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Research Article

pH-Dependent Swelling and Solute Diffusion Characteristics of Poly(Hydroxyethyl Methacrylate–CO–Methacrylic Acid) Hydrogels

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Poly(hydroxyethyl methacrylate–co–methacrylic acid) hydrogels can swell extensively in a high-pH medium where the carboxyl groups are ionized. The swelling equilibrium is a strong function of the methacrylic acid composition of the polymer and pH of the medium. The nonionized gel structure was found to be rather insensitive to the amount of cross-linker, tetraethylene glycol dimethacrylate (TEGDMA), incorporated, within the range of 0.5 to 3%. This result is supportive of the existence of secondary interactions that shield the effect of covalent cross-links. Phenylpropanolamine (PPA) was used as a probe solute to study the diffusion characteristics of the poly(HEMA–co–MA) gels. Its diffusion coefficient in the swollen matrices of different methacrylic acid compositions at various pH's was measured via a desorption method. It is evident that these diffusion coefficients follow Yasuda's free volume theory, which expresses an exponential relationship between the solute diffusivity in a swollen polymer membrane and the reciprocal of the membrane hydration. Although interactions exist between PPA and the hydrogel matrix, these interactions are not significant enough to perturb the free volume relationship established. This observation can be explained by the high ionic strength of the system.

KEY WORDS: hydrogel; pH-dependent swelling; diffusion; free volume.

INTRODUCTION

While the release kinetics of swelling polymers have received considerable attention (1–3), the drug release mechanism and kinetics of hydrogel materials whose swelling is pH dependent have not been reported. Potential applications of these systems include delayed and controlled oral delivery, altered gastrointestinal transit following gastric emptying, and site-specific gastrointestinal delivery based on regional pH differences (4,5). In order to access the potential of pH-dependent swelling systems, it is necessary to understand the mechanism of swelling and drug release from these systems.

Cross-linked hydrogels with ionizable side chains can swell extensively in aqueous media. The swelling behavior depends on the nature of the side groups as well as the pH of the medium. In this work, copolymers of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MA) cross-linked with tetraethylene glycol dimethacrylate (TEGDMA) were investigated. This report focuses on the studies of matrix swelling and its subsequent influence on the drug release rate. Phenylpropanolamine (PPA) was chosen to be the model compound for the release study due to its stability and water solubility. Since solute diffusion in hydrophilic polymers depends mainly on the water content of the matrix, the equilibrium swelling will be characterized at various pH's and copolymer compositions. The release characteristics of PPA from the swelling gel matrix are determined, and the diffusion coefficients of PPA in these swollen gels quantitated and subsequently correlated to the water content of the matrices. It is also anticipated that interactions between PPA molecules and the ionized gel matrix will occur. Therefore, the effect of the charge density on the PPA diffusion coefficient is investigated and the extent of its influence delineated.

MATERIALS AND METHODS

Synthesis of Poly(Hydroxyethyl Methacrylate–co–Methacrylic Acid) Hydrogels

The hydrogels were prepared from monomeric materials via a free radical mechanism. 2-Hydroxyethyl methacrylate[4] and methacrylic acid[4] were purified before use, while cross-linker tetraethyleneglycol dimethacrylate[4] was used as received. The detailed procedure of HEMA purification was discussed by Brinkman *et al.* (6). The HEMA monomer was extracted with hexane and followed by vacuum distillation (250 μHg; 55°C). Cuprous chloride was used as the polymerization inhibitor in the distilling flask. The methacrylic acid

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was relatively pure and was distilled only under vacuum (1.5 mm Hg; 45°C).

The hydrogel slabs were synthesized via solution polymerization. The monomer mixture contained 40% (w/w) water initially. Various monomer and cross-linker concentrations were used to prepare gels of different compositions. The methacrylic acid concentration ranges from 1 to 50% (w/w), and TEGDMA from 0.5 to 3% (w/w) in the monomeric mixtures. The monomer solution was then initiated with a redox couple of ammonium persulfate and sodium metabisulfite. The reacting mixture was injected into a mold made of two glass plates spaced 1.8 mm apart by a silicone rubber gasket. The reaction was allowed to run for 2 hr at 60°C. The resultant polymer was removed and washed in portions of fresh distilled water for at least 1 week before use to purge the residual reactants from the gel.

The hydrogel cylinders were fabricated in the polyethylene tubing (3-mm i.d.) via bulk polymerization. The methacrylic acid compositions used in monomeric mixtures were 10 and 30% (w/w), and the TEGDMA concentration was fixed at the level of 0.2% (w/w). The monomeric solution was initiated with 1% 2,2″-azobisisobutyronitrile (AIBN) and then injected into a straight polyethylene tubing. The two ends were then sealed and the entire enclosure was maintained in a 60°C water bath for 12 hr. The resulted polymer cylinder was removed and cut into segments 3 cm in length. The polymer gels were washed in portions of fresh distilled water for a period of at least 1 week before further use. Structural identification was not performed with these gels since the polymerization procedure for the methacrylate monomers was well established and documented (8–11). For the rest of the discussion, whenever methacrylic acid composition is described, it is intended to mean the composition of the monomeric solution from which the polymer is made.

Equilibrium Swelling Study

In the swelling study, only the hydrogel slabs made via solution method were used. Gels of different compositions were cut into squares of 1.8 × 1.8 cm^2 and equilibrated in 0.1 *M* HCl solutions until the weight was stabilized. The gels were then transfered to pH 7 buffers of 0.1 *M* ionic strength. Sample weight was followed and sufficient time was allowed to reach swelling equilibrium. The experimental temperature was maintained at 37°C throughout. Two indices, *SR* and *H*, were used to represent the equilibrium swelling behavior. The swelling ratio (*SR*) was defined by

$$SR = \frac{\text{equilibrium weight at pH 7}}{\text{equilibrium weight at pH 1}}$$

The matrix hydration (*H*) was defined by

$$H = \frac{\text{equilibrium swollen gel weight} - \text{dry gel weight}}{\text{equilibrium swollen gel weight}}$$

Drug Release and Measurement of Diffusion and Partition Coefficients

Phenylpropanolamine was used as obtained without further purification. Gels of different methacrylic acid compositions were used in these experiments. Drug loading was carried out by equilibrating the gel sample in a 2% drug solution at a proper pH. The ionic strength for both loading and extracting media was kept at 0.2 *M*. If the gel slab was used, a sample 3 cm in diameter was used. The loaded sample was clamped between a circular plexiglass ring and a base permitting release over one surface, and the composite was anchored in the extracting medium by a plexiglass rod. If the gel cylinder was used, the sample was held in a stainless-steel wire basket. The volume of the extracting fluid was 200 ml, and the stirring speed 120 rpm. PPA samples were assayed by an ion-pairing high-performance liquid chromatographic (HPLC) method.

The mathematical analysis employed in calculating diffusion and partition coefficients from the desorption experiments is based on a diffusion model developed by Lee (7). The advantage of this model is that the analysis allows the external bulk concentration to increase with time via a mass balance at the gel/bulk fluid interface. Experimentally, one then can use any bulk volume for extraction and the sink condition is not required. In addition, partition coefficient can be determined based on the initial loading and final equilibrium drug concentrations. The working equation for evaluating the diffusion and partition coefficients for planar geometry is

$$\tau = \frac{3\Lambda^2}{4}\left[\ln\frac{C_b - C_{b1}}{C_{b2} - C_{b1}} + \frac{1}{2}\left(\frac{C_{b2} - C_{b1}}{C_b - C_{b1}}\right)^2 - \frac{1}{2}\right] = \frac{Dt}{a^2} \tag{1}$$

where

$$\Lambda = \frac{C_{b\infty} - C_{b1}}{C_{b2} - C_{b\infty}} = \frac{V}{2KAa} \tag{2}$$

and for cylindrical geometry,

$$\tau = \frac{3}{40}\lambda^3\left[\left(\frac{C_{b2} - C_{b1}}{C_b - C_{b1}}\right) - 1\right]^3 + \frac{3(3\lambda + 5)}{160}\lambda^2\left[\left(\frac{C_{b2} - C_{b1}}{C_b - C_{b1}}\right) - 1\right]^2 \frac{3\lambda^2(5 - 3\lambda)}{80}\left[\left(\frac{C_{b2} - C_{b1}}{C_b - C_{b1}}\right) - 1\right] - \frac{3\lambda^2(5 - 3\lambda)}{80}\ln\left(\frac{C_{b2} - C_{b1}}{C_b - C_{b1}},\right) \tag{3}$$

where,

$$\lambda = \frac{C_{b\infty} - C_{b1}}{C_{b2} - C_{b\infty}} = \frac{V}{k\pi r^2 L} \tag{4}$$

The diffusivity can be calculated from the slope of the τ versus t plot, and k from the equilibrium concentration data using Eq. (2) or (4). Please refer to the Nomenclature for the definitions of various quantities involved in these equations.

RESULTS AND DISCUSSION

Swelling Equilibrium

Experimental SR values determined from gels of dif-

ferent compositions are reported in Table I. These data were fitted to a third-degree polynomial, with MA and TEGDMA concentrations being the independent variables. The regressed equation represents a three-dimensional response surface. If the contour lines, lines of equal SR values, are drawn to this surface and projected onto the $X-Y$ plane, the result is a two-dimensional representation of the three-dimensional surface. Figure 1 is such a plot. The trend of the surface reveals that the cross-linker concentration is a major determining factor of the swelling ratio with gels of a high methacrylic acid content. However, the cross-linking effect is insignificant in the low methacrylic acid-containing gels. Within the range of composition studied, the maximum SR observed is 8.02 with the gels of 50% methacrylic acid and 0.5% TEGDMA.

Figure 2 is the plot of matrix hydration versus methacrylic acid concentration at different pH's and cross-linker concentrations. The matrix hydration of the nonionized gels with the lowest methacrylic acid content, i.e., 1%, is about 0.38, which is in good agreement with the literature value for a pure poly(HEMA) gel (8,9). The error bars are within the symbols and thus not shown in the graph. It is of interest to note that for gels of different methacrylic acid contents at pH 1, the equilibrium state is not determined by the cross-linker concentration, as shown by the superimposed curves in Fig. 2. However, the cross-linking effect is readily revealed in the ionized gels at pH 7. This interesting finding suggests that some other forces besides the covalent cross-links are responsible for the stabilization of the unionized equilibrium structure. Refojo attributed these forces in pure poly(HEMA) gel to the hydrophobic interaction between the α-methyl groups on the polymer backbone (10). Ratner and Miller proposed the alternative explanation that the hydrogen bonding is the responsible interaction (11). These interactions, generally referred to as secondary structures, form the physical cross-links between the polymer chains which overshadow the effect of covalent cross-links. Either of these interactions is certainly likely to exist in the nonionized poly(HEMA-co-MA) gel matrices at pH 1 since both HEMA and nonionized MA units contain the necessary functionalities to allow these interactions to occur. When

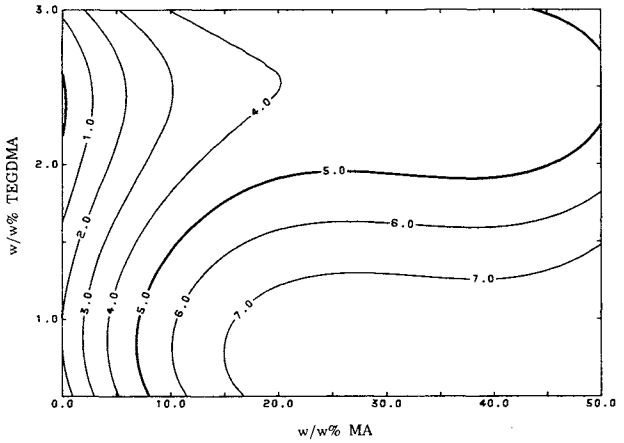

Fig. 1. Contour plot of swelling ratio, *SR*, as a function of MA and TEGDMA compositions.

the secondary structures are disrupted upon the ionization of carboxyl groups at pH 7, the effect of the covalent cross-links is readily revealed. This is evidenced by the separation of the top two curves at pH 7 in Fig. 2.

Effect of Swelling on the Diffusional Release of Phenylpropanolamine

Figure 3 demonstrates the effect of matrix swelling on PPA release from the poly(HEMA-co-MA) gel. The gel is composed of 50% methacrylic acid and 0.5% TEGDMA. Curve c is the release at pH 1 with drug loaded at pH 1, while curve a is the one with both loading and release at pH 7. There is thus no swelling involved in either of these cases. The middle curve (b) is the swelling release at pH 7 with drug loaded at pH 1. The swelling apparently accelerates the drug release process. This behavior suggests that the diffusional mobility of drug molecules is significantly increased in the matrix as a result of swelling. The diffusion and partition coefficients were then measured at various pH's representing different matrix hydrations. The desorption method based on Lee's (7) analysis is particularly suitable for the

Table I. Swelling Ratio, *SR*, of Poly(HEMA-co-MA) Gels of Different Compositions

	TEDGMA (w/w %)		
MA (w/w %)	0.5	1.5	3.0
1	1.97 (0.065, 3)[a]	1.86 (0.117, 3)	1.67 (0.104, 3)
4	3.47 (0.486, 3)	2.99 (0.182, 3)	2.58 (0.219, 3)
10	5.72 (0.137, 2)	4.83 (0.136, 3)	—
20	7.36 (0.140, 3)	6.15 (0.125, 3)	4.96 (0.137, 3)
50	8.05 (0.235, 3)	6.97 (0.246, 3)	5.78 (0.147, 3)

[a] Numbers in parentheses indicate SD and number of observations, respectively.

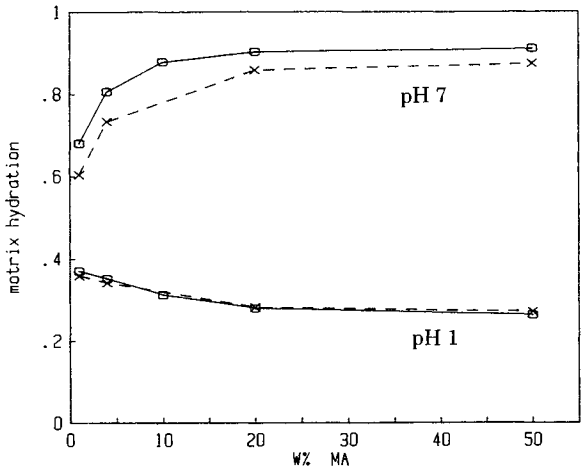

Fig. 2. Effect of polymer composition on *H* of poly(HEMA-co-MA) gels at pH 1 and 7. □ and ×, 0.5 and 3% TEGDMA, respectively.

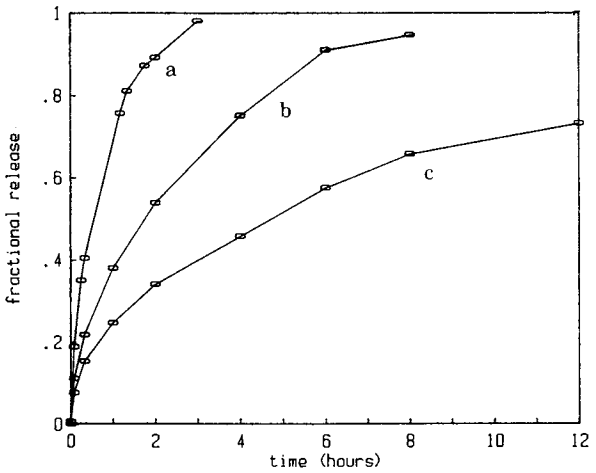

Fig. 3. Effect of swelling on PPA release from poly(HEMA–co–MA) gels. (a) Loading and release at pH 7. (b) Loading at pH 1; release at pH 7. (c) Loading and release at pH 1.

measurement because both parameters can be determined in one experiment. The aqueous boundary layer effect on the diffusional release of drug species such as PPA was shown to be negligible, as expected, by varying the stirring rate from 120 to 390 rpm.

Table II summarizes the diffusion and partition coefficient data obtained. If we focus on the data from 50% MA gels, it is clear that the PPA diffusion coefficient has a very marked dependence on the matrix hydration. There is about a 52-fold increase in diffusivity when H increases from 0.35 to 0.88. Yasuda (12) proposed a free volume theory to describe the relationship between the solute diffusivity in gel matrix and the matrix hydration. It takes the form of

Table II. Diffusion and Partition Coefficients of PPA in Swollen Poly(HEMA–co–MA) Gels of Different Compositions and at Various pH[a]

pH	MA content (%)	H[b]	$D \times 10^8$ (cm²/sec)	K	N
1	50	0.352 (0.0014)	2.50 (0.453)	1.41 (0.365)	3
3	50	0.377 (0.0002)	3.58 (0.351)	1.59 (0.0403)	4
5	50	0.639 (0.0211)	44.6 (3.83)	4.42 (0.670)	6
7	50	0.880 (0.004)	139.0 (25.6)	4.64 (0.402)	5
7	10	0.702 (0.001)	74.4 (0.721)	1.84 (0.035)	3
1	30	0.309 (0.0009)	2.36 (0.306)	0.54 (0.061)	3
5	30	0.527 (0.0015)	24.4 (1.49)	2.53 (0.218)	3
6	30	0.775 (0.0031)	98.3 (2.92)	2.44 (0.05)	3
7	30	0.838 (0.0006)	155.5 (5.50)	2.67 (0.055)	3

[a] Numbers in parentheses indicate SD. N is the number of experiments.
[b] Matrix hydration.

$$\ln D = \ln D_0 - k_f\left(\frac{1}{H} - 1\right) \tag{5}$$

where D_0 is the diffusivity of the solute in pure solvent medium, and k_f is a constant characteristic of the solute and the solvent molecules. According to this theory, the plot of ln$D$ vs $1/H - 1$ will be linear with the slope k_f and intercept lnD_0. Figure 4 is the free volume plot of PPA diffusivities in 50% MA poly(HEMA–co–MA) gels. Over the range of hydration studied, the apparent linearity is excellent.

The partition coefficient also increases with the matrix hydration. This is indicative of some significant interactions existing between the cationic PPA molecules and the ionized hydrogel matrices at high pH's. If this is the case, the diffusion coefficients measured must be apparent quantities since they include the interaction component. One way to visualize the effect of the interaction on the solute transport through the gel matrix is to include the reversible binding in the diffusion model. The mass transfer equation in one dimension then becomes

$$\frac{\partial c}{\partial t} = \frac{D}{1 + \gamma}\frac{\partial^2 c}{\partial x^2} \tag{6}$$

where γ is the binding constant (13). According to the model, the effective diffusivity D', $D/(1 + \gamma)$, will underestimate the diffusivity, D, by a factor of $1 + \gamma$. From the data obtained, one can compare the experimental D_0 value at $H = 1$ to the PPA diffusivity in pure water. The aqueous diffusivity of PPA was estimated by the Hayduk and Laudie method (14). The molal volume necessary for the calculation was the arithmetic average of the Schroeder and Le Bas estimates. Since the PPA molecule was cationic, the charged group was assumed to be hydrated by six water molecules. The following are the values obtained:

$$D_0(\text{regressed experimental}) = 1.82 \times 10^{-6}\ \text{cm}^2/\text{sec}$$
$$D_0(\text{Hayduk–Laudie}) = 5.51 \times 10^{-6}\ \text{cm}^2/\text{sec}$$

The experimental value is approximately threefold smaller than the estimated D_0. From this result and the partition coefficient data, we conclude that the interaction between PPA molecules and the poly(HEMA–co–MA) network does

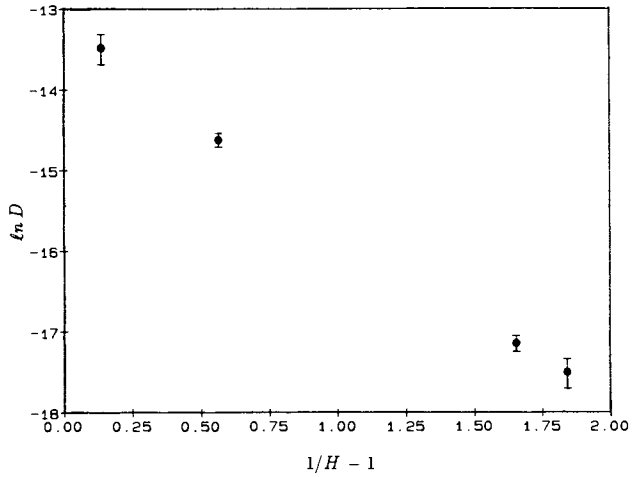

Fig. 4. Semilogarithmic plot of PPA diffusivity in 50% MA poly(HEMA–co–MA) gels at various pH's versus $(1/H) - 1$.

exist and the experimentally determined PPA diffusivities are apparent quantities because they include the effect of the interaction. This interaction however, does not perturb the apparent linearity of the free volume relationship according to Yasuda *et al.* (12).

To investigate further the effect of the influence of charge density on the free volume relationship, the PPA diffusivities were measured at various pH's in poly(HEMA–co–MA) gels of different methacrylic acid contents, i.e., 30 and 10%, while keeping the same ionic strength of the system, i.e., 0.2 *M*. The result is reported in Table II along with the partition coefficients determined. Figure 5 is the ln*D* vs $(1/H) - 1$ plot pooling all the PPA diffusivities obtained from 50, 30, and 10% methacrylic acid gels. If the interaction is indeed significant, one will observe some deviations from the linearity in the free volume plot, especially at the high-*H* range where the gels are ionized. It is readily seen from Fig. 5 that all data fall on the same line except the very last data point on the right-hand side. This result suggests that the influence of the charge interaction between PPA and the ionized matrix on the diffusional mobility of PPA molecules is minimal within the range of 0 to 50% methacrylic acid content. It can thus be concluded that the free volume in the swollen gel matrix is the major determinant of the PPA mobility. The reason for this observation can be attributed to the level of ionic strength used in these experiments. At the level of 0.2 *M*, it is apparently significant enough to have effectively reduced the ionic interaction between PPA and ionized groups on the side chains. The reason for the deviation of the last data point on the right-hand side in Fig. 5 is unclear. However, the data suggest that the nonionized structure of 30% methacrylic acid poly(HEMA–co–MA) gels is different from those of 50% methacrylic acid gels. This can be the case since the polymerization methods and conditions of synthesizing these two gels are quite different. However, this particular result does not affect the conclusion we have drawn above since, at this *H* value, the gel is in its nonionized state.

CONCLUSION

In summary, it was demonstrated in this paper that the swelling equilibrium of poly(HEMA–co–MA) gels was a strong function of the pH and methacrylic acid content in the polymer matrix. On the other hand, the equilibrium swelling of the nonionized poly(HEMA–co–MA) hydrogel was not determined by the TEGDMA within the concentration range of 0.5 to 3%. The secondary structure, possibly due to either hydrogen bonding or hydrophobic interaction in the nonionized poly(HEMA–MA) matrix, shields the effect of covalent cross-links and determines the equilibrium structure. This implies that, for the nonionized gels, one cannot use the covalent cross-link to control the swelling equilibrium and, thus, the solute mobility in the matrix. The secondary structure is disrupted upon the ionization of the carboxyl functionality in the matrix. The swelling has an accelerating effect on the PPA release process. This was shown to be due to the increase in the PPA diffusion coefficient. The variation of the diffusivity with the matrix hydration was shown to follow the free volume theory of Yasuda *et al.* From the partition coefficient data and the extrapolated D_o, it was concluded that a significant interaction exists between PPA and the polymer network. However, at an ionic strength of 0.2 *M*, gels of different ionic densities followed the same free volume relationship for measured PPA diffusivity, indicating that the free volume and not the charge density was controlling solute diffusion.

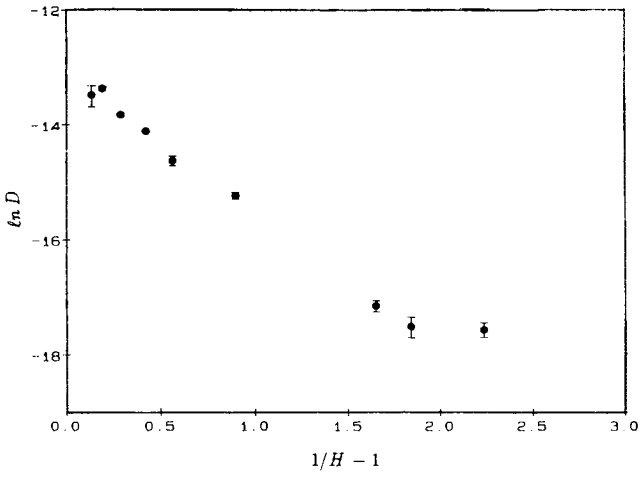

Fig. 5. Semilogarithmic plot of PPA diffusivity measured in 10 and 30% MA poly(HEMA–co–MA) gels at various pH's versus $(1/H) - 1$.

ACKNOWLEDGMENT

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NOMENCLATURE

- a Thickness of the planar sheet
- A Area of the release surface
- c Diffusant concentration
- C_b Drug concentration in the bulk fluid at time t
- C_{b1} Drug concentration in the bulk fluid at loading equilibrium
- C_{b2} Drug concentration in the bulk fluid at $t = 0$
- $C_{b\infty}$ Drug concentration in the bulk fluid at $t = \infty$
- D Mutual diffusion coefficient
- D_o Aqueous diffusivity of drug
- D' Effective diffusivity
- H Matrix hydration
- κ Free volume parameter
- k Partition coefficient of drug between the polymer gel and the bulk water
- r Cylinder radius
- SR Swelling ratio
- γ Binding constant

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