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A LOW-TEMPERATURE PRODUCTION METHOD FOR CATIONIC HYDROGELS

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Key Words: Dimethylaminoethylmethacrylate, Hydroxyethylmethacrylate, Cationic Gels, pH Sensitive Gels, Insulin Release

ABSTRACT

In this study, the preparation of pH sensitive hydrogels at a very mild temperature of +4°C, was described. Lightly cross-linked hydroxyethylmethacrylate-dimethylaminoethylmethacrylate (HE-MA-co-DMAEM) copolymer gels were produced by a copolymerization initiated by potassium persulfate in an aqueous medium. The amine containing comonomer (i.e., DMAEM) acted as an accelerator in the copolymerization reaction. Scanning electron microscopy indicated that the gel matrix comprised of a highly porous interior along with a skin layer around it. The effects of DMAEM concentration and the total monomer/water ratio on the equilibrium swelling behavior of the gels were examined. The gels produced with different DMAEM contents exhibited a highly pH dependent equilibrium swelling behavior. The extent of transition from the shrunken state to the swollen state was strongly related to the DMAEM content of the gel matrix. The effective diffusion coefficient of water was also determined by applying unsteady state diffusion model on the dynamic swelling and shrinking behaviors of the produced gels.

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INTRODUCTION

Cationic polyelectrolyte gels are usually produced by the copolymerization of an amine functional comonomer with an acrylate based one [1-5]. Siegel *et al.* studied the production and characterization of cationic polyelectrolyte gels produced by the copolymerization of n-alkyl methacrylate esters and dimethylaminoethylmethacrylate (DMAEM) [1-4]. The swelling behavior of cationic gels was explained by the moving penetrant front mechanism [2]. The effects of pH, buffer concentration and pK_a on the dynamic swelling behavior of methyl methacrylate-DMAEM copolymers were also investigated [3]. The gel swelling rate showed a linear dependence on the concentration of non-ionized buffer as determined by the Henderson-Hasselbach equation [3]. Chou *et al.* studied the dynamic swelling behavior of the hydroxyethylmethacrylate-co-DMAEM gels [5]. In their study, the results indicated that pH of the swelling medium ought to be such that the buffer was essentially unionized to enhance the swelling kinetics of these gels. Recently, the cationic gels, which were sensitive to both pH and temperature changes, were prepared by the random copolymerization of N-isopropylacrylamide and diethylaminoethylmethacrylate [6-7].

In some of the studies on the DMAEM containing polyelectrolyte gels, the polymerizations were performed usually at relatively high temperatures [1-5]. This case may be considered as a limitation for the use of these gels in the physical immobilization of biologically active agents. As a result, we proposed a relatively soft procedure for the preparation of hydroxyethylmethacrylate-dimethylaminoethylmethacrylate (HEMA-DMAEM) gels, in which the amine containing monomer was used as the accelerator for the gel formation. In this study, the equilibrium swelling behavior of the HEMA-DMAEM gels produced by the proposed polymerization procedure was defined and the effective diffusion coefficient of water within the gel matrices prepared by changing the DMAEM content and monomer/water ratio were estimated.

EXPERIMENTAL

Materials

The monomer, 2-hydroxyethylmethacrylate (HEMA, Sigma Chemical Co., USA) was distilled under vacuum. The comonomer, 2-dimetylaminoetylmethacrylate (DMAEM, Aldrich Chem. Co., USA) was used without further purification. Potassium persulfate (BDH Chemicals Ltd., UK) and N,N-methylenebisacrylamide (MBA, BDH Chemicals Ltd.) were selected as the initiator and the crosslinker, respectively. Aqueous buffer solutions for the gel swelling experiments were prepared with citric acid and NaOH (both from Fluka Chemie AG, Switzerland) stock solutions. Some of the buffer solutions were prepared by using formic acid, acetic acid or chloroacetic acid (Aldrich Chem. Co.) stock solutions.

Preparation of Copolymer Gels

The cylindrical copolymer gels were prepared by a block copolymerization method. A typical copolymerization procedure was described as follows: 0.5 ml HEMA, 0.15 ml DMAEM and 0.1 ml of aqueous MBA solution (5 mg MBA/ml) were mixed with 0.8 ml of distilled-deionized water in a cylindrical test tube (internal diameter: 8 mm, length: 80 mm). The test tube was put into a thermostated water bath at +4^{o}C and kept for 30 minutes for thermal equilibrium. 0.6 ml KPS solution (50 mg KPS/ml) at the same temperature was added into the homogenous copolymerization medium. The tube was purged with nitrogen for 2 minutes and sealed. The gelation was conducted at +4^{o}C for 24 hours. The gels (8 mm internal diameter and 40-75 mm in length in the variable production conditions) were removed from the glass tubes by applying pressure and cut into cylinders 4 mm in length. The gel cylinders from the each test tube were washed with 500 ml of distilled-deionized water three times by stirring the washing medium for 48 hours to remove any unreacted material (i.e., the monomers or the initiator) from the gel matrix. The production conditions of copolymer gels are summarized in Table 1. In the copolymerizations for investigation of gel swelling properties, the final monomer conversion values were determined by measuring the weight of dry copolymers. The lowest monomer conversion value was obtained as 96.9% (w/w) with the gel sample produced by 9.8% of DMAEM. The gels with higher DMAEM contents exhibited nearly quantitative monomer conversions. Therefore, the feed compositions given in Table 1 were very close to the final compositions of copolymers used for the investigation of gel swelling properties. The gels used for the determination of effective diffusion coefficient of water were prepared in a different cylindrical glass mold (25 mm in diameter and 10 mm in height). The cylindrical gels having a diameter of 25 mm in the production conditions were cut into discs 1.5 mm in height. In this group of gel synthesis, six gel samples were obtained by changing DMAEM/HEMA mole ratio and monomer/water volume ratio.

TABLE 1. The Production Conditions of HEMA-DMAEM Based Cationic Copolymer Gels

Polymerization conditions: Polymerization temperature: +4°C, Polymerization time: 24 hours.
MBA : 0.065 % mol (based on moles of total monomer).

The copolymerizations for gel formation kinetics:

DMAEM[a] (mol%)	HEMA[a] (mol%)	Monomer/Water (ml/ml)	KPS (mg/ml monomer)
1.4	98.6	0.37	9.1
6.7	93.3	0.37	9.1
12.6	87.4	0.37	9.1
15.3	84.7	0.37	9.1

The copolymerizations for investigation of gel swelling properties:

DMAEM[a] (mol%)	HEMA[a] (mol%)	Monomer/Water (ml/ml)	KPS (mg/ml monomer)
9.8	90.2	0.43	48.0
15.3	84.7	0.43	48.0
17.8[b]	82.2	0.43	48.0
20.1	79.9	0.43	48.0
22.4	77.6	0.43	48.0
17.8	82.2	0.21	48.0
17.8	82.2	0.26	48.0
17.8[b]	82.2	0.43	48.0
17.8	82.2	1.00	48.0

[a] The feed composition of copolymer (i.e., HEMA and DMAEM concentrations) was given.
[b] The same copolymerizations repeated in the table to show the systematic change of conditions.

Characterization of Copolymer

The surface morphology and the internal structure of HEMA-DMAEM copolymer was observed by a Scanning Electron Microscope (JEOL, JEM 1200EX, Japan). The copolymer disc produced with the DMAEM concentration of 17.8% mol (swollen in 0.05 N HCl solution having an ionic strength of 0.1) were subsequently freeze dried at -20°C. The dry gels were cut to obtain the cross sectional view of the internal structure. The samples coated with a thin layer of gold (about 100 A) *in vacuo* were examined in the scanning electron microscope.

Kinetics of Gel Formation

In order to follow the copolymerization kinetics, a group of gel formation experiments were performed with the conditions given in Table 1. In these experiments, DMAEM concentration in the monomer mixture was changed. After starting the copolymerization, the gel formation was stopped by quenching the gelation medium into a 100 ml of p-benzoquinone-methanol solution (20 mg p-benzoquinone/ml) at the designated copolymerization times. The solution was stirred for 6 hours for the removal of unreacted monomers from the partly formed gel matrix. The precipitated crosslinked copolymer was washed with methanol, distilled water and dried in vacuum at 40°C. Then, the dried copolymer was weighed. The total monomer conversion into the crosslinked copolymer gel (C_T) was calculated according to following expression:

$$C_T = W_G / (W_{HEMA} + W_{DMAEM}) \quad (1)$$

Where, W_G is the dry weight of precipitated copolymer, W_{HEMA} and W_{DMAEM} are the weights of HEMA and DMAEM monomers initially charged to the gelation medium, respectively. By considering the formation possibility of linear polymer during the copolymerization, it should be noted that the value of C_T represented the minimum value for overall conversion of monomers to the cross-linked copolymer.

pH Response of HEMA-DMAEM Copolymers

The equilibrium swelling ratios of gel samples were mostly determined in citrate buffer solutions having the pH values between 3 and 6. These solutions were prepared starting from 0.01 M citric acid stock solution. Phosphate buffer was used for the solutions having the pH values of 6 and 7. 0.05 N HCl (for pH:1.3) and 0.05 N NaOH (for pH:12.7) solutions were also included as the swelling media. The ionic strengths of all buffer solutions used in the equilibrium swelling experiments were adjusted to 0.1 by adding precalculated amount of NaCl into the medium at the desired pH value. All experiments were conducted at a constant temperature of 25°C by using a thermostatic water bath (Fryka, Kaltetechnik, Germany). The equilibrium swelling experiments were performed with the gel samples produced with the conditions given in Table 1.

In order to obtain the variation of equilibrium swelling ratio by the medium pH, four cylindrical gel blocks from each copolymer (each block was 8 mm in diameter and 4 mm in length in the production conditions) were incubated in a 100 ml of buffer solution at +25^{o}C for 48 hours. At the end of this period, the weight of the gel sample was recorded after removing the excess surface water with a laboratory tissue. Starting from the pH value of 1.3 (i.e., 0.05 N HCl medium) the medium pH was elevated up to 8. Between two successive equilibrium swelling experiment, the gel samples were extensively washed with distilled water for 24 hours and then incubated in the next medium. The equilibrium swelling ratio of the copolymer gel (ϕ) was defined as follows:

$$\phi=(W_e-W_d)/W_d \tag{2}$$

where W_e is the weight of the gel after establishment of equilibrium in the buffer solution and W_d is the dry weight of the gel.

To determine the effective diffusion coefficient of water within the gel matrices, four different step inputs were applied on each gel by changing the medium pH within the predetermined ranges. These ranges were selected as 1.3-4, 4-1.3, 6-12.7 and 12.7-6. The response of selected gel matrix against the applied step input was monitored by measuring the gel weight at the designated times.

Buffer Effect on the Swelling Behavior of Copolymer

The gels produced with a DMAEM concentration of 22.4% mol were collapsed in 0.05 N NaOH solution for 24 hours. Then, the collapsed gel cylinders were transferred into the buffer solutions prepared with different carboxylic acids at a constant pH of 3. These solutions were prepared from 0.05 M stock solutions of the respective carboxylic acids. The ionic strength was set to 0.1 by adding precalculated amount of NaCl into the each medium at pH, 3. The dynamic swelling behavior of the selected copolymer was followed by the determination of increase in the gel weight.

Formic acid buffer solutions were used for the determination of nonionized (acid form) buffer concentration effect on the dynamic swelling behavior of the HEMA-DMAEM copolymer produced with DMAEM concentration of 22.4% mol. The formic acid solutions (pH:3) having different nonionized acid form concentrations were prepared starting from the stock solutions with the total acid concentrations between 0.01-1 M. In the each formic acid buffer, the resulting ionic strength was brought to 0.1 by adding precalculated amount of NaCl.

RESULTS AND DISCUSSION

Various studies have been performed on the production methods and swelling behaviors of the polyelectrolyte gels containing DMAEM residues. Siegel and Firestone produced methyl methacrylate-DMAEM gels by using azobisizobutyronitrile as the initiator and divinylbenzene as the crosslinker in a block polymerization performed at 60°C (1-4). A similar polymerization procedure using azobisizobutyronitrile as the initiator and divinylbenzene as the crosslinking agent was also proposed by Chou *et al.* to produce methyl methacrylate-DMAEM and HEMA-DMAEM gels (5). They also conducted the copolymerization of the monomers at 60°C. However, the pH responsiveness of DMAEM containing copolymer gels may be used as a significant advantage for the applications in biomedical field and biotechnology. Most of these applications require the physical immobilization of bioagents (i.e., enzymes, cells or drugs) within the forming gel network. The soft character of the gel preparation procedure is very important to protect the biological agents from the undesired effects of the gel preparation medium (i.e., undesired chemical interactions between the bioagent and the ingredients in the gel formation medium or the deactivation of bioagents due to the high polymerization temperature). It is also evident that the final gel properties are strongly depend on the preparation conditions. The modification of gel formation methods for softening of preparation conditions may cause significant changes in the properties of the produced gels. By considering these reasons, we proposed a procedure conducted at +4°C for the preparation of HEMA-DMAEM copolymer gels. In the proposed method, the itself of the comonomer (i.e., DMAEM) was also used as the accelerator for the gel formation. The representative SEM photographs of the HEMA-DMAEM gel structure is shown in Figure 1. Note that these photographs were taken with the freeze-dried form of the gel swollen in an acidic medium at a pH of 1.3. The gel was produced with the DMAEM concentration of 17.8% mol. The internal structure of the gel matrix is given in Figure 1A. As seen here, the gel had a highly porous interior. The macropores up to 100 μm in size could be observed within the internal part. The SEM photograph mainly showing the surface morphology of the HEMA-DMAEM gel is given in Figure 1B. As seen

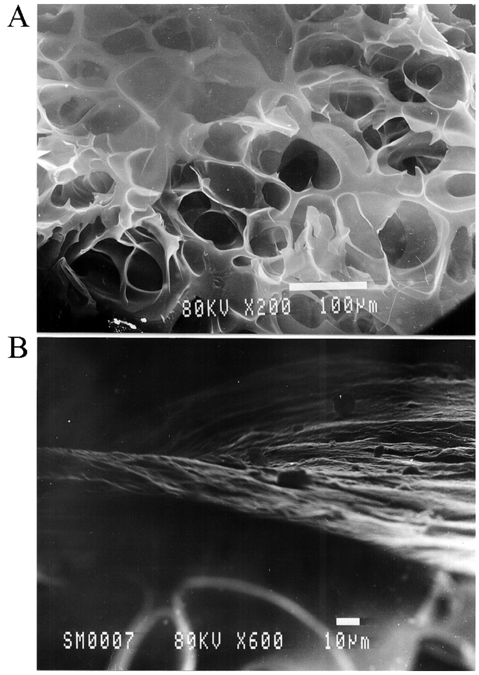

Figure 1. SEM photographs of the HEMA-DMAEM copolymer gel produced with the DMAEM concentration of 17.8% mol. (A) Internal structure, (B) Surface morphology. Magnification: 250X.

here, the exterior surface was significantly different than the gel interior. Although there were reasonably large macropores within the gel interior the surface included no macropores. As seen in Figure 1B, there was a skin layer on the surface of the gel matrix. The thickness of the skin layer was about 50 μm for the swollen polymer in acidic medium at pH 1.3. Of course, the skin layer plays an important role for increasing the internal mass transfer resistance in the diffusion of different agents into or from the gel matrix. The effects of production conditions on the kinetics of gel formation and the equilibrium swelling behavior of the produced copolymer gels are presented below.

DMAEM Concentration

In the first group of these experiments, the kinetics of gel formation was studied by changing the initial DMAEM concentration in the monomer mixture between 1.4-15.3% (based on total mole of monomer). The initiator and the crosslinker concentrations were 9.1 mg/ml monomer and 0.065% mol,

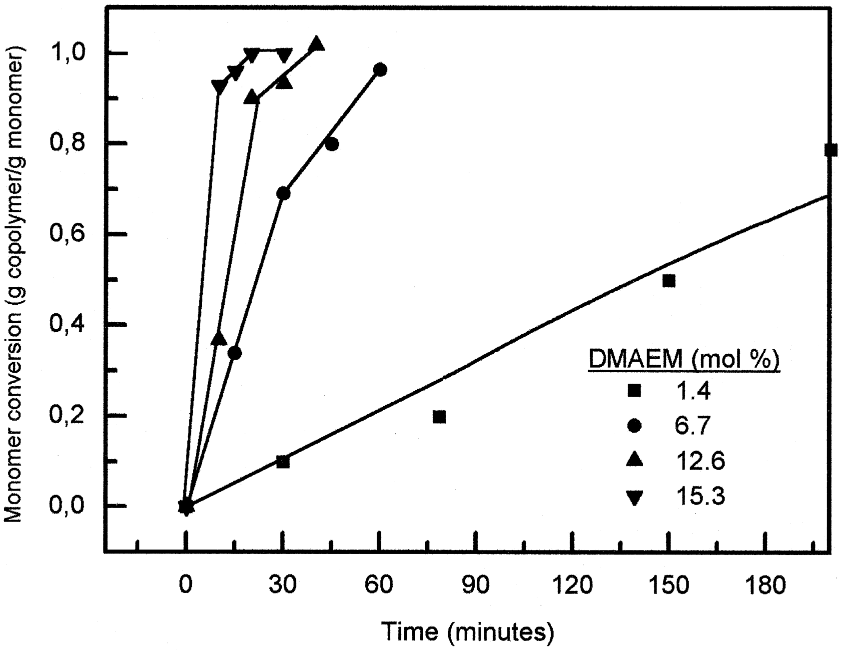

Figure 2. The effect of DMAEM concentration on the kinetics of gel formation, Polymerization conditions: Monomer/water ratio: 0.37 ml/ml, KPS: 9.1 mg/ml monomer, MBA: 0.065% mol, +4°C, 24 hours.

respectively. In this set sufficiently low initiator and DMAEM concentrations were selected to follow the gel formation. The copolymerizations were performed with a constant monomer/water volumetric ratio of 0.37 at +4°C. The total monomer conversion into the gel form was determined by stopping the gel formation at the designated times. The effect of DMAEM concentration on the kinetics of gel formation was presented in Figure 2. The complete conversion of monomers into the gel form could be achieved within about five minutes when the initial DMAEM concentration was 15.3%. However, the gel formation did not complete within 180 minutes with the initial DMAEM concentration of 1.4%. The rate of gel formation clearly increased with the increasing DMAEM concentration within the initial monomer mixture. It should be noted that no accelerator was used in the gel formation conducted at +4°C in the presence of KPS as the initiator. The increase in the copolymerization rate with the increasing DMAEM concentration may be explained by the accelerator function of the comonomer (i.e., DMAEM). As known, diamine containing chemicals (i.e., ethylene diamine, tetramethylethylene diamine) are frequently used with

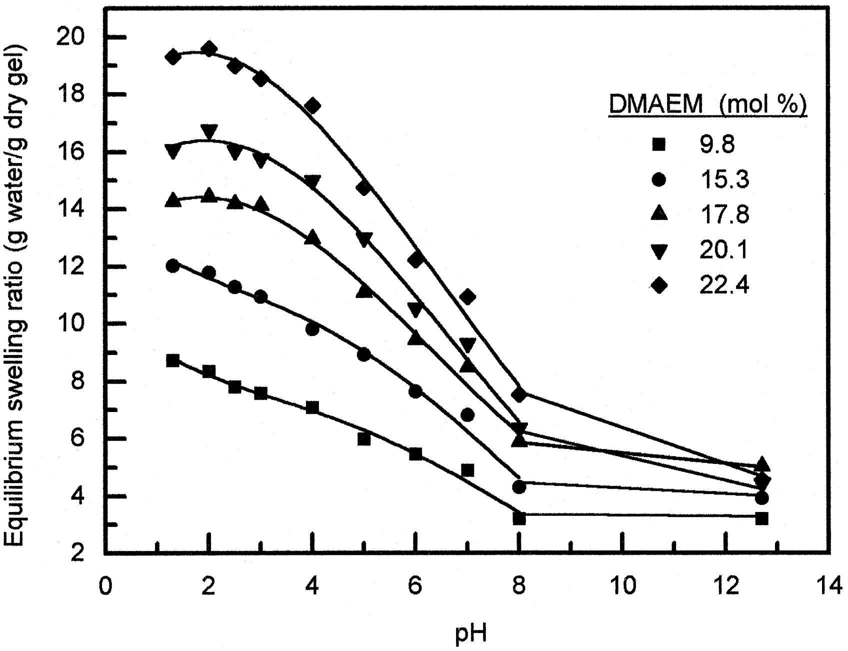

Figure 3. The effect of pH on the equilibrium swelling behavior of HEMA-DMAEM gels produced with different DMAEM concentrations. Ionic strength: 0.1, 25°C.

the persulphate type initiators, to carry out the gel formation at low temperatures starting from the hydrophilic monomers [8-11]. The role of DMAEM in the studied copolymerization process appears to be very similar to that of diamine compounds since the comonomer includes two dimethylamino groups. In our copolymerization method, the comonomer (DMAEM) possibly acted as an accelerator and formed an initiator system with KPS.

To observe the effect of DMAEM concentration on the equilibrium swelling behavior of HEMA-DMAEM copolymer, a set of gels were produced by changing the DMAEM concentration between 9.8-22.4% mol (Table 1). The cylindrical gel samples with 8 mm in diameter and 4 mm in height at the production conditions were used. The effect of pH on equilibrium swelling behavior of HEMA-DMAEM gels produced with different DMAEM concentrations is given in Figure 3. As seen here, the equilibrium swelling ratio significantly decreased with the increasing pH, especially in the range of 1 and 7 for the each gel. The gels produced with higher DMAEM concentrations exhibited higher equilibrium swelling ratios in the acidic pH region. As described in the literature, the balance of forces determining the equilibrium swelling behavior of HEMA-DMAEM gel is changed significantly by the medium pH [1, 12]. The tertiary amine side groups are protonated when the pH is decreased to the acidic region. Then, a higher degree of ionization in the acidic pH region provides higher swelling ratios. The degree of ionization of polyelectrolyte network is closely related to the amount of ionizable group content (i.e., DMAEM residues). The increase in DMAEM content of the copolymer provides higher degree of protonation in a certain acidic pH value, which in turn also causes an increase in the equilibrium swelling ratio.

In the literature, relatively sharper volume transitions at a pH of 7 were reported for the alkylmethacrylate-DMAEM copolymer gels (1). However, the volume transitions with the gels produced in our study were not as sharp as those obtained by Siegel *et al.* (Figure 3). DMAEM concentration and cross-linking density, the gel size and the type of swelling medium are the important factors affected on the phase transition behavior of these gels. In our study, DMAEM concentration in the pre-gel solution was changed between 9.8-22.4% mole. Siegel *et al.* produced alkylmethacrylate-DMAEM gels by changing DMAEM concentration between 7 and 30% mole. We selected very close values to those used in Siegel's study for the initial DMAEM concentration (i.e., 15.3 and 22% mole). Then, it was possible to make a comparison for the gels produced with the same DMAEM concentration. Although different crosslinking agents were used in the production of their and our gels, the concentration of crosslinker in the pre-gel solution was reasonably low in both studies. Therefore, the compared gels were in the lightly crosslinked form. The swelling media used in their and our studies were the same (i.e., 0.01 M citrate buffer). Siegel *et al.* used circular gel disks 9.5 mm in diameter and 0.27-0.32 mm in height. We used circular disks 8 mm in diameter, but 4 mm in height in our equilibrium swelling studies. Another factor having an effect on the phase transition behavior is the type of acrylate based monomer used in the synthesis of DMAEM containing gels. The alkylmethacylate monomers used in Siegel's study (i.e., methyl, ethyl, propyl, butyl and hexyl methacrylate) had a more hydrophobic character relative to HEMA (1). Significantly lower equilibrium water contents (about 0.05 g water/g copolymer) could be obtained with their copolymers at the pH values higher than critical value at which the volume transition was observed (i.e., pH:7.0) (1). The equilibrium water contents of our HEMA-DMAEM copolymers in the collapsed state were approximately 2-6 g water/g copolymer. The hydrophilic

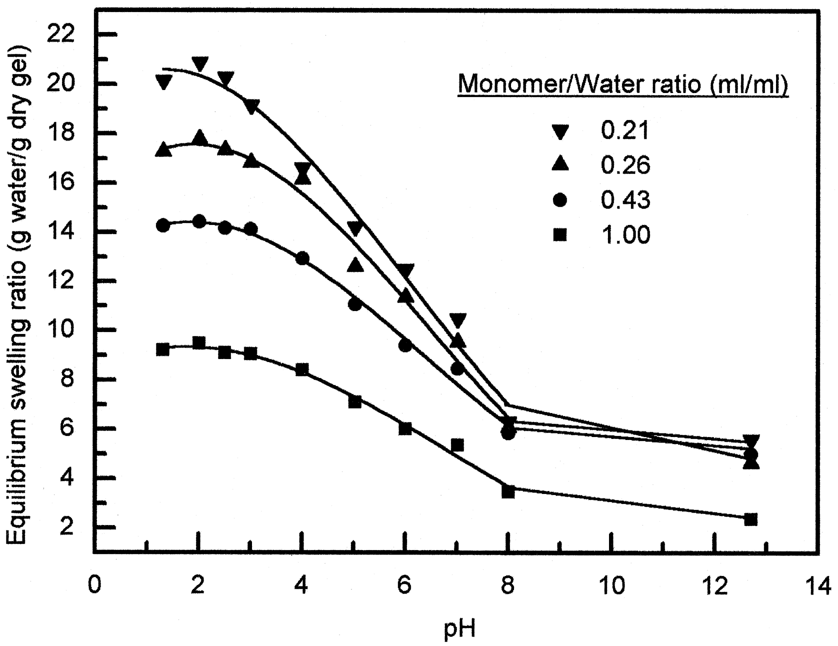

Figure 4. The effect of pH on the equilibrium swelling ratio of HEMA-DMAEM gels prepared with different monomer/water ratios. Ionic strength: 0.1, 25^{o}C.

character of poly(HEMA) segments in our copolymers possibly prevented a drastic decrease in the equilibrium water content after the pH of 7. Siegel *et al.* stated that the gels produced by the copolymerization of hydrophobic alkylmethacrylates with DMAEM were in the glassy state when the external pH was above the critical pH at which the volume transition occurred. Below the critical pH, the gels became rubbery in their highly swollen state [4]. They also proposed that the DMAEM carrying cationic gels exhibiting a smoother transition should be rubbery both in the collapsed and swollen states [4]. In the light of this discussion, the more soft transition observed in our case may also be attributed to the rubbery form of the HEMA-DMAEM gels both in the collapsed and swollen states.

Monomer/Water Ratio

The production conditions of the gels used in this set of experiments are given in Table 1. The cylindrical gel samples were cut into discs with 8 mm in

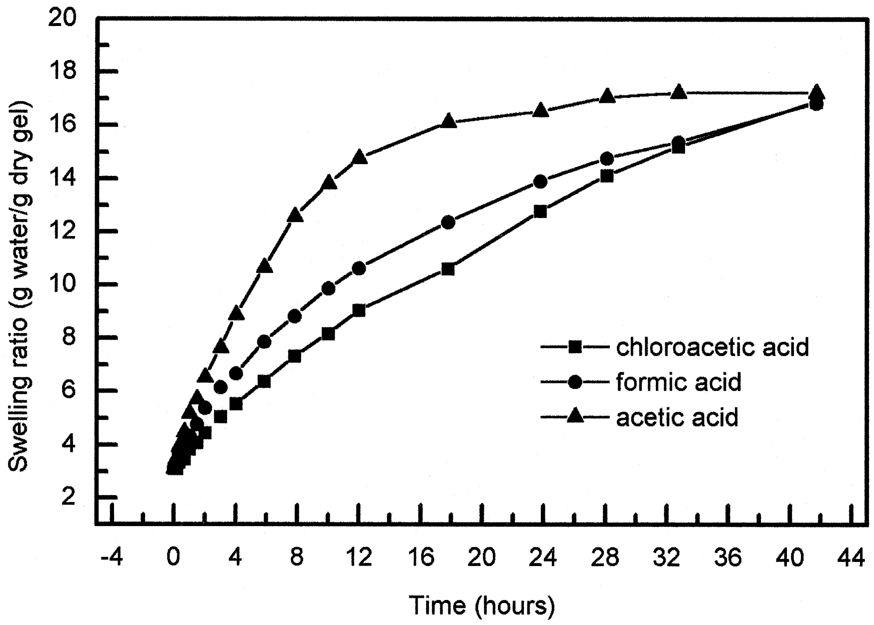

Figure 5. The variation of swelling ratio with the time in the buffer solutions prepared with different carboxylic acids. (Gel DMAEM content: 22.4% mol, buffer properties: pH:3.0, Ionic strength: 0.1, 25°C).

diameter and 4 mm in length at the production conditions. The variation of the equilibrium swelling ratio of the gels produced with different monomer/water ratios by the medium pH is given in Figure 4. As seen here, for a certain pH value in the acidic region, the equilibrium swelling ratio of the gel increased with the decreasing monomer/water ratio (i.e., increasing amount of water in the gelation medium). To use higher amount of water in the gelation medium possibly resulted in a gel sample with higher porosity at the production conditions. Therefore, the gels produced with the higher porosities exhibited higher swelling ratios especially in acidic pH values.

Buffer Type and Concentration

To observe the effects of buffer type and concentration on the dynamic swelling behavior of gels, the carboxylic acid buffers (chloroacetic, formic and acetic acids with respective pK_a's of 2.74, 3.75 and 4.75) were used [3, 5]. pH and ionic strength were set to 3 and 0.1 in all solutions. The pK_a value of DMAEM was determined as 7.7 [13]. To observe an appreciable swelling be-

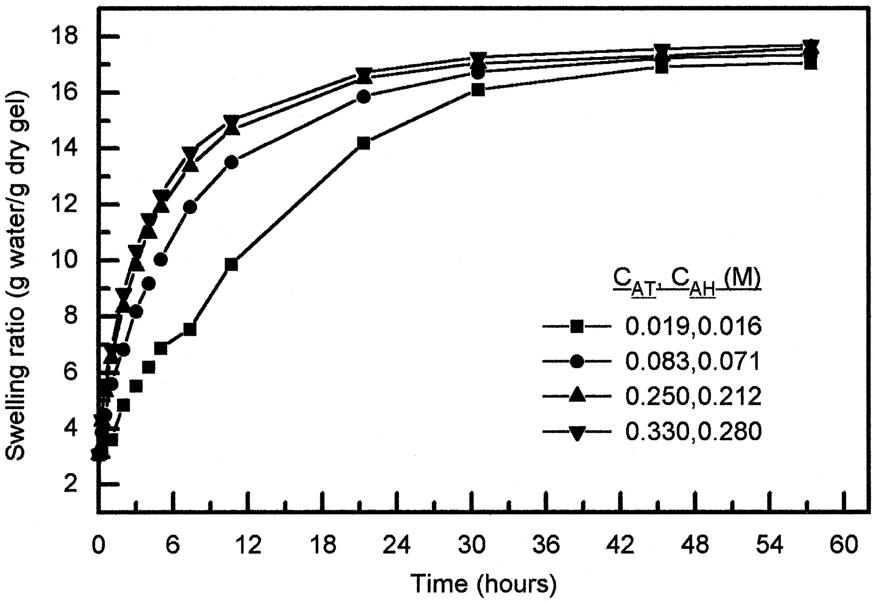

Figure 6. The variation of swelling ratio with the time in the formic acid buffer solutions having different C_{AH} values. (Gel DMAEM content: 22.4% mol, buffer properties: pH:3.0, Ionic strength: 0.1, 25^{o}C).

havior, a swelling medium having a pH value which was relatively lower than the pK_a value of the polybasic gel was selected [5]. The gel cylinders produced with DMAEM concentration of 22.4 % mol and having 8 mm in diameter and 4 mm in length in the production conditions were used for testing of the buffer effect. Before the swelling experiments, the gel samples were collapsed in 0.05 N NaOH solution up to the equilibrium. The variation of swelling ratio with the time in the buffer solutions prepared with different carboxylic acids are given in Figure 5. As seen here, the swelling rate increased with the increasing pK_a of the carboxylic acid buffer. Similar results were also observed with the methyl methacrylate-DMAEM and ethyl methacrylate-DMAEM gels, elsewhere [2, 3]. In the presence of higher K_a value, the concentration of unionized acidic form of the buffer is higher. This leads to an increase in the number of total hydrogen ions available in solution. Then, the protonation rate of amine groups in the gel matrix increases. The increase in the swelling rate can be explained by the increasing protonation rate of amine groups. To verify this explanation, a series of buffer solutions were prepared with formic acid and the concentration of unionized (acid form) buffer concentration (C_{AH}) was changed by changing the total buffer concentration ($C_{A,T}$) at a constant pH value of 3. The dynamic swelling behavior of the same gel was followed within the formic acid buffer solutions having different C_{AH} values. The variation of dynamic swelling ratio with the time is given in Figure 6. As seen here, the swelling rate clearly increased with the increasing total buffer concentration (i.e., the increasing unionized acid form concentration).

It should be noted that a dynamic swelling curve indicating a constant swelling rate during the whole swelling process was obtained under similar conditions (i.e., in formic acid buffer at pH:3) for 78/22 mol % HEMA/DMAEM copolymer produced at 60°C [5]. The linearity of the observed swelling curve originated from the rubbery character of the gel at the beginning of the copolymerization process (i.e., in the shrunken state). In our case, slightly different from this finding, a faster initial swelling rate were observed in formic acid buffer media, with the copolymer gel produced by the HEMA/DMAEM mol ratio of 77.6/22.4 (Figure 6). This result may be evaluated as further evidence indicating the rubbery character of the collapsed HEMA-DMAEM copolymers produced at +4°C.

Mathematical Model

Different mathematical models are available in the literature for the definition of the swelling and shrinking kinetics of stimuli sensitive gels [14-22]. One of these approaches is the unsteady state diffusion model (i.e., Fick's second law) [18-22]. This approach was used by Gehrke *et al.* to determine the effective diffusion coefficient of water during swelling and shrinking of a poly(NIPA) gel matrix having planar geometry [18-21]. We also applied an unsteady state diffusion model on the dynamic behavior of HEMA-DMAEM gels to estimate the effective diffusion coefficient of water during dynamic swelling and shrinking processes. The cylindrical gel samples with 25 mm in diameter and 1.5 mm in length in the production conditions were used in the diffusion coefficient determinations. The ratio of crossectional area to the lateral one was 8.33 in the production conditions. Therefore, these gels may be considered in the slab form. The mass balance for water diffusion during swelling or shrinking of a disc-shaped gel may be given as follows [22]:

$$D \frac{\delta^2 C}{\delta z^2} = \frac{\delta C}{\delta t} \qquad (3)$$

where z and t are the axial distance and the time, respectively. C is the concentration of water within the gel matrix at any length and at any time. D is the effective diffusion coefficient of water within the gel matrix and it may be assumed to be constant when the change of gel size is small during the shrinking or swelling process. The boundary conditions and the initial condition may be given by the following expressions.

$$z=-L \quad \text{and } t>0 \quad C=C_s \tag{4}$$

$$z=+L \quad \text{and } t>0 \quad C=C_s \tag{5}$$

$$t=0 \quad -L< z<+L \quad C=C_o \tag{6}$$

The solution of Equation 3 with the conditions of 4, 5, and 6 yields the concentration profile of water within the gel matrix.

$$\frac{C - C_o}{C_s - C_o} = 1- \frac{4}{\pi} \sum_{n=0}^{\infty} \{(-1)^n/(2n+1)\} \exp \{- D(2n+1)^2\pi^2 t/4L^2\} \operatorname{Cos}\{(2n+1)\pi z/2L\} \tag{7}$$

If M_t is the diffused amount of water which entered of left the slab in time t and M_∞ is the same magnitude after infinite time, the ratio of M_t/M_∞ can be obtained by using Equation 8.

$$(M_t / M_\infty) = 1- \sum_{n=0}^{\infty} \{ 8/(2n+1)^2\pi^2\} \exp \{-D(2n+1)^2\pi^2 t/4L^2\} \tag{8}$$

As seen here, Equation 8 can be used for the estimation of effective diffusion coefficient of water within the gel matrix. To follow the constant gel size assumption, only M_t/M_∞ values obtained until 50% of the total weight change in a certain step input were taken into account as dependent variables for the estimation of effective diffusion coefficients. In our study, four different step inputs on the medium pH were applied to induce the gel swelling/or shrinking. First, the gels equilibrated at a pH of 1.3 were transferred into the citrate buffer medium having a pH of 4. Then the shrinking of gels at pH 4 was monitored by following the decrease in gel weight. In the next step, the gel beads equilibrated at pH 4 were again transferred into the medium at a pH of 1.3. The swelling of gel in this medium was again followed. These two inputs were applied for the determination of effective diffusion coefficient of water during the swelling and shrinking processes occurred in the acidic pH region (i.e., between 1.3 and 4). To determine the effective diffusion coefficient of water both in the shrinking or swelling occurred in the basic pH region, two step inputs were applied similarly by changing the medium pH from 6 to 12.7 and from 12.7 to 6.

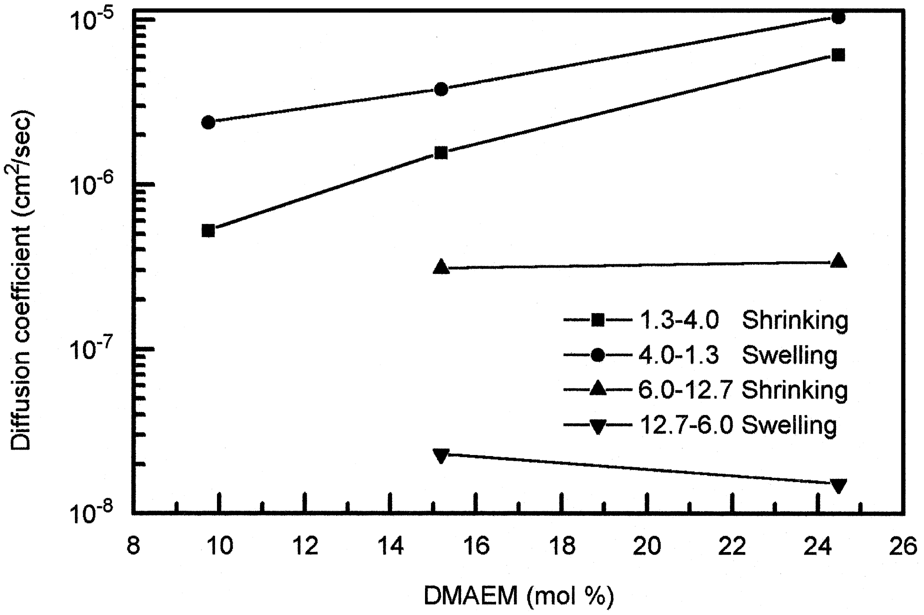

Figure 7. The variation of swelling and shrinking diffusion coefficients of HEMA-DMAEM gels with the DMAEM content of the copolymer.

In the application of step inputs, we tried to keep the pH intervals as large as possible to observe an appreciable and easily measurable change in the gel weight for the calculation of accurate M_t/M_∞ values over the swelling and shrinking periods. The M_t/M_∞ values were calculated based on the weight change of the gel matrices at the each step input. The effective diffusion coefficient estimations based on Equation 8 were performed on an IBM computer, by using a nonlinear curve-fitting algorithm written in Basic language. The time and M_t/M_∞ values of each gel matrix in a certain step input were used as the independent and dependent variables, respectively. The standard deviations for M_t/M_∞ values were calculated by evaluating three response curves for the same gel. Reasonably small standard deviation values with all input types indicated that the gel response was reversible and reproducible. The variation of estimated effective diffusion coefficient of water with the DMAEM concentration of the copolymer gel is shown in Figure 7. In the production of these gels, DMAEM concentration was changed between 9.7 and 24.3 mol%. The initiator and crosslinker concentrations were 48 mg/ml monomer and 0.065 mol%. The gel matrices were produced by the monomer/water volumetric ratio of 0.43. As seen in Figure 7, the effective diffusion coefficients for water were obtained in a

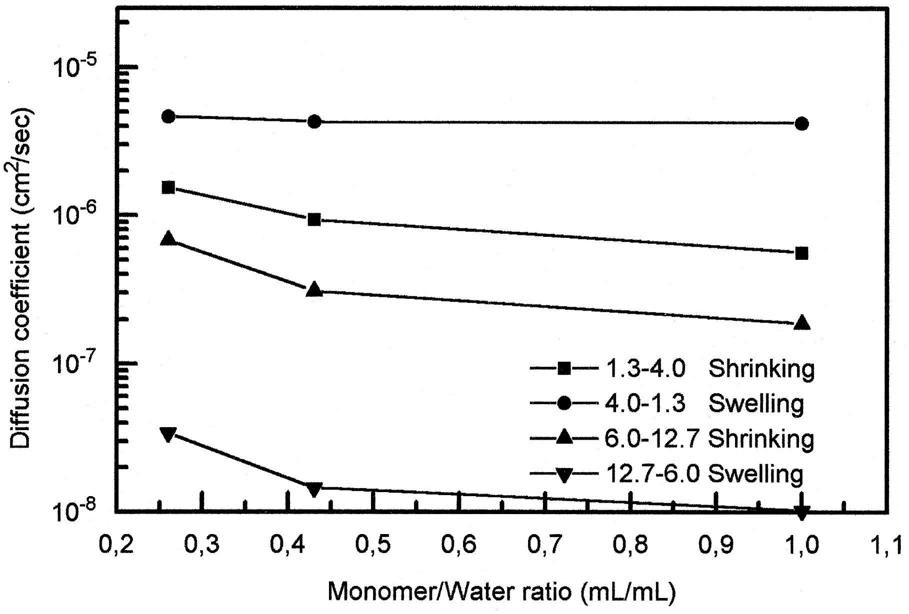

Figure 8. The variation of swelling and shrinking diffusion coefficients of HEMA-DMAEM gels with the initial monomer/water ratio of the copolymer.

very broad range (between 1x10^{-8} and 1x10^{-5} cm^2/s) depending on the type of applied step input and copolymer composition. For a constant copolymer composition, higher effective diffusion coefficients both in the shrinking and swelling (termed as shortly shrinking and swelling diffusion coefficients) were estimated by the step inputs applied in the acidic pH region (pH values between 1.3 and 4) relative to those in the basic pH region (i.e., pH values between 6 and 12.7). The swelling and shrinking diffusion coefficients in the acidic pH region were mostly greater than 1x10^{-6} cm^2/s (i.e., two upper curves in Figure 7). No appreciable change was observed in the swelling and shrinking diffusion coefficients with the DMAEM content of the copolymer in the basic pH region. However, the swelling and shrinking diffusion coefficients in the acidic pH region significantly increased with the increasing DMAEM content of the copolymer. By applying the step inputs in the basic pH region (i.e., between 6.0 and 12.7), a reproducible and appreciable response could not be obtained for the copolymer gel prepared with 9.7% mol DMAEM content. Then, the swelling and shrinking diffusion coefficients in the basic pH region were not calculated for this gel. The another result obtained Figure 7 was that the swelling diffusion coefficient was higher than that of the shrinking in the acidic pH region for a certain gel while an opposite tendency was observed in the basic pH region. Figure 7 indicated that the effective diffusion coefficient of water within HEMA-DMAEM gel was a strong function of the medium pH. The variation of the effective diffusion coefficient of water with the monomer/water ratio of the gel was shown in Figure 8. In the production of these gels, the monomer/water ratio was changed between 0.26-1.0. The initiator and crosslinker concentrations were 48 mg/ml monomer and 0.065 mol%. The DMAEM concentration in the monomer phase was 17.8 mol%. As seen in Figure 8, both the shrinking and swelling diffusion coefficients decreased with the increasing monomer/water ratio. This decrease was especially clear for the swelling and shrinking diffusion coefficients obtained by the step inputs applied in the basic pH region (i.e., between 6-12.7).

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