Swelling Behavior of Hydroxyethylmethacrylate Hydrogels Modified by Copolymerization with Furfuryl Acrylate

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SYNOPSIS

Hydrogels of biomedical interest were prepared by the free radical copolymerization of 2-hydroxyethylmethacrylate, **H**, with furfuryl acrylate, **A**, at low and high conversion. The microstructural analysis of the copolymer system was carried out by nuclear magnetic resonance (NMR) spectroscopy, taking into consideration statistical parameters according to the Mayo–Lewis copolymerization model. The hydration process in physiological conditions was studied gravimetrically at 37°C, following the kinetics of swelling of homogeneous thin films. A diffusion mechanism based on the stress relaxation model of copolymer chains accounts satisfactorily for the experimental data obtained. The diffusion coefficients determined according to the classical Fickian uptake kinetics are very sensitive to the copolymer's composition. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Natural and synthetic polymers that are not soluble in water, but experience a noticeable swelling in contact with an hydrated medium, form a wide family of materials known as hydrogels. They are extensively used in the biomedical field including soft contact lenses,[1,2] wound dressings,[3,4] blood compatible surfaces,[5,6] drug release systems,[7–10] biomembranes,[11,12] surgical prostheses,[13,14] etc.

Among the synthetic hydrogels those prepared from 2-hydroxyethylmethacrylate (**H**) by free radical polymerization or copolymerization with other acrylic or vinyl monomers has been largely used from the pioneering work of Woodhouse in 1934 and the development of commercial products from the interesting work on these systems by the Czechoslovak school on polymer chemistry directed by Otto Wichterle.[15,16]

The control of the swelling process and the maximum hydration degree can be attained by the use of amorphous polymeric systems crosslinked with a small amount of a tetrafunctional monomeric component. The hydration degree and the swelling kinetics of this kind of systems is controlled mainly by the crosslinking density,[17–19] but dipolar interactions between functional side groups of the macromolecular chains,[20] hydrogen bonding,[21] and hydrophobic secondary forces[22] are responsible for the cohesion and mechanical properties of the gel.

In the case of poly(hydroxyethylmethacrylate) systems, it is possible to control the diffusion rate and the degree of hydration by using copolymer systems prepared with the appropriate amount of a second comonomer with hydrophobic character. In this case, the average composition of the copolymer system and the distribution of the hydrophobic monomeric units are the responsibility of the swelling behavior and the diffusion of the swelling agent into the gel.[23–25]

In the last few years we have studied the behavior of hydrogels prepared by the free radical copolymerization of 2-hydroxyethylmethacrylate with small amounts (< 30 wt %) of an acrylic derivative supporting hydrophobic but polar side groups of biomedical interest,[26] and more recently we have reported the swelling behavior of N-vinylpyrrolidone-furfuryl methacrylate copolymer systems prepared by free radical polymerization with a content in the acrylic monomer lower than 30 wt %.[27] The

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diffusion process was explained according to a second-order kinetics, taking into account the average composition of the copolymer system and the distribution of comonomeric furfuryl methacrylate units along the macromolecular chains, determined by the reactivity of the corresponding monomers in the free radical polymerization process.

In this work the study of the swelling behavior of copolymer systems prepared by the copolymerization of 2-hydroxyethylmethacrylate with furfuryl acrylate is described.

EXPERIMENTAL

Monomer Preparation and Purification of Materials

Furfuryl acrylate (**A**) was prepared by transesterification of methyl acrylate with furfuryl alcohol in the presence of sodium carbonate as catalyst and ionol as inhibitor. The product was distilled, dissolved in chloroform, and passed through a chromatographic column containing silica gel 60 (Macherey-Nagel, Germany). The eluent was analyzed by thin layer chromatography using Kieselgel 60 F 254 (Merck) as the stationary phase. The selected fraction was rotoevaporated in order to separate the solvent and distilled.

2-Hydroxyethyl-methacrylate (**H**), supplied by Hydron Europe Ltd., containing less than 0.05 wt % of ethylene glycol dimethacrylate, was distilled under reduced pressure of nitrogen and the fraction of bp 87–89°C/5 mm Hg was collected.

2,2'-Azobisisobutyronitrile (AIBN) was purified by fractional crystallization from methanol, mp 104°C.

N,N-dimethylformamide (DMF) was dried over anhydrous magnesium sulfate for 2 days and later with phosphoric anhydride overnight. After drying, DMF was distilled under reduced pressure of nitrogen. Other reagents were of extra-pure grade and used as purchased.

Copolymerization

Copolymerization reactions were performed in DMF solution at $50 \pm 0.1°C$, in Pyrex glass ampules sealed off under high vacuum. Monomer and initiator concentrations were 1.0 mol/L and 1.5×10^{-2} mol/L, respectively. The sealed ampules were shaken vigorously and immersed in a water bath held at the required temperature of polymerization. After the proper reaction time, the ampules were removed from the bath and at once the content was poured into a large excess of diethyl ether. The precipitated samples were washed with the precipitant mixture and dried under vacuum until constant weight was attained.

Polymer Characterization

The copolymers obtained from different mixtures of **A** and **H** were analyzed by ^{1}H-NMR spectroscopy with a Bruker AM-200 spectrometer working at 200 MHz. The spectra were recorded at 40°C on 5% (w/v), deuterated dimethylsulphoxide solutions, with a 2400-Hz spectral width, flip angle of 30°C (2-μs pulse), a pulse repetition time of 2 s and 128 transients. A 16 K Free Induction Decay (FID) was acquired and zero filled to 32 K before Fourier transformation.

The molar fraction of monomer units incorporated in the copolymer chains was determined from the ^{1}H-NMR spectra of copolymer samples prepared with different monomer feed. The analysis was performed by comparing the integrated intensities of resonance signals with chemical shifts of 6.45 and 6.55 δ, assigned to the protons in position 3 and 4 of the aromatic furfuryl ring and 3.65 and 3.95 δ assigned to the oxyethylene protons of the $HO—CH_2—CH_2—$ side residue of 2-hydroxyethyl methacrylate units (see Scheme I).

Preparation of films

Films of 0.4–0.5 mm thickness were prepared by slow evaporation of a solution of 0.25 g of the copolymer in 2 mL of DMF. Copolymers prepared with 2.5, 5, 10, 20, and 30 wt % of furfuryl acrylate were used. In order to obtain homogeneous discs, a cylindrical mold of Teflon (25 mm diameter and 5 mm deep) was prepared. After evaporation and drying at reduced pressure, transparent, clear films of 0.15 mm thickness were obtained. To eliminate completely the solvent, DMF, the films prepared were exhaustively dried at high vacuum (10^{-3} mm Hg) and 100°C during three or four days if necessary. The absence of DMF was tested by thermogravimetric analysis with a sensitivity higher than 0.001 mg. In addition the ^{1}H-NMR spectrum of the polymeric system in solution of DMSO-d_6 did not give any detectable presence of DMF. On the other hand, after swelling in pure water the samples were redried at high vacuum until constant weight and the composition was analyzed by ^{1}H-NMR spectroscopy, giving values practically similar to the initial composition within the experimental error of the technique ($< 1.0\%$).

Swelling Behavior

The study of the swelling behavior of films was followed gravimetrically by measuring the weight gain with the time of immersion in 10 mL of distilled water at 37°C. At the desired time the film was weighted after drying the surface. Measurements were taken until the equilibrium was reached, that is, when three consecutive measurements gave the same weight.
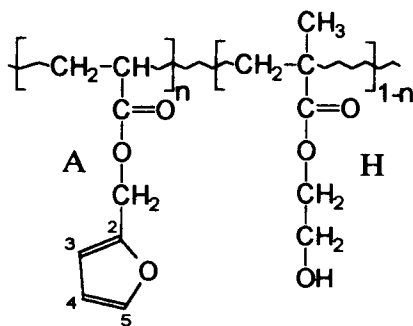
RESULTS AND DISCUSSION

Recently we reported the study of the free radical copolymerization of furfuryl acrylate **A**, with 2-hydroxyethylmethacrylate **H**, in DMF solution at 50°C, initiated by AIBN,[28] [Initiator] = 1.5×10^{-2} mol/L. The analysis of copolymer samples prepared at very low conversion (< 5 wt %) by ^{1}H-NMR spectroscopy in the conditions outlined in the experimental section, gave the average composition of copolymer chains expressed as the molar fraction of monomer units **A** and **H** along the macromolecular chains. The chemical structure of the repeating acrylic and methacrylic units is shown in the Scheme I. The side groups of both acrylic units have interesting physicochemical characteristics, since the hydrophilic character of the HO— side groups in **H** units provides an effective element to have intra or intermolecular interactions through hydrogen bonding and polar connectivities, as well as strong interactions with water molecules. These interactions are responsible for the characteristic water wettability and swelling behavior of poly-**H** chains.[29] However, the introduction of **A** units into segments of **H** units along the macromolecular chains can modify the hydration behavior of the corresponding polymeric systems. In fact, the furan ring in furfuryl side residues is a rather polar aromatic group sep-

arated from the acrylic ester function by a very flexible methylene group (see Scheme I). Therefore, although this residue provides a hydrophobic character, the polarity of the oxygenated aromatic ring may affect noticeably the interactions with the hydroxylic groups of the neighboring **H** units or even with the HO— groups of the surrounding macromolecules. In this sense, an emerging hierarchy of interactions has been recognized[30] for water with polymeric systems bearing polar side groups, which in order of decreasing strength are: ion–ion > water–ion > water polar $\simeq$ polar–polar $\simeq$ water–water > water–hydrophobic groups.[24]

This variety of interactions makes very difficult a correct interpretation of data from hydrated polymers, since factors like the plasticizer effect of water depending on the temperature, the structural organization into the gel matrix according to the polymer segment mobility,[30] or even polymer conformational changes can accompany the hydration process.[24] Fortunately, the **A–H** system is not crosslinked, and therefore we can study the microstructure of copolymer chains by NMR spectroscopy, avoiding in addition the complex effects of crosslinking in the hydration process, which permits applying very simple diffusion models to the swelling process as a function of the average composition of the dry system.

We have reported recently[28] the kinetic parameters for the free radical copolymerization of the **H–A** couple in the experimental conditions of the present work. From the analysis by ^{1}H-NMR of the average composition of copolymers prepared at low conversion (< 5 wt %) over a wide interval of feed compositions, the reactivity ratios r_A and r_H as well as the statistical parameters like conditional probabilities of addition, were determined. The most probable values of the reactivity ratios were r_A = 0.93 and r_H = 1.42. Data of the average composition of copolymer samples prepared at low conversion, after 30 min of polymerization, as well as at high conversion, after 24 h of reaction, are collected in Table I together with the corresponding conversion degree reached. It is interesting to notice that there is not a great difference of the average composition of copolymer samples prepared at low and high conversion from rather similar feed composition. For example, copolymers prepared from a feed with 9 and 10 mol % of **A** presented a composition of 6 mol % at high conversion and 8 mol % at low conversion, respectively, and copolymers with a content of **A** units of 20 mol % are obtained from feed compositions of 25 and 27 mol % at low and high conversion, respectively. This means that the

Scheme 1

Table I Composition Data of the Free Radical Copolymerization of Furfuryl Acrylate, A, and 2-hydroxyethylmethacrylate, H, in DMF Solution at Low and High Conversion, $[I]_0 = 1.5 \times 10^{-2}$ mol/L

System	Feed Composition (Molar Fraction)		Copolymer Composition (Molar Fraction)		Conversion, wt %
	F_A	F_H	f_A	f_H	
Low conversion	0.10	0.90	0.08	0.92	3.5
	0.15	0.85	0.12	0.88	2.3
	0.20	0.80	0.15	0.85	2.8
	0.25	0.75	0.20	0.80	2.4
	0.30	0.70	0.24	0.76	2.6
High conversion	0.02	0.98	0.01	0.99	82.2
	0.04	0.96	0.03	0.97	81.6
	0.09	0.91	0.06	0.94	80.8
	0.18	0.82	0.12	0.88	81.9
	0.27	0.73	0.20	0.80	81.3

average composition of copolymer chains does not change drastically with conversion, as it is expected from the values of both reactivity ratios, which are very close to the unity. Figure 1 shows the composition diagram for the free radical copolymerization of this system. The circles correspond to experimental composition data for copolymers prepared at low conversion, whereas the square points are the
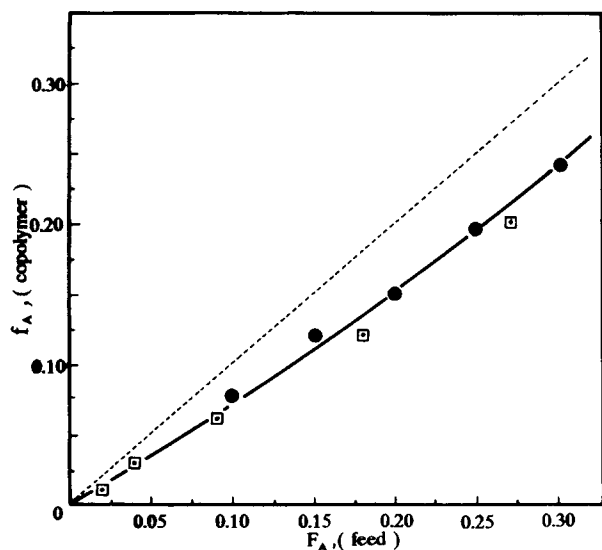

Figure 1 Composition Diagram of H–A copolymers prepared by free radical copolymerization. (●) Experimental data at low conversion; (□) data at high conversion; (——) diagram predicted by the Lewis–Mayo equation with r_A = 0.93 and r_H = 1.42; (— — —) diagram for an ideal copolymerization system.

experimental data for copolymers prepared at high conversion. The continuous line corresponds to the variation of the average composition according to the classical model of Mayo and Lewis,[31] and the straight dotted line represents an ideal system with both reactivity ratios equal to the unity. It is clear from this figure that the composition data of copolymer chains fit the diagram drawn with the reactivity ratios considered in the present work, which in addition is rather close to the ideal behavior. This means that copolymer chains with a homogeneous distribution of comonomeric units are obtained, independently of the conversion degree. Moreover, according to the kinetic parameters and considering the integrated copolymerization equation reported by Skeist,[32] deviations of the copolymer or feed compositions with conversion are negligible up to very high conversion degrees (> 90 wt %).

As indicated in the last column of Table I, conversions about 80–82 wt % after 24 h of reaction are reached, and it is not possible in the experimental conditions of this work to obtain total conversion. This is because the reaction follows the so-called dead-end polymerization model described by Tobolsky in 1960,[33] which considers that a deactivation of free radicals is produced by ineffective collisions, the concentration of active initiator decreases exponentially with the reaction time, reaching a limiting conversion.

Figure 2 shows the microstructural distribution of H and A monomeric units along the copolymer chains with the molar fraction of furfuryl acrylate in the copolymer chains. The distribution has been expressed as the molar fraction of A centered se-
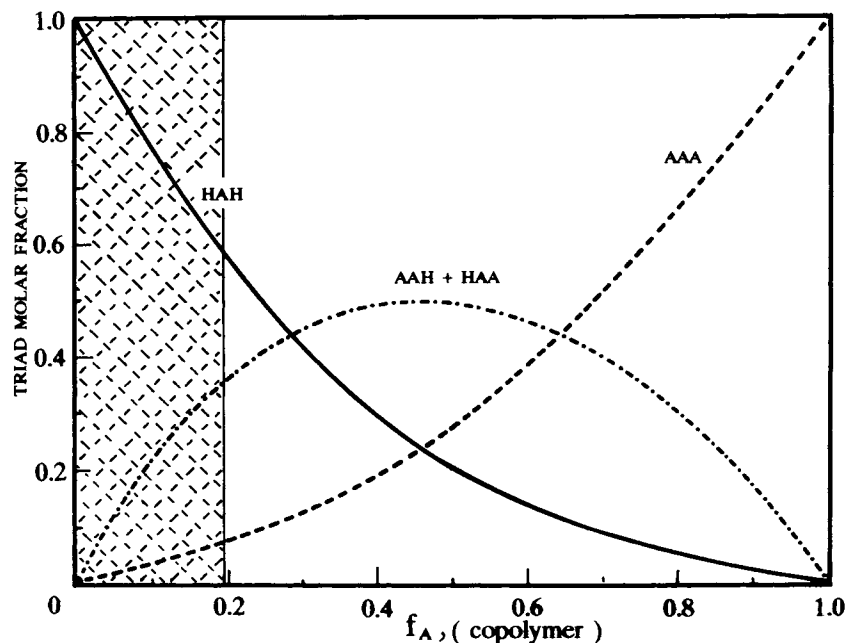
Figure 2 Statistical distribution of A-centered sequences of triads, as a function of the furfuryl acrylate molar fraction in the copolymer chains.

quences of triads (three consecutive units), i.e., **AAA, AAH + HAA,** and **HAH.** The composition interval of interest in the present study corresponds to the striped area in the diagram, in which it is clearly seen that a distribution of furfuryl acrylate units isolated in sequences of hydroxyethylmethacrylate segments can be expected for copolymers prepared with an **A** molar fraction lower than 0.10–0.15. This means that polar interactions between the side hydroxy groups of **H** units with the furan ring of **A** units are favored against interactions between neighboring aromatic furan rings, which probably has important consequences in the swelling process.

In order to study the hydration process and the influence of the composition and microstructure of copolymers in the kinetic of swelling, films of systems prepared with 2.5–30 wt % of **A** were obtained by slow evaporation of solvent from diluted DMF solution as reported in the experimental section. The dry films of the furfuryl acrylate–hydroxyethyl methacrylate copolymers were brittle, with glass transition temperatures well above the temperature of the experiments, $T_g \simeq 70$–$85°C$, depending on the composition.[28] After immersion in water at $37°C$ the films readily swell in an extension that depends on the composition of the film. As the films gained in thickness, they became soft and rubbery, but having relatively good mechanical strength not showing any measurable yield.

The hydration degree was determined measuring the weight of films at different times, according to the equation[34]:

$$H = \frac{W_w - W_0}{W_w} \tag{1}$$

where W_0 is the weight of the dry sample and W_w is the weight of the wet sample at different times of treatment. The maximum degree of hydration H_{max}, was considered as the equilibrium hydration degree, H_α.

Figure 3 shows the variation of the hydration degree as a function of the swelling time for films prepared from copolymers with the composition indicated in the figure. In all cases, the equilibrium of hydration is reached in a very short period of time (< 60 min) for all the compositions studied. However, there is a marked effect of the copolymer composition on the equilibrium hydration degree reached in the experiments, H_α, ranging from 0.26 for films with a content of **H** of 99 mol %, to 0.14 for films with a 80 mol % of **H.** This is a consequence of the strong hydrophobic character provided by the introduction of furfuryl acrylate units in the chains.

In a recent publication[27] in which we studied the swelling behavior of films of furfuryl methacrylate (**F**) and vinylpyrrolydone (**P**) copolymers of different composition, we found linear dependence of the equilibrium swelling degree on the copolymer com-
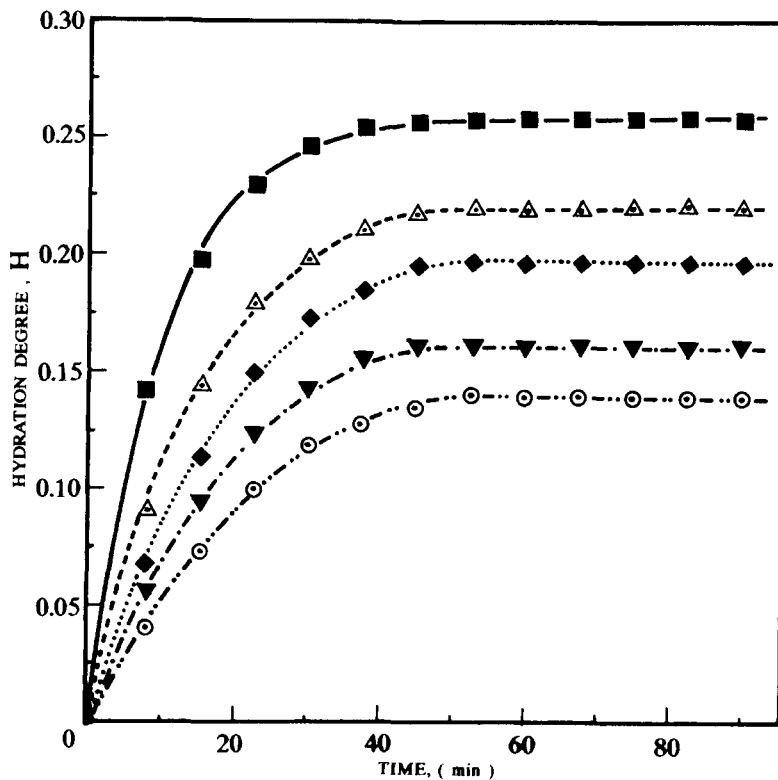
Figure 3 Swelling isotherms (37°C) of films prepared from **A–H** copolymers with a **H** molar fraction, f_H of (■) 0.99; (△) 0.97; (◆) 0.94; (▼) 0.88; and (⊙) 0.80.

position, which was also attributed to the presence of hydrophobic **F** units in the copolymer chains. In Figure 4, the equilibrium hydration degree is plotted against the mole fraction of the hydrophobic com-

ponent for both copolymer systems. It can be seen that the composition dependence of H_∞ for the **A–H** copolymers can also be represented approximately by a straight line. However, the slope of the latter
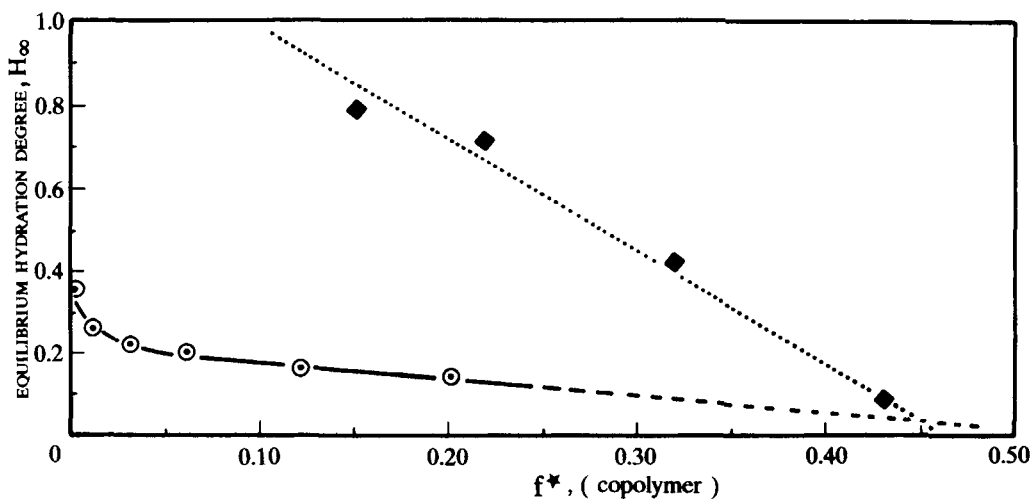

Figure 4 Variation of the equilibrium hydration degree with the composition of the copolymer systems: (⊙) **A–H** and (◆) **F–P.** $f^* = f_A$ or f_F.

is much smaller, indicating a stronger dependence of H_α on composition for the **F–P** copolymers.

There are at least two important differences between both systems, arising from the microstructural characteristics of these systems. As we reported earlier[27] the great difference in the reactivity of **F** and **P** in the free radical polymerization provides copolymers with long sequences of vinylpyrrolidone and furfuryl methacrylate units distributed along the macromolecular chains, whereas, as indicated above, the distribution of furfuryl acrylate units along the copolymer chains is more uniform. This makes the very rich vinylpyrrolidone systems soluble in the hydrated medium, but they become insoluble when the molar fraction of **F** units is about 0.15,[27] and the equilibrium hydration degree has a strong dependence on the average composition. In the case of **A–H** copolymer, the films prepared are not soluble for all the interval of composition tested, and the equilibrium hydration degree decreases rapidly by the introduction of 2–3 mol % of **A** in the copolymer chains, but for higher contents of **A** a smooth, practically linear diagram is obtained, as shown in Figure 4. An interesting conclusion from the diagrams shown in this figure is that the straight lines of both systems present a cross-point for copolymers with an **A** or **F** molar fraction about 0.45. This means that the hydrogels prepared with this composition present the same swelling characteristics, but the distribution of **F** and **A** units may be rather different. This fact may be interesting to consider specific applications of the corresponding systems as biocompatible coatings or support matrices for the control release of pharmacologically active compounds.

As shown in Figure 3, the rate of diffusion changes with time of treatment, being maximum in the initial steps. In general, for stiff films, the rate-determining factor of the swelling process is the stress relaxation of the copolymer chains corresponding to the osmotic swelling pressure.[35,36] This results in a softening as water permeates into the mass of the film, with the corresponding decreasing of the T_g of the system. This is strongly affected by the hydrophobic character of the furfuryl acrylate units of the copolymer chains. In this sense, Figure 5 shows the change of the diffusion rate of water at 37°C expressed by the ratio dH/dt as a function of time. The diagrams obtained indicate that the relative rate of swelling decays exponentially with the time of treatment and becomes practically equal to zero after a period of about 60 min. The decay function depends on the composition of the copolymers in the sense that the decrease of the rate of swelling with the time is enhanced for systems with high content in the hydrophilic component, i.e., hydroxyethyld-
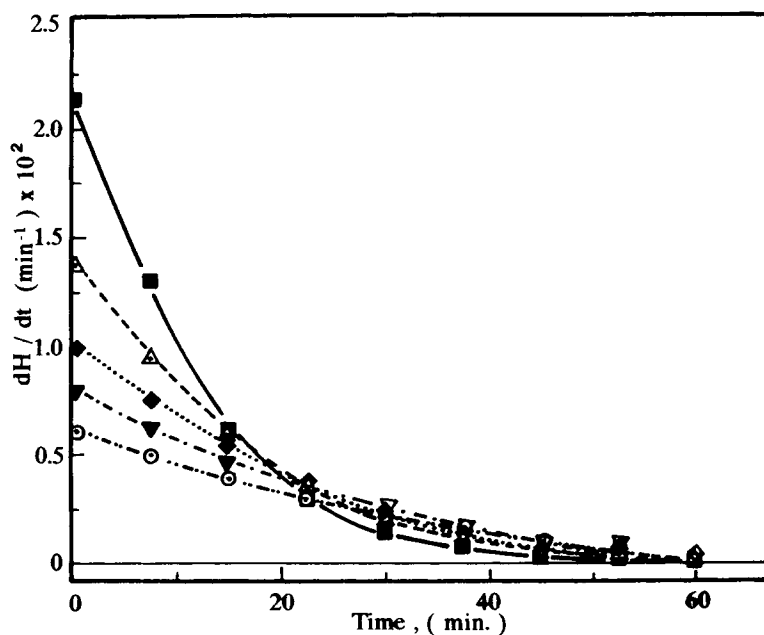

Figure 5   Variation of the relative swelling rate dH/dt, as a function of the time of treatment at 37°C for **A–H** copolymers with composition; f_H: (■) 0.99; (△) 0.97; (♦) 0.94; (▼) 0.88, and (⊙) 0.80.

methacrylate. However, the diagrams become smoother as the hydrophobic character of the system increases. A similar behavior was observed for F–P copolymers,[27] but the initial diffusion rate was less sensitive to the composition than in the case of A–H systems, probably because of the microstructural differences indicated above.

It is well-known that the solution of the differential form of Fick's law for thin sheets, neglecting diffusion through the edges can be expressed as a function of the reduced uptake (M_t/M_∞) and $t^{1/2}$, according to the Eq. (2), being M_t and M_∞ the mass of water taken up at time t and infinite time, respectively;[19,37]

$$\frac{M_t}{M_\infty} = 4 \sqrt{\frac{Dt}{\pi l^2}} \qquad (2)$$

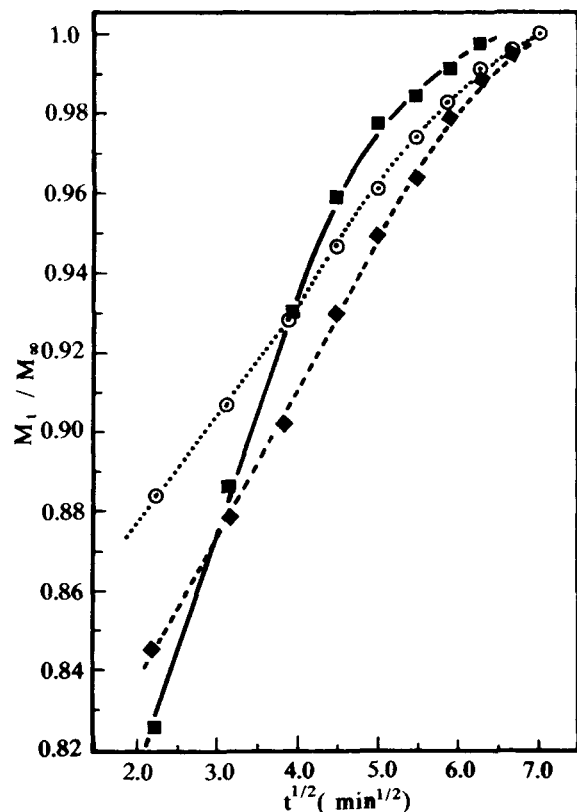D is the diffusion coefficient and l the average thickness of the film.
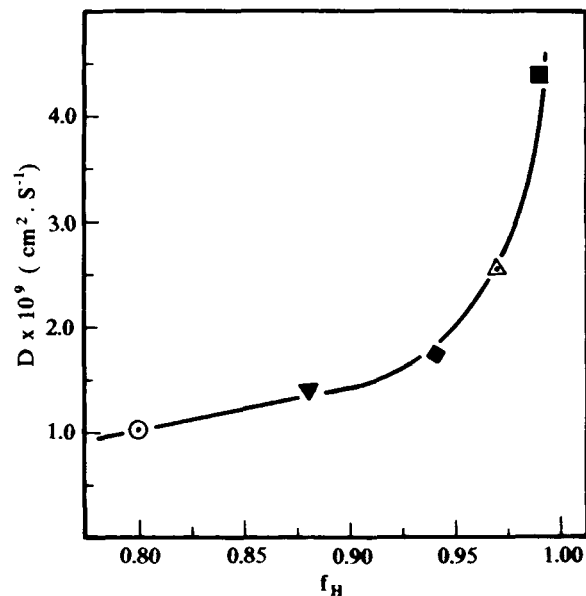

Figure 7   Variation of the diffusion coefficient D of thin films with the molar composition f_H of A–H copolymers.

One criterion of Fickian behavior considers that the diagram obtained should be linear at least up to values of the reduced sorption about 0.6. Figure 6 shows the diagrams obtained for films prepared with
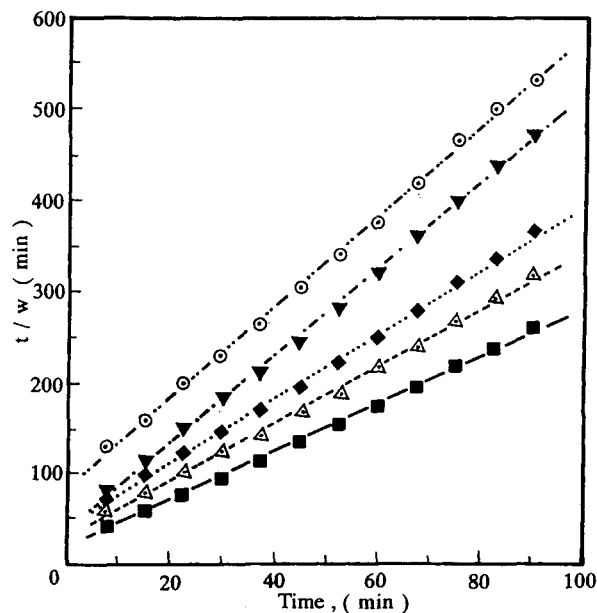

Figure 6   Reduced sorption of A–H films prepared with different composition f_H: (■) 0.99, (♦) 0.94, (☉), and –0.80.

Figure 8   Variation of the reciprocal rate of swelling defined in Eq. (3), as a function of the swelling time for A–H copolymers, with the composition, f_H: (■) 0.99; (△) 0.97; (♦) 0.94; (▼) 0.88; and (☉) 0.80.

three compositions. In all the cases the experimental points follow a straight line up to a reduced sorption that depends on the composition of the corresponding film, but in all cases higher than 0.95. From the straight lines and taking into consideration the thickness of films, the diffusion coefficients of the copolymers were determined. Figure 7 shows the variation of the diffusion coefficients with the average molar fraction of **H** in the copolymer samples. It is clearly a noticeable effect of the composition on the diffusion coefficient of the systems and demonstrates that the introduction of a little fraction of **F** in the copolymer chains produces a drastic decreasing of the corresponding diffusion coefficient.

It is clear that extensive swelling the behavior deviates from the classical Fickian, law and as it has been pointed out by Schott[38] recently, in these cases it is possible to consider that the reciprocal of the average rate of swelling (t/w) is related to the time of treatment by the linear equation:

$$\frac{t}{w} = A + Bt \qquad (3)$$

here w is the swelling or solvent uptake at time t, defined as

$$w = \frac{W_w - W_0}{W_0} = H \frac{W_w}{W_0} \qquad (4)$$

here W_w and W_0 and H have the meaning given in Eq. (1), and A and B are two coefficients whose physical sense can be interpreted as follows: at long time of treatment, $Bt \gg A$ and according to Eq. (3), $B = 1/w_\alpha$ i.e., the reciprocal of the equilibrium swelling or maximum hydration equilibrium degree. On the contrary, at very short time of treatment, $A \gg Bt$ and in the limit, Eq. (3) becomes

$$\lim_{t \to 0} \left(\frac{dw}{dt} \right) = \frac{1}{A} \qquad (5)$$

therefore, the intercept A represents the reciprocal of the initial swelling rate. Figure 8 shows the diagrams obtained by the application of our swelling data to Eq. (3). In all cases straight lines with an excellent correlation coefficient are obtained.

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