink (8). As far as swelling results are concerned, it can be concluded that the prepared hydrogels' swelling behaviors are largely dependent upon the ionic strength of the swelling medium.

3.6 Effect of Temperature

Equilibrium swelling studies were conducted as a function of temperature at pH 7.4 phosphate buffer solution with the ionic strength of 0.15 M, Figure 4, and all of the samples reached their highest equilibrium swelling degree at 10°C. This behavior may be attributed to the hydrogen bond between the water molecules and the polymer chain. When the temperature is increased to 50°C, the free water moves from the external medium into the hydrogel, causing the hydrogels to swell to a higher degree compared to those at 37°C. This swelling behavior, in response to temperature change, is quite different from the ones in the literature. For example, Lee and Lin investigated the influence of temperature on the swelling properties of acrylate-based hydrogels containing HEMA and AA and they experienced minimum swelling at 55°C compared to lower temperatures (16).

3.7 Effect of Crosslinker Amount

One of the effective ways of modifying the water imbibing capacity of hydrogels is to bring about a change in the crosslink density of the network by incorporating varying amounts of crosslinker in the feed mixture of the hydrogel (17). For this purpose, swelling properties of hydrogel samples were investigated by changing the amount of crosslinker used in the preparation of Sample 3, EGDMA, from 2.64×10^{-4} to 1.32×10^{-4} mol (from 1.68 mol%, based on the total monomer, to 0.84 mol%) and keeping the amount of HEMA, AA, initiator and percent neutralization, as 73.1% for both samples, constant. Figure 5 shows that Sample 3 containing 0.84 mol% EGDMA reached a relatively high

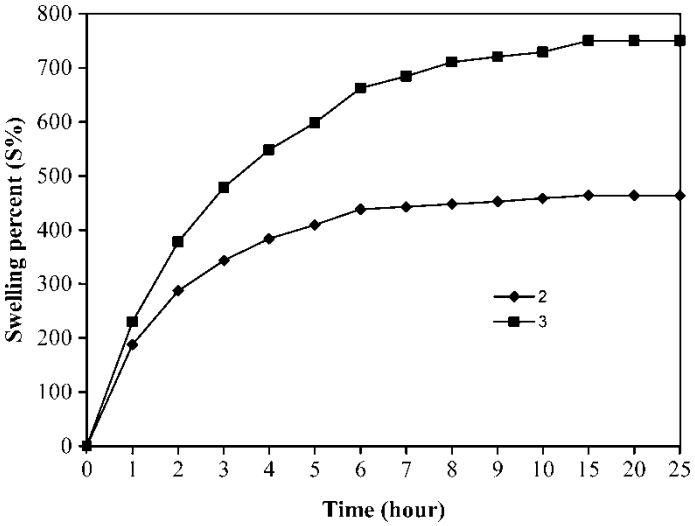

Fig. 5. Effect of crosslinker content on the swelling kinetics of Sample 2 (2.64×10^{-4} mol EGDMA) and Sample 3 (1.32×10^{-4} mol EGDMA) in pH 7.4 phosphate buffer with ionic strength of 0.15 M at 37°C.

Table 2. Various swelling parameters of hydrogels at pH 7.4 phosphate buffer solution with ionic strength of 0.15 M at 37°C

Sample no.	Characteristic contant, k	Swelling exponent, n	Coefficient of regression equation, r	Water transport mechanism
1	0.41	0.78	0.9944	Non-fickian
2	0.37	0.80	0.9909	Non-fickian
3	0.29	0.77	0.9955	Non-fickian

equilibrium swelling value, 750%, compared to Sample 2, 464%, at the end of the 25th hour. This result can be explained by the fact that decreasing the crosslinking ratio results in a decrease in the number of crosslinks per unit volume. As a consequence of this decrease, the free space available between crosslinks increases and the molecules find more space to diffuse into the hydrogel and thus, the swelling degree of the hydrogel increases. In addition, with the lowering of crosslinking ratio, rigidity of the polymer network decreases, resulting in enhancement in the movement of polymeric chains and as a result of this, more water molecules get into the hydrogel.

3.8 Effect of AA Content

The effect of AA content in the feed mixture on the swelling percent of the hydrogel has been investigated. For this purpose, the amount of AA in the feed mixture was changed from 3.65×10^{-3} mol, Sample 1, to 5.47×10^{-3} mol, Sample 2. The results shown in Figure 3 indicate that the equilibrium swelling value increased from 366 to 464% when amount of AA was changed from 3.65×10^{-3} to 5.47×10^{-3} mol. This increase in the swelling percent of the hydrogel can be attributed to the increased amount of carboxylic acid groups in the polymer chain, resulting in an increase in the electrostatic repulsive effect of the carboxylate groups. Thus, Sample 2 swelled to a higher degree compared to Sample 1, owing to the increased amount of AA.

3.9 Analysis of Kinetic Data

When a glassy polymer is placed into a solvent, the solvent penetrates into the polymer and this results in swelling by entering spaces between macromolecular chains of the polymer. In order to analyze solvent transport mechanism of the polymeric samples, the first 60% of the fractional water uptake, M_t/M_∞, is analyzed using the following equation (18):

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

Where M_t is the mass of water absorbed at time t, M_∞ is the amount of water absorbed at equilibrium, k is hydrogel characteristic constant and n is the swelling exponent describing type of the solvent transport mechanism. The constants n and $k$are calculated from the slope and intercept of the plots of $\ln(M_t/M_\infty)$ values vs. ln t values obtained from the swelling studies.

For a cylindrical sample, the value of $n = 0.45$ shows a Fickian water transport mechanism, while $n = 0.89$ indicates a Case II transport mechanism and for $0.45 < n < 0.89$, the water transport mechanism is non-Fickian, indicating that the both diffusion and polymer relaxation processes are resposible from the water uptake of the polymer (18). The values of k, n, coefficient of regression equation, r, and the type of solvent transport mechanism were reported in Table 2. It indicates that values of n are in between 0.77 and 0.80 and solvent tranport mechanism for the Samples 1, 2, and 3 is a non-Fickian type. Thus, it can be concluded that the solvent transport mechanism for the three samples is both diffusion and chain relaxation controlled. The effect of chain relaxation on the solvent transport into the polymer can be attributed to the electrostatic repulsion between adjacent ionized carboxylate groups.

3.10 Reversibility Studies

Figure 6 presents the effect of pH cycling on the swelling behavior of hydrogel Samples 1, 2, and 3. Swelling medium pH was changed from 8.0 to 4.0, and the same cycle was repeated three times. The first swelling study was carried

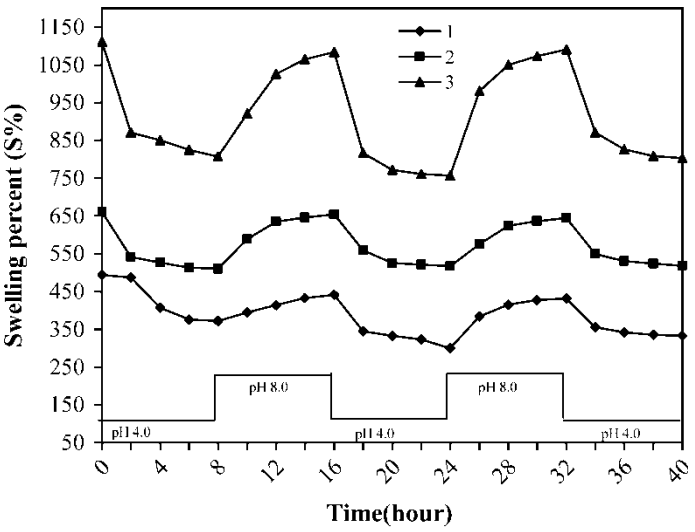

Fig. 6. Cyclic swelling behavior of various hydrogels in phosphate buffers with ionic strength of I = 0.15 M at 37°C.

out at a pH 8.0 buffer so that hydrogel samples reach their equlibrium swelling values and then hydrogels were transferred into pH 4.0 medium for 8 h, followed by 8 h in a pH 8.0 buffer solution. In a pH 8.0 buffer solution, carboxylic acid groups, COOH, ionize, resulting in the formation of carboxylate groups, COO^-. Since the carboxylate groups in the polymeric chain repel each other, swelling increases rapidly. On the contrary, when the hydrogel samples were transferred into the pH 4.0 medium, the carboxylate groups are protonated and carboxylic acid groups, COOH, are obtained, resulting in decrease in the electrostatic repulsive forces between carboxylate groups. As a result, swelling percent values of the hydrogel samples decrease at pH 4.0 medium.

Experimental results confirmed that Samples 1 and 3 did not indicate any pH-dependent reversible behavior. Apart from the Samples 1 and 3, swelling percent values for the Sample 2 were almost the same after each 8 h period for both of the swelling media of pH 4.0 and 8.0, indicating the pH-dependent reversible behavior. Moreover, Sample 2 did not lose its mechanical strength in the harsh conditions of swelling medium.

4 Conclusions

It was proved that the swelling behavior of novel poly(HEMA-co-AA-NH_4Ac) hydrogel was dependent on the pH of the external medium, ionic strength, and amount of crosslinker. In addition, pH-reversibility and effect of temperature on the swelling properties of the hydrogel samples were also investigated and it was determined that Sample 2 showed pH-reversible behavior in response to pH-cycling from 4.0 to 8.0. The mechanism of water diffusion into these hydrogels was determined to be a non-Fickian type since the values of swelling exponent were in the range of 0.77–0.80. Furthermore, hydrogel mesh size is of special importance in the drug release studies because of the screening effect of the hydrogel. For this reason, hydrogel mesh size should be large enough for the drug molecules to pass through the hydrogel mesh. The experimental values of the mesh sizes of the hydrogels were in the range of 14.17–126.7 Å at the pH values of 2.0–8.0. This mesh size range is large enough for the most drugs including peptide and protein drugs. It should be emphasized that the pH-sensitive behavior of the prepared hydrogels are of importance in oral drug delivery. Finally, the synthesized ammonium acrylate-based hydrogels may be good candidates for the removal of toxic metal ions via complexation and ion-exchange mechanism since they contain -$COONH_4$ and -COOH groups attached to the macromolecular chains.

5 References

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