

The Equilibrium Water Content of Some Thermoplastic Hydroxyalkyl Methacrylate Polymers

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Synopsis

The equilibrium water content (EWC) of thermoplastic 2-hydroxypropyl methacrylate and 2-hydroxyethyl methacrylate homopolymers from technical grade monomer and of copolymers of the latter with methyl methacrylate has been measured in distilled water and in phosphate-buffered saline (PBS). In distilled water, as expected, EWCs increased monotonically with the proportion of hydrophilic monomer in the polymer and showed only a small dependence on molecular weight. In contrast, the degree of swelling (and in some cases dissolution) and "freezable" water content of polymers in PBS were shown to be anomalously high and to be a consequence of ionization at pH 7.4 of methacrylic acid incorporated into the polymer in small quantity (< 1 mol %) as an impurity. Initial studies indicated a strong relationship between copolymer molecular weight and small molecule permeability in distilled water.

INTRODUCTION

Hydrogel chemistry based on the hydroxyalkyl methacrylates is a mature discipline impacting on areas as diverse as contact lens manufacture,¹ implant matrices for the restoration of connective tissues,² burn wound dressings,³ and surface modifiers of more rigid materials for vascular implants,⁴ to name a few. More exotic applications would include, for example, their use as potential matrices for the microencapsulation of mammalian cells in organ replacement and cell and tissue culture technology.^{5,6} The single most important attribute of these materials is their ability to swell in contact with water to produce a soft gel with a low modulus and a high permeability to oxygen, water, and low molecular weight solutes.

Recently, we prepared and characterized a number of thermoplastic hydroxyalkyl methacrylate homopolymers and copolymers using a wide range of molecular weight and hydrophilicity,⁷ to serve our research on microencapsulation of cells.⁶ We naturally measured the equilibrium water content (EWC) of each polymer with surprising results, some of which we report here, along with those of certain ancillary experiments.

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MATERIALS AND METHODS

Polymers

The purification of the monomers and the synthesis of the homopolymers and copolymers was described earlier.⁷ Homopolymers of methyl methacrylate (MMA), hydroxyethyl methacrylate (HEMA), and hydroxypropyl methacrylate (HPMA) as well as a series of HEMA-MMA copolymers (25/75, 50/50, 75/25 mol ratio) were investigated. Three series, with different levels of initiator were investigated: series I with 1 mol % azobisisobutyronitrile (AIBN), series II with 0.1 mol % azobismethylisobutyrate (AMIB), and series III with 0.01 mol % AIBN. In addition, a copolymer of HEMA and MMA with methacrylic acid (MMA) (45% HEMA, 45% MMA, 10% MAA) was prepared by refluxing the monomer mixture with 0.1 mol % AMIB for 4 h in 95% ethanol under nitrogen (yield: 49.5 wt % of monomers).

Viscometry

Polymer viscosities in pure dimethylformamide (DMF) and in DMF containing lithium bromide (LiBr) at $35 \pm 0.05^\circ\text{C}$ were obtained using a Cannon #200 suspended level Ubbelohde viscometer. Solvent flow times ranged from ~ 200 s for DMF to approximately 215 s for DMF containing 1% (w/v) LiBr. Measurements were performed on solutions of relative viscosity between 1.1 and 1.5 as is common practice.⁸

Equilibrium Water Contents (EWC)

Thin (approximately 0.5 mm thick), transparent, void free films were prepared by hot pressing polymer between sheets of clean tinfoil (~ 2000 lb pressure/ 180°C , 1 min). Dry films were weighed (W_1), immersed in deionized distilled water (48 h), blot-dried with tissue and reweighed (W_2), and then vacuum dried at $\sim 70^\circ\text{C}$ to constant weight (W_3).

The percentage dissolution or loss of leachable material was expressed as

$$\frac{(W_1 - W_3)}{W_1} \times 100 \quad (1)$$

The EWC was then expressed as

$$\frac{(W_2 - W_3)}{W_2} \times 100 \quad (2)$$

In another set of experiments the EWC of solution cast, air-dried films of series II polymers was measured in distilled water and in phosphate-buffered saline solution (w/v, 0.8% NaCl, 0.115% Na_2HPO_4 , 0.02% KH_2PO_4 , pH 7.4). In these experiments the EWC was defined as

$$\frac{(W_2 - W_1)}{W_2} \times 100 \quad (3)$$

Freezable Water Content

The freezable water content of preweighed polymer was obtained by differential scanning calorimetry (DSC) using a DuPont 1090 thermal analysis system. Water swollen polymer of weight W_4 in a hermetically sealed DSC pan was heated from -40 to 30°C at a rate of $5^\circ\text{C}/\text{min}$ in the DSC apparatus. Data points were collected at a rate of 5/s, stored, and manipulated with proprietary DuPont software using a cell constant obtained by calibration with Indium metal. The weight of freezable water (W_5) in the sample was calculated from the magnitude of the observed melting endotherm by assuming its latent heat of fusion to be equal to that of distilled water.⁹ The freezable water content of the polymer was then derived from the expression

$$(W_5/W_4) \times 100 \quad (4)$$

Polymer Derivatization

By Immersion in Saline or Buffer Solutions

A thin film of polymer was solution cast onto a 1 mm thick semiconductor grade silicon wafer (Bell Northern Telecommunications), air-dried, immersed 24 h in saline (0.9% w/v NaCl, unbuffered) or various buffer solution of different pH, rinsed with distilled water, and then vacuum-dried for examination by infrared spectroscopy. The buffer solutions varied from pH 2.1 (0.01M HCl) to pH 7.0 and were prepared from certified buffer tablets supplied by Perkin-Elmer (pH = 3.00, 7.00) BDH (4.00) and Coleman (pH = 5.00, 6.00).

By Deposition from Alkaline Solvent

A 10% (w/v) solution of polymer was prepared in a "carbonyl"-free solvent tetrahydrofuran (THF) for the MMA homopolymer, methanol for the HEMA and HPMA homopolymers, and the 75% HEMA copolymer and THF/methanol mixtures for the other two HEMA copolymers. A drop of 1N ethanolic KOH was added to 0.5 mL of these solutions, and a thin polymer film cast onto a NaCl disk for examination by infrared spectroscopy.

By Treatment with Sulfur Tetrafluoride (SF₄) Gas

A thin film of polymer was cast from a "carbonyl"-free solvent onto a germanium crystal (Harrick Scientific) and treated with SF₄ gas (Matheson) at 0°C in a polyethylene wash bottle equipped with gas inlet and outlet ports. The bottle was flushed for 10 min with SF₄, capped and left overnight to complete the reaction. The bottle was then flushed with nitrogen and the sample removed for examination by infrared spectroscopy.

Infrared Spectroscopy

Transmission IR spectra at 4 cm^{-1} resolution of polymers derivatized by immersion in saline or buffer were obtained using a Nicolet 7199 FT-IR spectrometer equipped with a mercury cadmium telluride detector. Transmis-

sion IR spectra at 4 cm^{-1} resolution of the remaining derivatized polymers were obtained using a Perkin-Elmer 1500 FT-IR spectrometer equipped with a triglycidyl sulfate detector. Usually 100 scans were sufficient to obtain a good signal to noise ratio in both instruments. Sample thicknesses were adjusted to keep the optical densities of absorption bands of interest below 1.0.

Polymer Permeability

Polymer films of thickness 50–125 μm were cast onto polished slabs of Teflon from a good solvent. After solvent evaporation, membranes were softened in warm water, removed from the Teflon, and stored at least 4 days in distilled water to reach swelling equilibrium and remove leachable impurities.

The diffusion cell was constructed of two equivolume chambers cut from poly(methyl methacrylate) blocks.¹⁰ The precleaned chambers were bolted together and separated by the water-swollen film. Each chamber was agitated continuously by a magnetic stirrer during the course of the experiment. The upstream chamber (A) was filled with 20 g/L glucose in distilled water to begin the experiment. Small (20 μL) samples were removed periodically from the downstream chamber (B), and the glucose concentration was estimated by enzymatic digestion in a YSI27 glucose analyzer.

The membrane permeability was calculated from the rate of increase of glucose concentration in the downstream chamber according to the relationship

$$\ln \frac{C_A^0}{C_A - C_B} = \frac{2P_D A}{V \cdot t_m} t \quad (5)$$

since the concentration in the downstream reservoir at $t = 0$ is zero.²⁴ This reduces at short times, when $C_A - C_B \approx C_A$, to

$$C_B = \left(\frac{P_D A C_A^0}{V t_m} \right) t \quad (6)$$

where C_A, C_B = concentration in upstream (A) and downstream (B) chamber at time t , C_A^0 = concentration in upstream chamber at $t = 0$, A = membrane area = 3.3 cm^2 , t_m = membrane thickness (cm), P_D = diffusive permeability (cm^2/s), V = volume of solution in both chambers = 18 cm^3 , and t = time (s).

RESULTS AND DISCUSSION

It is generally believed that the equilibrium water content (EWC) of 2-hydroxyethyl methacrylate (HEMA) hydrogel polymers is relatively insensitive to crosslink density¹¹ due to the formation of a secondary hydrogen bond network.¹² The EWC of the noncrosslinked HEMA-containing polymers studied here provides a test of hydrogel behavior at effectively zero crosslink density.

Polymer Viscometry

Earlier molecular weight investigations were hampered by the polyelectrolyte behavior of some polymers in dimethylformamide (DMF),^{7,13} which resulted in nonlinear Huggins plots. Here ionic dissociation was suppressed by the addition of lithium bromide (LiBr). The behavior of the 50% HEMA copolymer (series 3) in DMF with 0.25% (w/v) LiBr is illustrated in Figure 1. Although not a true Huggins plot, as we did not employ the technique of dialysis dilution to ensure a constant activity of added electrolyte,¹⁴ the limiting viscosity number (LVN) so obtained was expected to be similar to that of the corresponding uncharged polymer in DMF, provided that the added electrolyte did not excessively collapse the polymer chains. The effect of LiBr concentration on the LVN of HEMA and HPMA homopolymers is shown in Figure 2. The polyelectrolyte character of polyHEMA was effectively suppressed by the addition of low concentrations of LiBr. In common with many other such polymers, its LVN approached a limiting value at higher concentrations of added salt.¹⁵ The behavior of polyHPMA was more complex. Polyelectrolyte behavior was again suppressed at low concentrations of added salt, but solution dimensions apparently increased somewhat at higher salt concentrations. It was presumed that polyelectrolyte behavior originated in weakly acidic impurities which were introduced to the polymer during polymerization (see below). Hence chain expansion at high concentrations of added salt may be a consequence of enhanced acidity and hence dissociation of the acid in the salt solution.¹⁶ In contrast, the LVN of the uncharged poly(methyl methacrylate) was relatively insensitive to added LiBr over a wide concentration range, although solution dimensions did decrease a little presumably due to collapse of the polymer chain in the highly polar concentrated salt solutions.

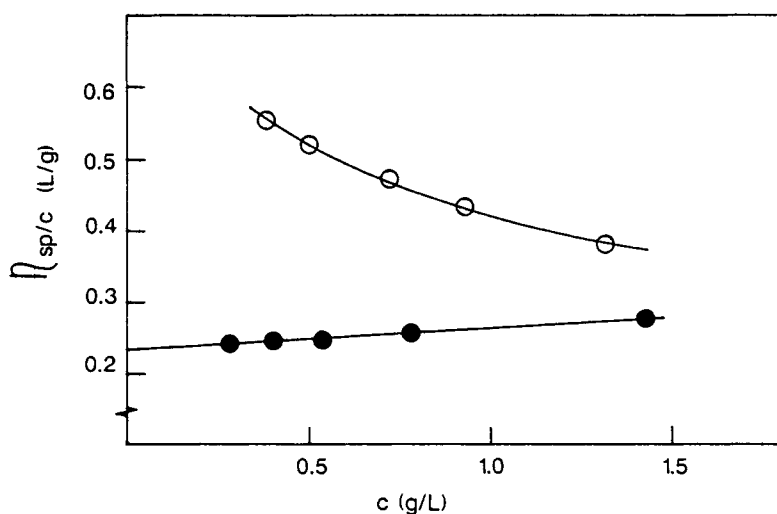


Fig. 1. Reduced specific viscosity (η_{sp}/c) curve for series III polyHEMA in dimethylformamide (DMF, ○) and in DMF containing 0.25% (w/v) lithium bromide (●).

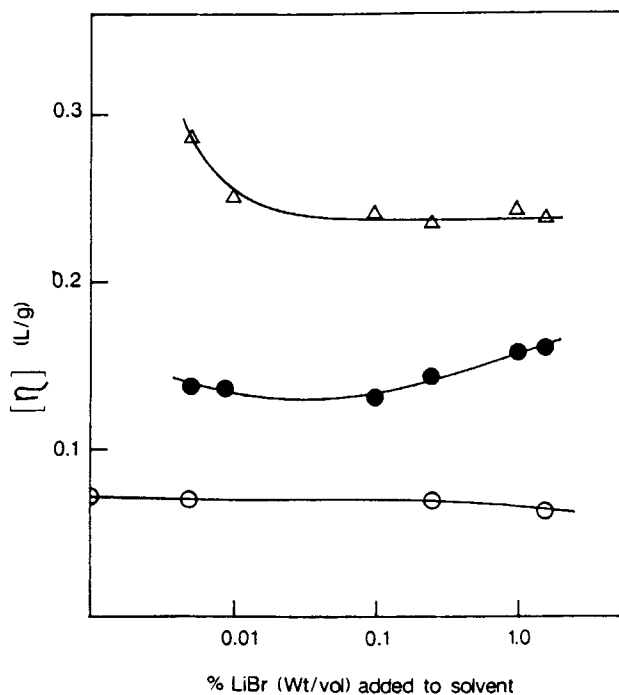


Fig. 2. Variation of limiting viscosity number ($[\eta]$ or LVN) in dimethylformamide of series III polyMMA (○), series III polyHEMA (△), and series III polyHPMA (●) with added lithium bromide concentration. LVN determined by extrapolation of Huggins plots.

The LVN of all polymers in DMF containing 0.25% (w/v) LiBr are listed in Table I. Weight average molecular weights of poly(methyl methacrylate) polymers were calculated from LVNs in pure DMF using an established relationship.^{7,17} With the assumption that the HEMA homopolymers contained only a small amount of ionizable material (a reasonable assumption in view of the relative insensitivity of polymer LVN to high salt concentrations), then approximate molecular weights may be obtained by use of appropriate Mark-Houwink constants ($K \sim 8.5 \times 10^{-5}$, $a \sim 0.72$).¹⁸

As expected, series I, II, and III polymers covered a wide range of molecular weights. The molecular weights increased across each series with the propor-

TABLE I
Limiting Viscosity Numbers ($[\eta]$, mL/g) of Polymers in
Dimethylformamide Containing 0.25% (w/v) LiBr

Series	polyMMA	HEMA-MMA copolymers			polyHEMA	polyHPMA
		25% HEMA	50% HEMA	75% HEMA		
I	13.0 (37.2×10^3) ^a	18.6	21.4	25.1	29.8 (84×10^3) ^b	26.7
II	20.5 (82.9×10^3) ^a	33.0	64.6	59.0 ^c	70.3 ^c (280×10^3) ^b	65.5 ^c
III	69.0 (419×10^3) ^a	94.8	133.0 ^c	150.0 ^c	235.0 ^c (1.5×10^6) ^b	143.0 ^c

^a \bar{M}_w of polyMMA (see text).

^bApproximate \bar{M}_w of polyHEMA (see text).

^cBehave as polyelectrolyte polymers in dimethylformamide.

tion of HEMA in the polymer presumably due to the effect of ethylene glycol dimethacrylate, a crosslinking agent and byproduct of HEMA synthesis,¹⁹ which was not fully removed in monomer purification.⁷

Equilibrium Water Content (EWC) and Permeability in Distilled Water

The EWC in distilled water of hot pressed polymer films are shown in Table II along with those from the literature of crosslinked hydrogels of similar composition. Water uptakes increased monotonically across each series as the hydrophobic MMA monomer was progressively replaced by the more hydrophilic HEMA monomer. As expected, HEMA homopolymers swelled more than HPMA homopolymers.¹² From this data it can be clearly seen that the EWC of HEMA-containing polymers, even at the limit of zero crosslink density, were indeed governed by thermodynamic considerations and were independent of polymer architecture as many others have stated.^{12,20}

The EWC and freezable water content (FWC) are generally regarded as important parameters governing gel permeability^{1,11,21,22} at very low crosslink densities.²³ To test the applicability of this rationale to thermoplastic polymers, we compared the permeability to glucose of two polymers of similar composition, and hence similar EWC and FWC, but of markedly different molecular weight. Under steady state conditions, the permeability to glucose was determined from the slope of the plot of downstream concentration against time, according to eq. (6). For the 75% HEMA copolymer, the permeability was 16.8×10^{-9} cm²/s for the series I, low molecular weight copolymer and 2.7×10^{-9} cm²/s for the higher molecular weight, series III copolymer.

The former copolymer was very soft with little or no structural integrity, in contrast to the higher molecular weight copolymer which was resilient and almost leathery in its response to applied stress. Low molecular weight elastomers with their higher chain end concentrations are more able, through rotation, to maximize configurational entropy by chain disentanglement. Per-

TABLE II
Equilibrium Water Uptakes of Polymers in Distilled Water^a

Series	%Water uptake					
	polyMMA	HEMA-MMA copolymers			polyHEMA	polyHPMA
		25% HEMA	50% HEMA	75% HEMA		
I	2.2 ± 0.9	6.5 ± 0.8	15.6	24.2 ± 0.1 ^b	42.8 ± 3.2 ^c	21.1
II	2.7 ± 0.1	7.2 ± 0.4	14.6 ± 2.2	25.1 ± 0.5	36.4 ± 2.6 ^c	21.3 ± 0.7
III	1.8 ± 0.1	5.5 ± 0.1	13.2 ± 1.3	26.1 ± 0.3	36.4 ± 0.7	21.3 ± 2.6
Cross linked hydro gels	2.3 ^d	6.8 ^d	14.1 ^d	25.5 ^d	37.5 ^e	

^a ± SD, *n* = 3, calculated using eq. (2).

^b Very soft.

^c Very soft gel with little structural integrity.

^d Ref. 17.

^e Ref. 18.

happens this unusually large variance in permeability is a reflection of chain entanglement density and its effect on pore radius.²⁵ If such is the case, then the simple relationship to water content outlined above may be insufficient to describe the permeability of such polymers. Other parameters such as processing history, soak time, and temperature may play their part in determining membrane configuration and hence permeability.

Water Contents in Other Media

The equilibrium water content (EWC) as calculated using eq. (3) of solution cast films of series II polymers in distilled water and in PBS are compared in Figure 3. The EWCs of polyHPMA, polyHEMA, and copolymers of the latter with a low percentage of MMA were much higher in PBS than in distilled water. We thought this unusual as the swelling behavior of crosslinked hydroxyalkyl methacrylate hydrogels has been shown to be relatively insensitive to solution pH¹ and tonicity.^{11,20}

We also measured the freezable water content (FWC) of these polymers as such is thought to be essential for efficient diffusion of salts and macromolecular solutes.²⁶ Our results, summarized in Table III, indicate anomalously high

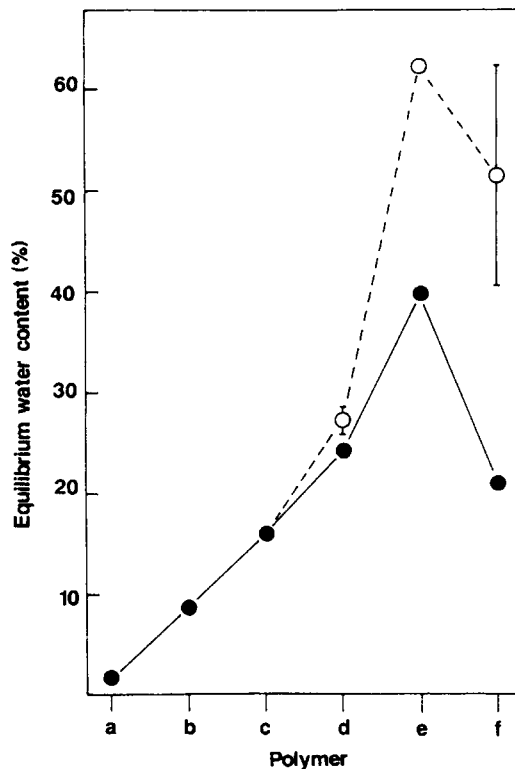


Fig. 3. Equilibrium water content of solution cast films of series III polymers in distilled water (●) and in phosphate-buffered saline (○): (a) polyMMA; (b) = 25/75 HEMA/MMA; (c) 50/50 HEMA/MMA; (d) 75/25 HEMA/MMA; (e) polyHEMA; (f) polyHPMA; (g) 45/45/10 HEMA/MMA/MAA.

TABLE III
 "Freezable" Water Content of Series II Polymers in Distilled Water
 and in Phosphate-Buffered Saline (PBS) Solution^a

Polymer	Uptake (%)	
	In distilled water	In PBS
PolyMMA	Negligible	Negligible
HEMA-MMA		
25% HEMA	Negligible	Negligible
50% HEMA	Negligible	Negligible
75% HEMA	2.2 ± 0.3	4.0 ± 0.4
PolyHEMA	19.8 ± 1.4	39.8 ± 3.1
PolyHPMA	Negligible	64.4 ± 4.4

^a Calculated using eq. (4), ±SD, $n = 3$.

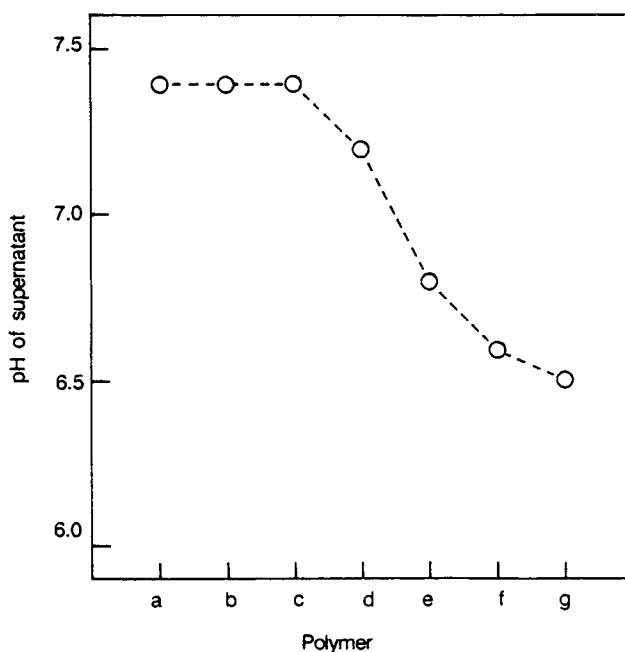


Fig. 4. Final pH of phosphate buffered saline after contact with series II polymers: (a) polyMMA; (b) 25/75 HEMA/MMA; (c) 50/50 HEMA/MMA; (d) 75/25 HEMA/MMA; (e) polyHEMA; (f) polyHPMA; (g) 45/45/10 HEMA/MMA/MAA.

values of FWC in the more hydrophilic series II polymers in contact with PBS, most notably polyHPMA, which appears to be on the brink of dissolution (FWC ~ EWC).

The final pH of the PBS after equilibration with series II polymers is shown in Figure 4. Although not a quantitative experiment, these results indicate the presence of acidic impurities in the more hydrophilic series II polymers, sufficient to overwhelm the buffer capacity of the PBS. This effect appears to

increase from series III polymers through series II polymers to series I polymers. Note that the true EWC would be even higher if some polymer had dissolved.

Characterization of the Acidic Impurity

The presence of acidic impurities was confirmed by reaction of thin films of polymer with sulfur tetrafluoride (SF_4) gas, which quantitatively converts hydroxyl groups to fluorides and carboxylic acids to the corresponding acid fluoride.²⁷ Infrared spectra of some derivatized series I polymers are shown in Figure 5. Acidic functionality in polyHEMA and polyHPMA is revealed by the sharp, well-resolved acid fluoride absorbance at 1822 cm^{-1} . The absence of this absorbance in the spectrum of polyMMA after treatment is proof of the stability of the methacrylate ester group to attack by SF_4 , and confirms that acid functionality is revealed (in the hydrophilic polymer) but not created by the gas.

Carboxylic acid groups in polymeric materials can also be converted to the corresponding carboxylate anion for spectroscopic identification.²⁸ The infrared spectra of some base-treated polymers are illustrated in Figure 6. PolyHEMA and polyHPMA both exhibit the broad absorbance at 1575 cm^{-1} characteristic of methacrylate anions in contrast to the absence of this absorbance in the IR spectrum of base-treated polyMMA. Also shown is the IR spectrum of polyMMA, which had been precipitated from a more highly basic solution. The strong, sharp absorbance at 1630 cm^{-1} shown in the figure was found to be characteristic of the products of base hydrolysis of all the

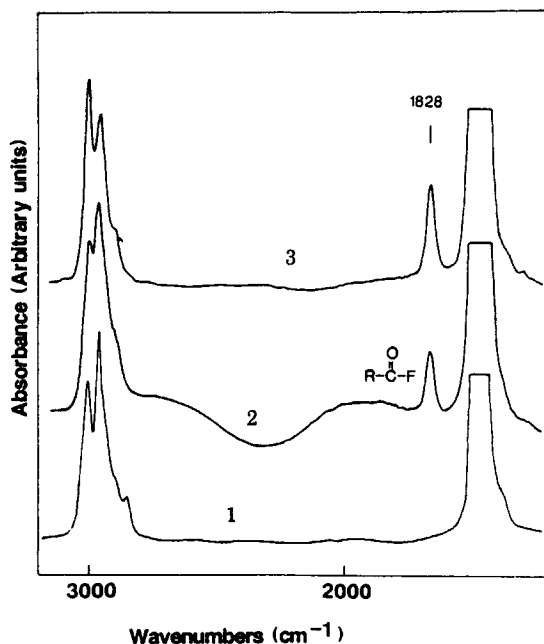


Fig. 5. Infrared spectra of (1) polyMMA (series I), (2) polyHEMA (series I), and (3) polyHPMA (series I) after 24 h exposure to sulfur tetrafluoride gas.

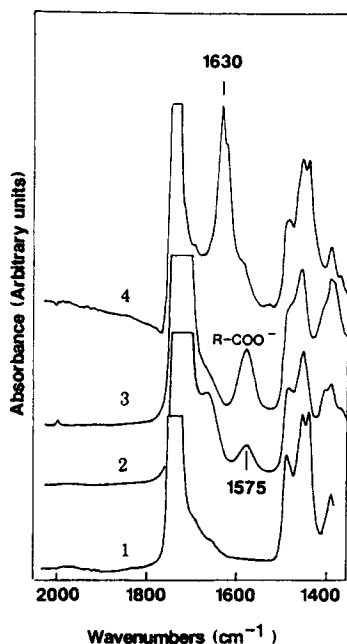


Fig. 6. Infrared spectra of (1) polyMMA (series I), (2) polyHEMA (series I), (3) polyHPMA (series I), all cast from dilute KOH solution (0.1*M*), and (4) infrared spectrum of polyMMA (series I) cast from "concentrated" KOH solution (approx. 0.5*M*).

thermoplastic polymers under investigation. Its absence in the IR spectrum of base-treated polymers would, therefore, suggest the absence of any base hydrolysis in those polymers.

We also examined the infrared spectrum of polyHEMA, which had been soaked in distilled water, isotonic saline, and phosphate-buffered saline (PBS) solution (Fig. 7). The absence of any ionization in distilled water confirms the weakly acidic nature of the impurity. This would probably explain the close agreement between the EWC of our polymers in distilled water and those of other workers in the same medium. Ionized material was formed in polymer which had been soaked in isotonic saline solution. Salt solutions are known to enhance the acidity of weak acids by stabilizing the products of self-ionization.¹⁶ As expected, acidic material was ionized in PBS solution at pH = 7.4.

Further evidence of the weakly acidic nature of the impurity was obtained from the variation with pH of EWC of polyHPMA. The EWC increased monotonically from $16.7 \pm 0.9\%$ at pH = 2.1 to $24.1 \pm 2.5\%$ at pH = 6.0 while the polymer dissolved in buffer solution at pH = 7.0.

We have shown before that the HEMA and HPMA monomers used to make these polymers were contaminated with approximately 0.7 and 0.9 wt %, respectively, of methacrylic acid,⁷ a reactant used in the preparation of both monomers. If methacrylic acid (MMA) was the major acidic impurity, then the absence of ionization in distilled water would be explained—for example, polyMAA and copolymers with styrene achieve 5.0% ionization of neutralization only at pH values above 7.0 at polymer concentrations of $2 \times 10^{-2} N$.²⁹ The presence of ionization in "isotonic" saline solution would also be ex-

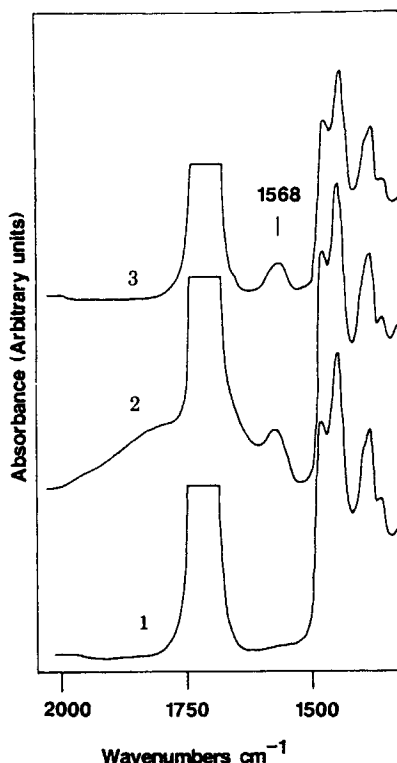


Fig. 7. Infrared spectra of polyHEMA (series II) after immersion for 24 h in (1) distilled water, (2) isotonic saline, and (3) phosphate-buffered saline solution.

plained—a pH of 5.8 is sufficient to achieve 5.0% ionization of methacrylic acid groups in the presence of 0.1M added sodium chloride.³⁰ Finally, we note the behavior of the HEMA/MMA methacrylic acid copolymer, which swelled only $15.9 \pm 0.6\%$ water in distilled water but dissolved in PBS.

The free radical reactivity ratios of MAA with MMA depend to a large extent on the polarity of the polymerization solvent.³¹⁻³³ Assuming similar behavior with HEMA and HPMA monomer, it would be reasonable to assume that MAA monomer is preferentially excluded from copolymer formed in 95% ethanol. If so, then limiting average concentrations of 0.7 and 0.9 wt % can be assumed for MAA in polyHEMA and polyHPMA, respectively. That more MAA is incorporated into polymers at high conversion is indicated from comparisons of EWC among the different series. For example, the EWC of series III HPMA (a low conversion polymer) in PBS was only 2.2% above that in distilled water in contrast to series I HPMA (a high conversion polymer), which dissolved in PBS.

CONCLUSIONS

Thermoplastic hydroxyalkyl methacrylate polymers prepared by solution polymerization from purified monomers contain small (< 1 wt %) amounts of copolymerized methacrylic acid (MAA). At the sufficiently low pH of distilled water, this acid is protonated, with the result that EWCs agree well with literature values determined for crosslinked hydrogels. In solutions of higher

pH, or in the presence of added salt, MAA impurities are ionized, and, lacking the constraints imposed by network crosslinks, enormously expand the polymer chains through long range inter- and intramolecular repulsions, sometimes to the point of dissolution.

The effect casts some doubt on the wisdom of using the EWC of thermo-plastic hydroxyalkyl methacrylate polymers in (acidic) distilled water on a routine basis to estimate performance at pH = 7.4, except for those polymers prepared from monomers scrupulously free of acidic impurities.

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