Controlled Drug Release by Polymer Dissolution. I. Partial Esters of Maleic Anhydride Copolymers— Properties and Theory

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Synopsis

The kinetics of drug release from a series of partial esters of vinyl acetate–maleic anhydride has been investigated. These polymers in their un-ionized forms are hydrophobic and water insoluble, but in their ionized forms they are water soluble. Polymer dissolution is pH sensitive, and different half-esters have a characteristic pH range above which they are soluble and below which they are insoluble. When films are placed in buffered media, they erode at a constant rate that depends on the pH of dissolution of the polymer and on the pH of the buffered medium. Dissolution of the polymer is limited to the polymer–buffer medium interface, and drugs dissolved or uniformly dispersed in the polymer are released by zero-order kinetics. A detailed model has been developed that successfully correlates dissolution behavior and various experimental parameters.

INTRODUCTION

Sustained drug delivery is a major current area of research, and a number of reviews on this topic have recently been published.[1,2] There are several fundamentally different types of sustained drug delivery devices; these can be broadly classified into diffusional, osmotic, and erosional. In diffusional and osmotic devices, the drug delivery rate is essentially independent of the biologic environment and can thus be predicted. However, unless the diffusional or osmotic delivery system is capable of bioerosion, it must be removed once its delivery role has been completed. In some applications this is not always feasible, or desirable, and therefore polymeric devices that can controllably deliver a drug by erosion into toxicologically innocuous degradation products can represent a broadly applicable drug delivery system.

The simplest approach to a bioerodible drug delivery system is to disperse or dissolve the drug in a water-soluble polymer, either natural of synthetic, and let the polymer slowly dissolve in the aqueous medium. Some measure of control over dissolution time can be achieved by blending the polymer with various hydrophobic substances. Another approach is to retard the dissolution of a water-soluble polymer by introducing hydrolytically unstable crosslinks, which results in a hydrophilic gel that slowly dissolves as the crosslinks cleave. However, utilization of a water-soluble polymer as a major constituent produces a highly hydrophilic polymer matrix that will be completely permeated by water. Thus, solubility of the drug in water becomes a major factor, and drug release from such a matrix will be principally determined by drug diffusion and water solubility.

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A more desirable approach involves the synthesis of hydrophobic, water-insoluble polymers that can release a drug by erosion of the matrix but from which only a minimal amount of the drug is released by a diffusion process. It is clear that if the erosion process is confined to the polymer–water interface and if the total area of the device does not significantly change with time, then constant, or zero-order, drug release kinetics can be expected. Furthermore, such a matrix would represent a generic delivery system from which many drugs could be released at a preselected delivery rate by simply varying drug loading and/or polymer erosion rate.

In principle, we can achieve solubilization of a hydrophobic polymer by a chemical reaction that can take place either at a pendent group of the polymer or within the polymer backbone. Clearly, when the chemical reaction is confined to the pendent group of a polymer, no backbone cleavage takes place and one of the reaction products is a hydrolytically stable, water-soluble polymer. We can also conceive of intermediate situations where both backbone cleavage and reaction of side groups take place. In this case, side-group reaction might be the rapid process that leads to chain solubilization and hence drug release, whereas backbone cleavage might be the slow process that allows ultimate metabolic elimination of the polymer from the body.

These different cases are designated as types I, II, and III and are shown schematically in Figure 1. In this paper we describe examples of type I polymers, where the solubilization reaction is an ionization reaction of a pendent carboxyl group.

Hydrophobic polymers that are solubilized by an ionization reaction of a pendent carboxyl group are well known, and the dissolution and drug release of partially esterified copolymers derived from ethylene–maleic anhydride or methyl vinyl ether–maleic anhydride constitute the subject of many publications.[3-13] Results reported in the present study are also based on these polymer
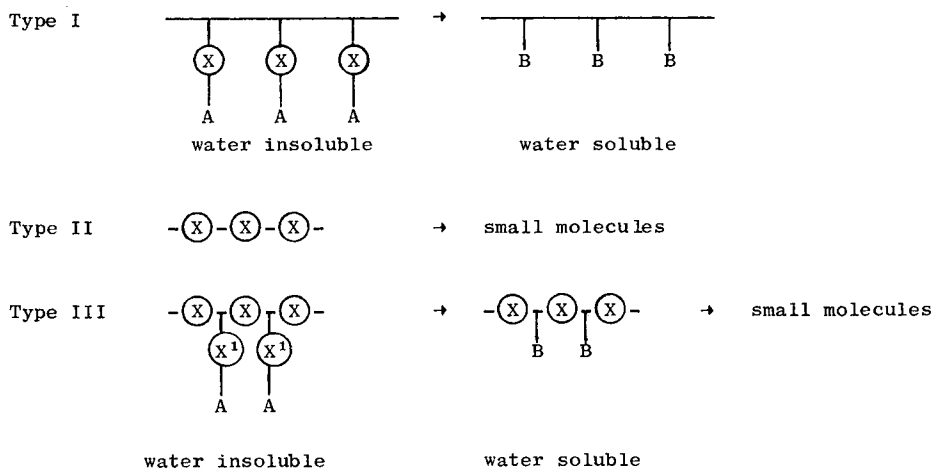

Fig. 1. Various solubilization mechanisms for hydrophobic polymers.

systems. However, whereas previous work emphasized the use of such polymers as enteric coatings, that is, tablets coated with a protective polymer designed to dissolve in the intestine, our interest has centered entirely on drug-containing polymer devices that continuously release a drug in cavities of the body other than the gastrointestinal tract, such as the uterus or the interior conjunctival cul-de-sac of the eye.

Partially esterified copolymers derived from ethylene–maleic anhydride or methyl vinyl ether–maleic anhydride are readily prepared from the commercially available alternating copolymers as shown below:
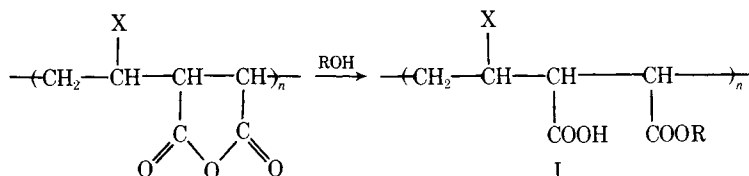
where $X = OCH_3$ for the methyl vinyl ether copolymer and $X = H$ for the ethylene copolymer.

These copolymers in the un-ionized state are hydrophobic and water insoluble, but in the ionized state they are water soluble. The solubilization process can be generically represented as follows:
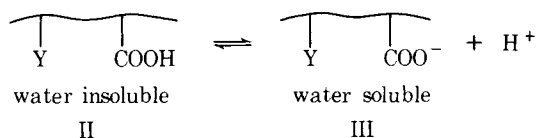
The copolymer can thus be viewed in terms of two essential components: a solubilizing group —COOH and a hydrophobic group Y. Such a group need not be an ester group; it can be any hydrophobic group and, in fact, can be the hydrocarbon portion of the polymer backbone. Although in this paper we present data based only on structure I, other similar polymers can be constructed and are currently under investigation in our laboratory.

EXPERIMENTAL

Synthesis of Polymers

Esterified to 50%. The reaction generally involved heating the commercially available methyl vinyl ether–maleic anhydride copolymer (Gantrez AN 169, high molecular weight products; or Gantrez AN 119, low molecular weight products of the General Aniline Film Corp.) with excess alcohol at 125°C under anhydrous conditions for a sufficient number of hours until an infrared analysis showed a minimum amount of residual anhydride. As the length of the alcohol chain increased, longer reaction times were required. The solution was then cooled and the product was precipitated by addition to petroleum ether or methanol. Again, as the length of the R group increased, the product became progressively more soluble in petroleum ether until in the dodecyl case it was necessary to change to methanol as the precipitant. The product was washed well with boiling hexane and pulverized.

Esterified to More than 50%. Ten weight arts of Gantrez AN 169 were mixed with 50 weight parts of the desired (five- or four-carbon) alcohol. The mixture was stirred at 120°–125°C until the half-ester was produced (18–24 hr) as determined by IR inspection of the reaction solution.

Concentrated sulfuric acid (two drops in 1 ml of the five- or four-carbon alcohol for each 10 g polymer) was then added to the reaction solution. The solution was stirred at 120°–125°C and progress of the reaction was followed by IR observation. When the carboxyl absorption pattern indicated the desired percent esterification, the reaction solution was worked up. Work-up was achieved by removing excess alcohol by repeated dissolution of the material in acetone and precipitating the product with petroleum ether. Residual solvents were removed by vacuum drying at room temperature.

Water Sorption

Equilibrium water sorption was obtained by soaking weighed ∼300-micron-thick films in pH 2 buffer solutions for two days at 37°C. The films were then removed from the buffer solution, blotted dry, and again weighed.

Titrations

The pK_a and pH at which the polymer precipitates were obtained by titration of the sodium salt of the partial ester with HCl under nitrogen at 37°C. In this procedure the half-ester was first converted to the sodium salt by the addition of a known excess of NaOH and then back-titrated with $0.1M$ HCl. Care was taken to maintain equilibrium throughout the titration. As the soluble salt was converted to the insoluble acid, the solution turned turbid, and this pH was noted. Some of the more hydrophobic polyacids swelled but did not dissolve in alkali, even at pH 11–12. However, on addition of HCl the solution turned from a clear gel to a flocculent precipitate, and the pH for this transition was noted.

Erosion Rate Measurement

Films containing ∼10 wt-% of dispersed hydrocortisone alcohol tracer were cast from acetone or ethanol. Small samples in the shape of discs (4–6 mm in diameter) were then cut from this film with a punch. Alternatively, the tracer drug and polymer were compounded on a rubber mill, and the films were pressed in a heated Carver press at ∼80°C. No significant difference in erosion rates was noted between samples prepared by solution casting or by compression molding.

The rate of erosion of the polymer discs was determined by either (1) measuring the rate of appearance of the tracer compound in the erosion solution; or (2) placing several weighed discs in the erosion medium, removing samples at regular intervals, drying, and weighing to determine polymer loss, and finally, dissolving and analyzing to determine tracer loss. The use of an inert tracer to monitor erosion rate is not new. Ueberreiter and Asmussen,[14–16] for example, have used dispersed carbon black particles. However, by choosing a UV-sensitive material we have considerably simplified routine erosion ratestudies.

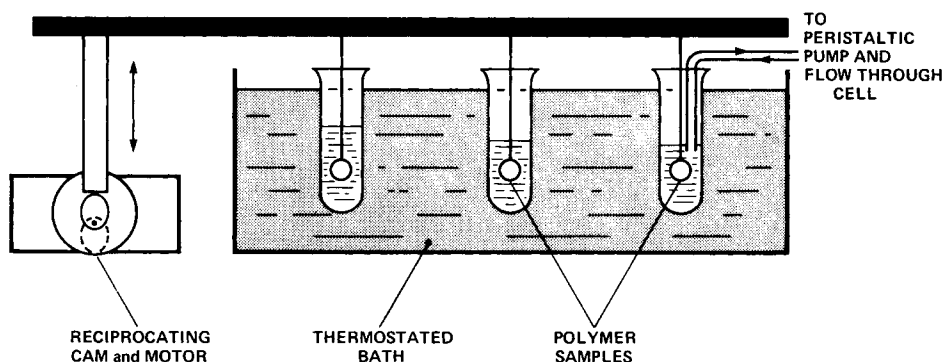The erosion apparatus is shown in Figure 2. Test samples were mounted in

Fig. 2. Apparatus for measurement of drug release rates from eroding polymers.

Dacron bags attached to a wire dipping into a test tube of buffer solution. This wire was in turn connected to a bar moved vertically by a reciprocating mechanism. The velocity of stirring could be varied from 2.3 cm/min to 350 cm/min. Most measurements were carried out at a stirring speed of ~140 cm/min. The appearance of hydrocortisone alcohol tracer in the buffer solution was monitored by periodically circulating the solution through a flow-through UV cell with a peristaltic pump.

RESULTS AND DISCUSSION

Polymer Properties

One of the interesting features of the polymer systems discussed herein is that they exhibit a characteristic pH range above which they are soluble and below which they are insoluble. This pH range is quite sharp, about 0.25 pH units, and changes with the number of carbon atoms in the ester side group. The pH of precipitation for a series of half-esters of methyl vinyl ether–maleic anhydride has been obtained by converting the acid to the water-soluble sodium salt, back-titrating with HCl, and noting the pH at which the solution first becomes turbid. The titration curves are shown in Figure 3. The pK_a of the polyacid can also be estimated from these curves as about 6.0 and was found to be relatively independent of the nature of the ester group. Figure 4 shows the almost linear dependence of pH of precipitation on the number of carbons in the ester group. This dependence has been noted previously, and our own data are in good agreement with those published by Lappas and McKeehan.[3]

This behavior can be readily understood by considering the number of ionized carboxyls necessary to solubilize the polymer chain. These can be calculated from the known pH of dissolution and acid pK_a and are shown in Table I. It is clear that very little ionization is necessary to solubilize polymers with small ester groups and that progressively more ionization is required to solubilize the higher esters. Consequently, polymers with small alkyl groups dissolve at low pH values; but as the hydrophobicity increases, the dissolution pH also increases. The same argument holds for polymers having the same ester grouping but different degrees of esterification. The higher the degree of esterification, the more hydrophobic the polymer and, consequently, the higher the dissolution pH. This relationship is shown in Figure 5 for a series of n-butyl and n-pentyl esters of varying degrees of esterification.
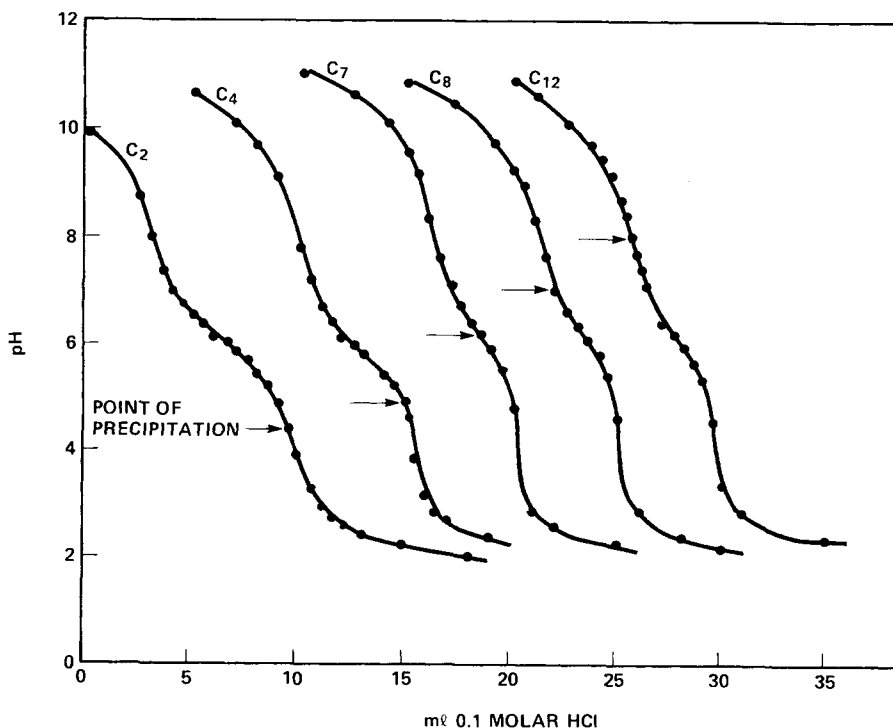
Fig. 3. Titration curves for a series of half-esters of methyl vinyl ether–maleic anhydride co-polymers.

TABLE I
Fraction of Ionized Carboxyls at the Dissolution pH Assuming Acid $pK_a = 6.0$

Alkyl group	Dissolution pH	Fraction of ionized carboxyls
C_2H_5	4.4	3
C_3H_7	4.8	6
C_4H_9	5.1	11
C_6H_{13}	5.9	44
C_7H_{15}	6.2	61
C_8H_{17}	6.6	80
C_9H_{19}	7.0	91
$C_{10}H_{21}$[a]	7.4	96
$C_{12}H_{25}$[a]	8.0	99

[a] Swells but does not dissolve.

Further evidence of the effect of alkyl group size on polymer hydrophobicity is the equilibrium water uptake for a series of half-esters of methyl vinyl ether–maleic anhydride films, which are shown in Figure 6. The water uptake of the films was measured at pH 2 where virtually all the acid groups are un-ionized and hence the polymer is in its most hydrophobic form. The data show a significant dependence on size of alkyl group up to the n-hexyl half-ester and little difference thereafter. As the pH of the solution in which the polymer is immersed is increased, the water sorption also increases, reflecting the effect of ionization of the carboxyl groups; and at some point the polymer dissolves. This increase is shown in Figure 7.
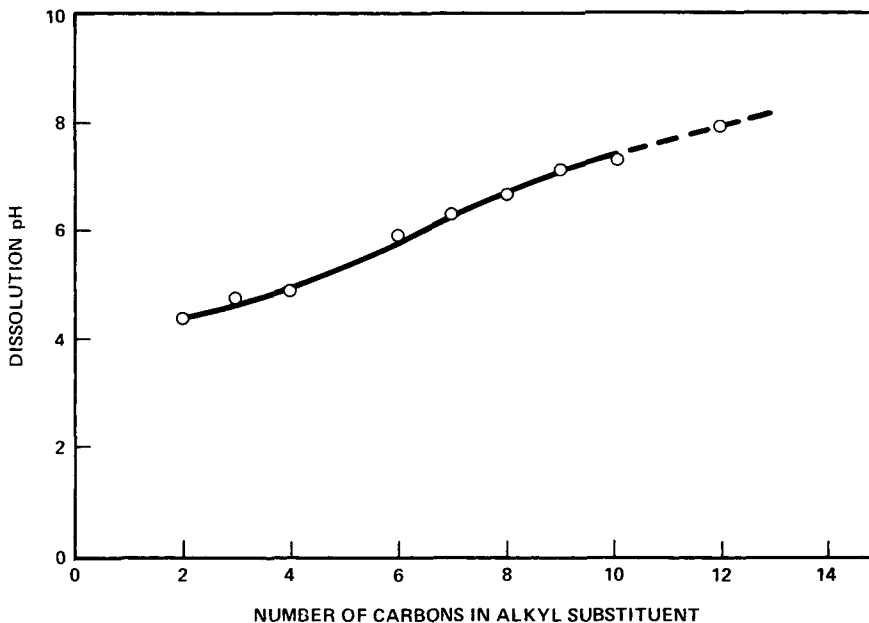
Fig. 4. Relationship between pH of precipitation and size of ester group in half-esters of methyl vinyl ether–maleic anhydride copolymers.
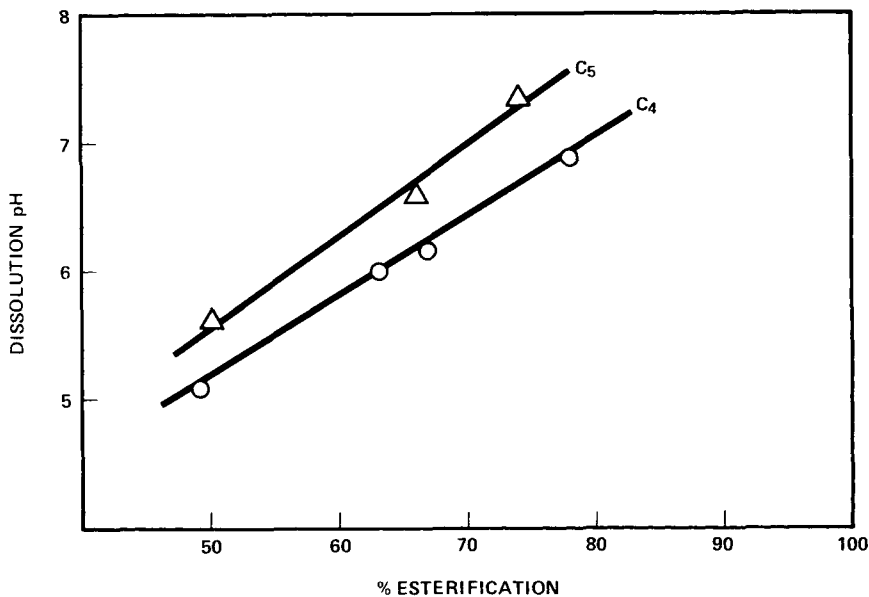

Fig. 5. Relationship between pH of precipitation and degree of esterification for n-butyl and n-pentyl half-esters of methyl vinyl ether–maleic anhydride copolymers.

The number of moles of water per mole of polymer repeat unit, calculated from the experimental water sorption measurements, are shown in Table II. It is interesting to note that after the n-butyl half-ester, there is only about one molecule of water per repeat unit. Therefore, in this particular polymer system, the absorbed water is probably not free but is very likely bound to the carboxyl groups.
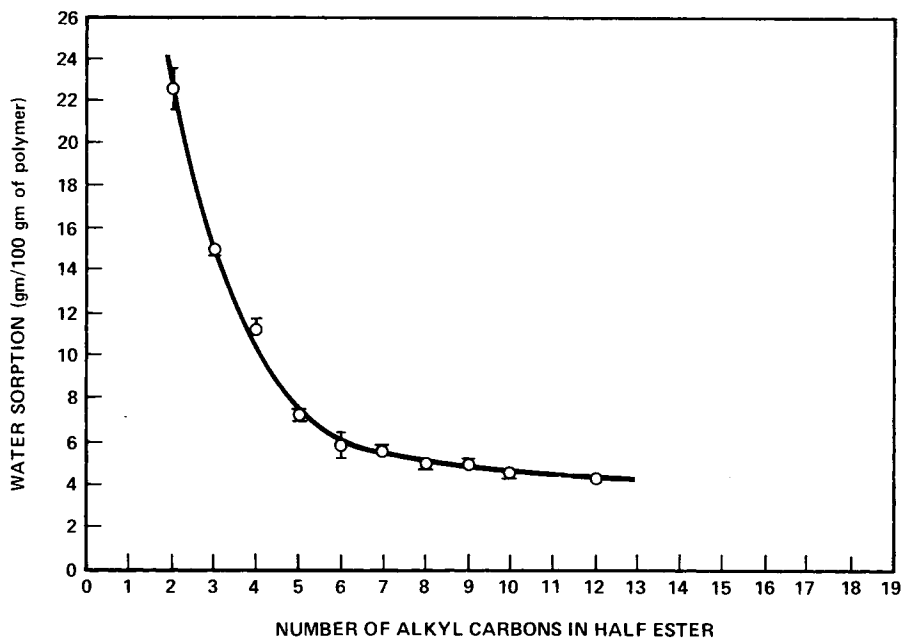
Fig. 6. Equilibrium water uptake as a function of size of ester group in half-esters of methyl vinyl ether–maleic anhydride copolymers.

TABLE II
Water Sorption at pH2

Alkyl group	Polymer equivalent weight	Experimental water sorption, g/100 g polymer	No. of water molecules per polymer unit
C_2H_5	202	22.6	2.5
C_3H_7	216	15.0	1.8
C_4H_9	230	11.3	1.4
C_5H_{11}	244	7.1	1.0
C_6H_{13}	258	5.8	0.8
C_7H_{15}	272	5.5	0.8
C_8H_{17}	286	5.0	0.8
C_9H_{19}	300	4.8	0.8
$C_{10}H_{21}$	304	4.5	0.8
$C_{12}H_{25}$	342	4.2	0.8

Figure 8 shows the polymer dissolution rate and rate of hydrocortisone alcohol release for n-butyl half-ester polymer films containing the dispersed drug. Each pair of points represents a separate device where the amount of drug released by the device into the wash solution was determined by UV measurements and the amount of polymer dissolved was calculated from the total weight loss of the device. The excellent linearity of both polymer erosion and drug release over the total lifetime of the device provides strong evidence for a surface erosion mechanism and negligible diffusional release of the drug. The latter result was verified by placing a drug-containing film in water at a pH low enough so that no dissolution of the matrix took place and periodically analyzing the aqueous solution for hydrocortisone alcohol. None was found over a period of several days.
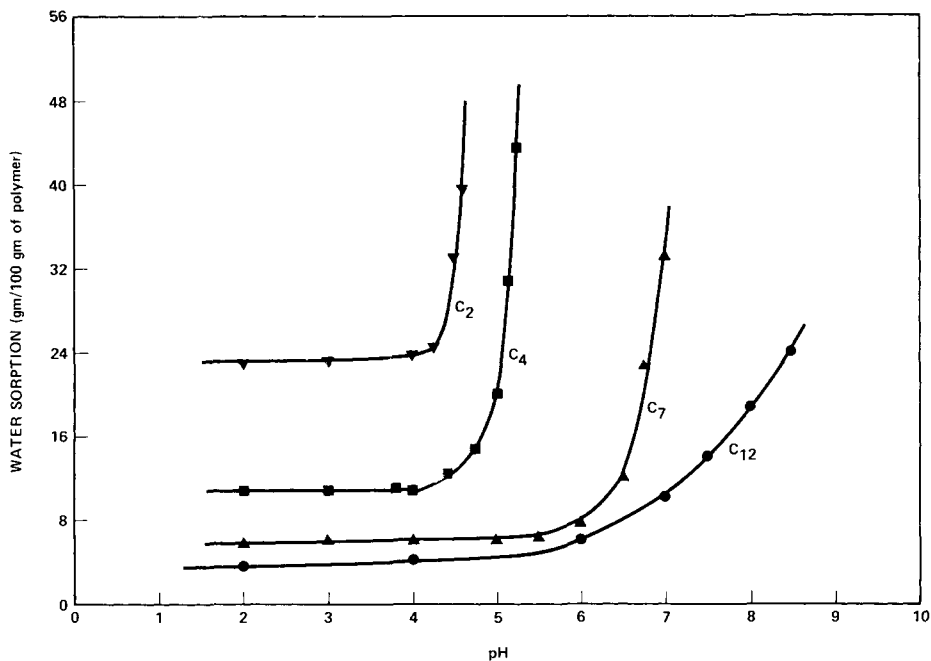
Fig. 7. Water sorption as function of pH for a series of half-esters of methyl vinyl ether–maleic anhydride copolymers.
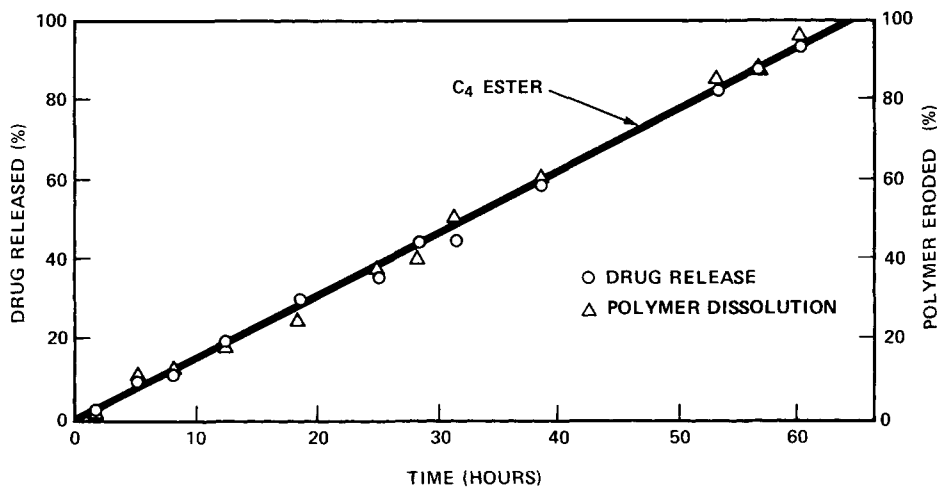

Fig. 8. Rate of polymer dissolution and rate of release of hydrocortisone alcohol for the n-butyl half-ester or methyl vinyl ether–maleic anhydride copolymer containing 10 wt-% drug dispersion.

Figure 9 shows the effect of size of alkyl group on rate of release of hydrocortisone alcohol for a series of partial esters measured at pH 7.4. All drug release rates again show excellent linearity and also a strong dependence on the size of the alkyl group. Since in all experiments depletion of drug also coincided with total polymer dissolution, it can again be assumed that drug release and polymer erosion occur concomitantly.

The effect of pH on rate of release of hydrocortisone alcohol dispersed in the
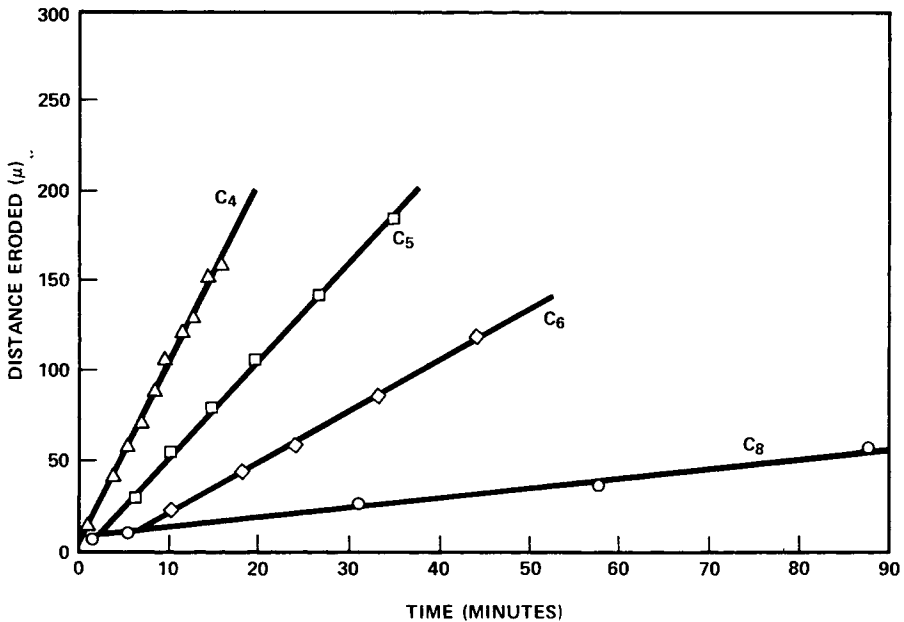
Fig. 9. Effect of size of ester group in half-esters of methyl vinyl ether–maleic anhydride copolymers on rate of erosion at pH 7.4.

n-butyl partial ester is shown in Figure 10. The data show a clear dependence of erosion rate and drug release on the pH of the eroding medium and, as expected, a progressive decrease in rate as the critical dissolution pH is approached.

Data presented thus far show that the partial ester–polymer system is a useful polymer matrix for zero-order drug delivery because it does show the desired surface erodibility and because the erosion rate at any given pH can be adjusted by selecting the appropriate ester alkyl group. However, attempts to use this matrix for delivery of drugs that have water solubilities substantially higher than hydrocortisone alcohol (0.42 mg/ml), such as chloramphenicol (2.5 mg/ml) or idoxuridine (2.0 mg/ml), were only partially successful in that some leaching of the drug took place under conditions of very slow erosion and the observed drug release rate was a combination of diffusion and erosion.

Erosion Mechanism

As a class, the polymers described in this paper represent a series of weak polyacids. In their unionized form, these polyacids are known to be insoluble in water, and the titration curves presented in Figures 3 and 4 reflect the pH at which the polymers first dissolve. Dissolution is thus dependent on ionization. Therefore, it can be anticipated, and indeed it is found experimentally, that the erosion rate of these polymers depends on the pH and buffer capacity of their environment. A model for the erosion kinetics is presented here that is consistent with experimental observations.
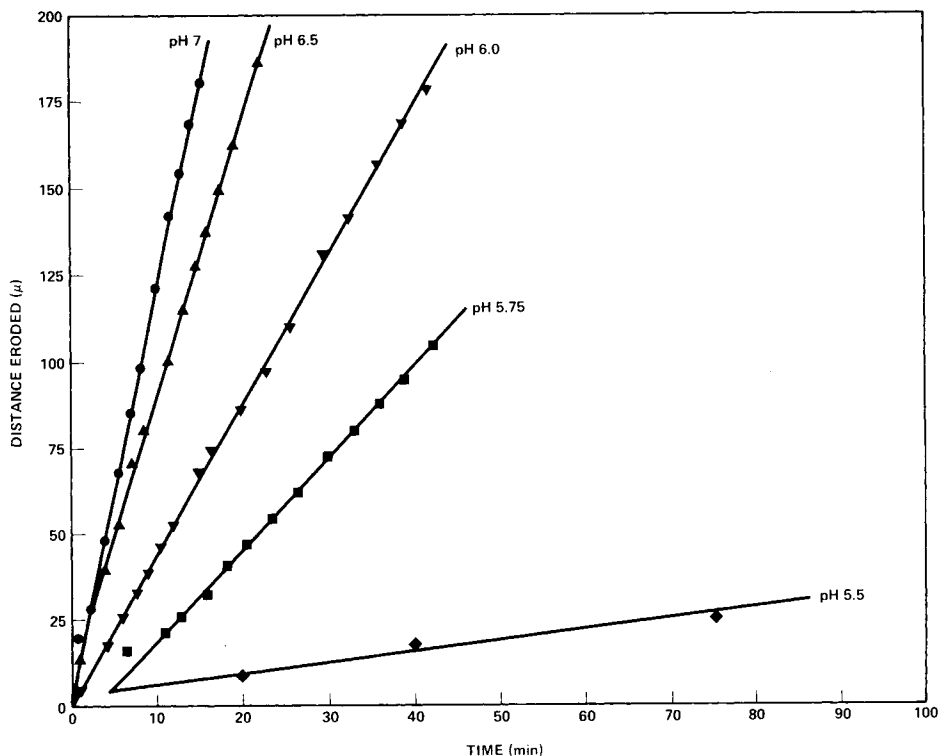
Fig. 10. Effect of pH of erosion medium on rate of erosion of half-esters of methyl vinyl ether–maleic anhydride copolymers.

Polymer dissolution is a heterogeneous process, occurring only on the surface of the material. There, the polymer is adjacent to an aqueous phase of high dielectric constant, and the acid dissociation constant is that normally measured in aqueous media. The interior of the polymer, however, is highly hydrophobic and the acid strength is reduced accordingly. Data for acetic acid illustrate this point nicely: in water, the pK_a is 4.8, whereas in methanol, a medium of lower dielectric constant, it is 9.5.[17] A similar situation prevails in the polyacids described here. Even though water may permeate the polymer matrix, the dielectric constant remains well below that of an aqueous solution, and polymer dissociation in the interior is retarded. Further, the statistically very small fraction of polymer molecules in the interior that dissociate sufficiently to become water soluble are trapped within a matrix of insoluble polymer; only solubilized polymer at the surface can participate in the erosion process.

Polymer erosion thus occurs through the dissociation of polymer molecules at the surface followed by diffusion of ionized polymer along with its associated counterions (i.e., hydrogen ions) through the aqueous boundary layer surrounding the polymer matrix. The process is abetted by the presence of a buffer in the solution because the buffer carries hydrogen ions from the surface.

The model of polymer erosion is depicted in Figure 11. At the eroding polymer surface, dissociation of the polyacid, PH, occurs according to the reaction $PH \rightleftharpoons P^- + H^+$, characterized by the equilibrium constant
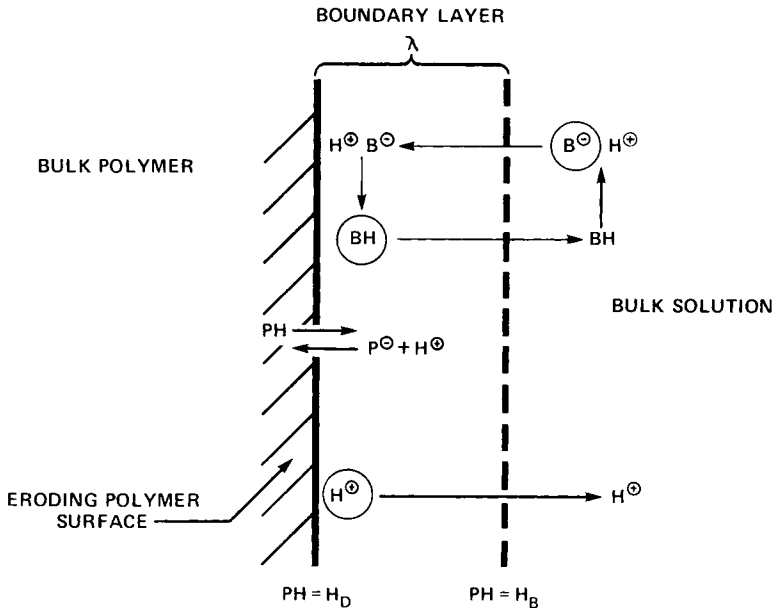
BOUNDARY LAYER

Fig. 11. Model for erosion mechanism.

$$K_P = \frac{[P^-][H^+]}{[PH]} \qquad (1)$$

where $[P^-]$ is used here to denote the concentration of dissociated carboxylate groups in equivalents/cm^3. Similarly, $[PH]$ is the concentration of undissociated carboxylic acid groups in equivalents/cm^3. The model proposes that as the carboxyl groups on the polymer at the surface ionize, solubilizing the polymer, the liberated hydrogen ions accumulate and cause a drop in pH at the surface layer. This pH drop will continue until the pH reaches a value such that further ionization and solubilization does not take place. This is the pH of dissolution obtained from the titration curves of the polymer. A buffering agent is present in the aqueous phase, and its dissociation is denoted by $BH \rightleftharpoons B^- + H^+$, characterized by the equilibrium constant

$$K_B = \frac{[B^-][H^+]}{[BH]} \qquad (2)$$

The concentration of hydrogen ions at the surface of the eroding polymer, that is, the concentration at the pH of dissolution, is denoted by $[H_d]$, and the concentration of hydrogen ions in the bulk solution is denoted by $[H_b]$. Diffusion of hydrogen ions, solubilized polymer, and buffer occurs across some boundary layer of thickness λ adjacent to the polymer matrix. In the bulk solution where the hydrogen ion concentration is lower, the buffer tends to be in its dissociated form, whereas adjacent to the polymer matrix where hydrogen ions are being liberated, the buffer tends to be in its protonated or undissociated form.

Thus, hydrogen is carried away from the surface of the polymer by two mechanisms: simple diffusion of hydrogen ions down the hydrogen ion concentration gradient and diffusion of BH. The buffer thus acts as a shuttle,
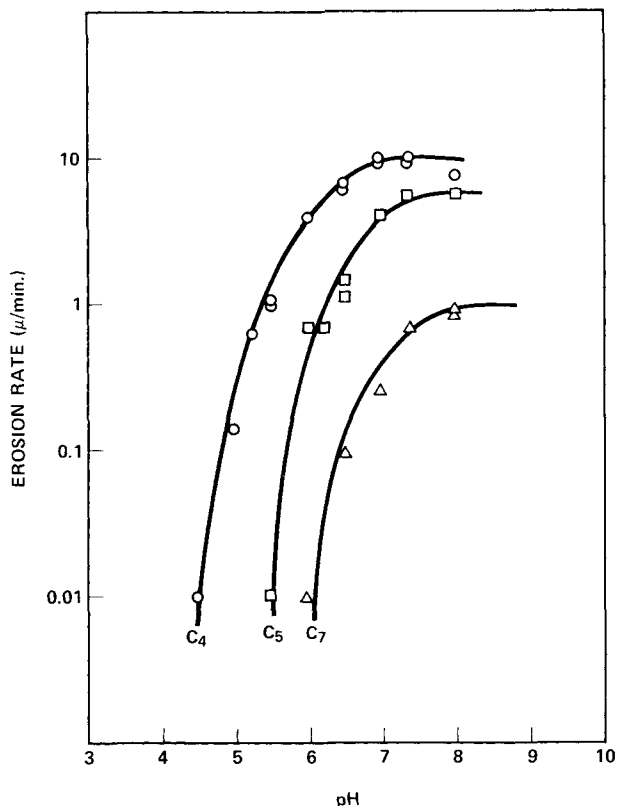
Fig. 12. Erosion rate as function of pH for various half-esters of methyl vinyl ether–maleic anhydride copolymers.

picking up hydrogen ions at the eroding polymer surface, carrying them across the boundary layer, releasing them to the bulk solution, and diffusing back to the polymer surface in the form of B⁻ ions. Because the buffer concentration in the experiments cited below $(0.1M)$ was much larger than the hydrogen ion concentration $(<10^{-4}M)$, transport of hydrogen ions by coupling with the buffer dominates the flux of hydrogen ions alone, in spite of the fact that hydrogen ions are considerably more mobile within the boundary layer.* The erosion rate can be derived in terms of known or measurable quantities through any arbitrary plane in the boundary layer.

The flux of solubilized polymer, J_{P^-}, expressed as equivalents of carboxylate groups/cm²-sec, is related to the flux of the other ions within the boundary layer by the requirement for charge neutrality:

$$J_{P^-} + J_{B^-} = J_{H^+} \tag{3}$$

Furthermore, since at steady state there is no accumulation of buffer anywhere within the system, we have

$$J_{B^-} = -J_{BH} \tag{4}$$

where J_{BH} is the flux of un-ionized buffer, in equivalents/cm²-sec. Thus,

$$J_{P^-} = J_{H^+} + J_{BH} \tag{5}$$

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* Subsequent to our formulation of this model, we have come across a conceptually similar model proposed by Nogami et al.[18] to rationalize the rate of solution of benzoic acid derivatives.
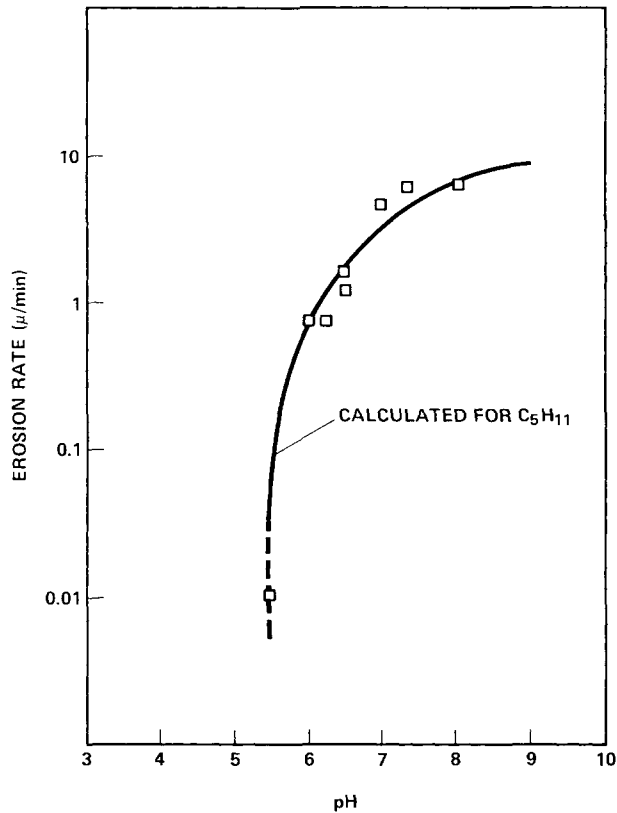
Fig. 13. Calculated and observed erosion rate as function of pH for n-pentyl half-ester of methyl ether–maleic anhydride copolymers.

and, from Fick's law, we have

$$J_{\mathrm{P-}} = -D_{\mathrm{H+}}\frac{d[\mathrm{H^+}]}{dx} - D_{\mathrm{BH}}\frac{d[\mathrm{BH}]}{dx} \tag{6}$$

We are interested, of course, in the total flux of solubilized polymer. We can express this as J_{P_T},

$$J_{P_T} = J_{\mathrm{P-}}\frac{[\mathrm{P}_T]}{[\mathrm{P^-}]} \tag{7}$$

where $[\mathrm{P}_T]$ is the total concentration of carboxyl groups, ionized plus un-ionized, expressed as equivalents/cm^3. As solubilized polymer chains diffuse away from the polymer surface, they carry both ionized and un-ionized carboxyl groups, and the ratio of these two concentrations is simply given by the degree of dissociation $[\mathrm{P^-}]/[\mathrm{P}_T]$. Hence we can restate eq. (6) as follows:

$$J_{\mathrm{P}_T} = \frac{[\mathrm{P}_T]}{[\mathrm{P^-}]}\left(-D_{\mathrm{H+}}\frac{d[\mathrm{H^+}]}{dx} - D_{\mathrm{BH}}\frac{d[\mathrm{BH}]}{dx}\right) \tag{8}$$

This equation reflects the dual modes of diffusive hydrogen ion transport, as hydrogen ion alone and coupled to the buffer flux. We can now substitute for the unknown quantities in eq. (8) in terms of known or measurable quantities
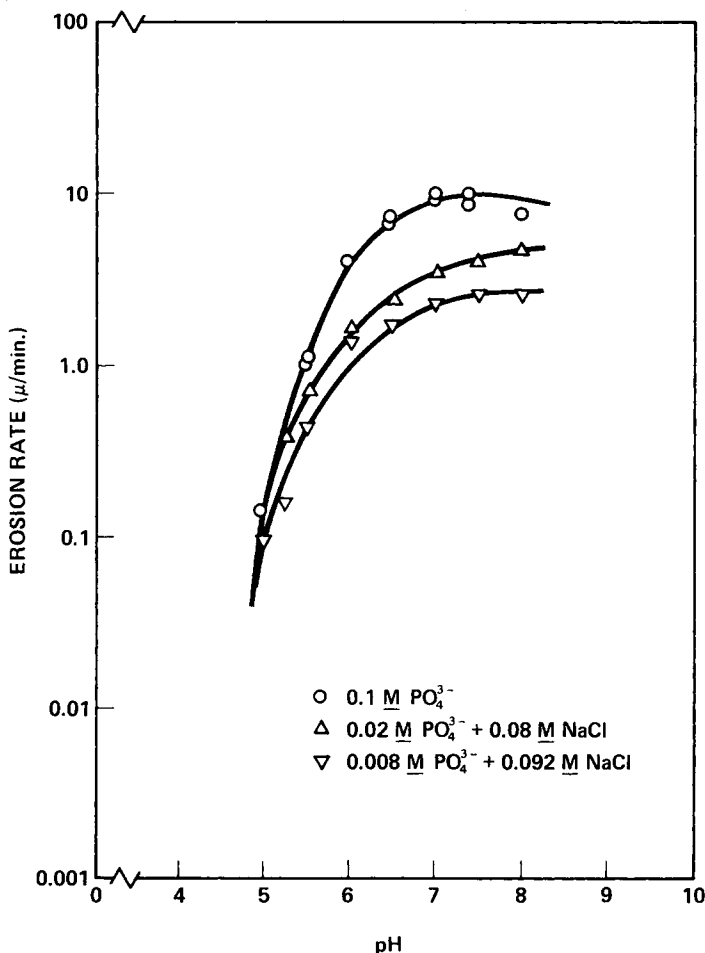
Legend on plot:

○ 0.1 $\underline{M}$ PO$_4^{3-}$

△ 0.02 $\underline{M}$ PO$_4^{3-}$ + 0.08 $\underline{M}$ NaCl

▽ 0.008 $\underline{M}$ PO$_4^{3-}$ + 0.092 $\underline{M}$ NaCl

Fig. 14. Erosion rate of n-butyl half-ester of methyl vinyl ether–maleic anhydride copolymer as function of phosphate buffer concentration.

by means of eqs. (1) and (2). Thus,

$$J_{P_T} = - \left[\frac{[H^+] + K_P}{K_P} \right] \left[D_{H^+} \frac{d[H^+]}{dx} + [B_T] D_{BH} \frac{d([H^+]/(K_B + [H^+]))}{dx} \right]$$

(9)

where $[B_T]$ is the total buffer concentration, $[B_T] = [B^-] + [BH]$.

Equation (9) can now be integrated over the boundary layer thickness, using the boundary conditions $[H^+] = [H_d]$ at $X = 0$, and $[H^+] = [H_b]$ at $X = \lambda$. The result, after rearrangement, is

$$J_{P_T} = \frac{D_{H^+}}{K_P \lambda} \left(\frac{[H^+]^2}{2} + K_P [H^+] \right) \Big|_{H_b}^{H_d} + \frac{[B_T] D_{BH}}{K_P \lambda} \left(\frac{[H^+][K_P - K_B]}{K_B + [H^+]} \right.$$
$$\left. + K_B \ln \frac{(K_B + [H^+])}{K_B} \right) \Big|_{H_b}^{H_d} \quad (10)$$

Finally, the polymer erosion rate γ, in cm/sec, is obtained from eq. (10) by the relationship

$$\gamma = \frac{J_{P_T}E}{\rho} \qquad (11)$$

where E is the gram-equivalent weight of the polymers (gram per carboxylate-containing mer unit) and ρ is the polymer density.

It is implicit in the derivation of eq. (10) that the mobility of the negatively charged ions in the boundary layer is equal to the mobility of the positively charged ions. If this is not the case, a streaming potential will develop across the boundary layer and the slower moving ions will exert a retarding force on the faster ions and the faster ions will exert an accelerating force on the slower ions. The result is to modify the diffusion coefficients in eq. (10) by a factor proportional to the difference in mobilities. Fortunately, this difference in mobility may not be large since the principal negative charge-carrying group, the ionized polyacid, although of a high molecular weight and with a proportionately low diffusion coefficient, carries many negative charges per molecule. Therefore, the total charge-carrying ability of the various ionized species may be fairly close. However, in our analysis this is not taken into account, and, if present, it will lower the calculated erosion rates.

Factors Affecting Polymer Erosion Rate

Even though eq. (10) is somewhat complex, it can be used to rationalize the polymer erosion properties described below.

Effect of pH. Figure 10 shows erosion rates for the n-butyl partial ester in
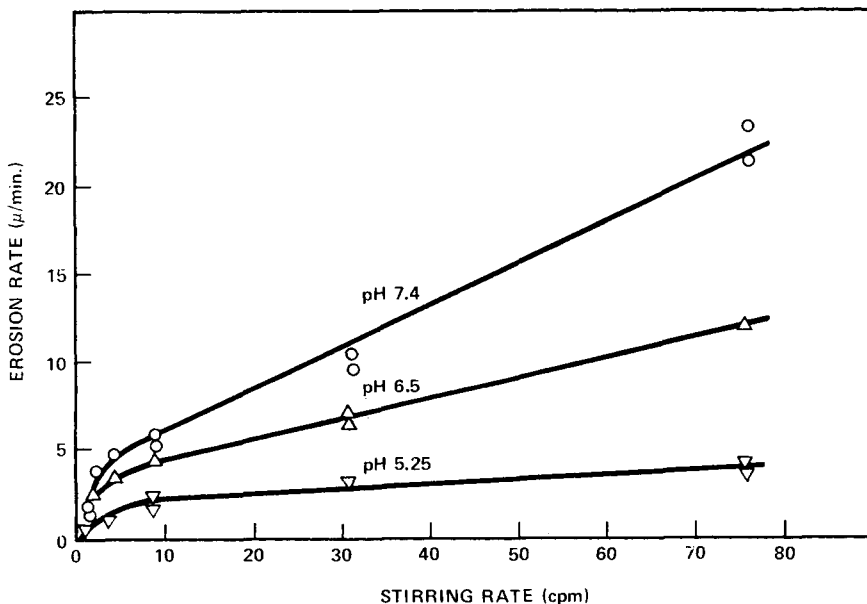

Fig. 15. Erosion rate of n-butyl half-ester of methyl vinyl ether–maleic anhydride copolymers as function of stirring speed.
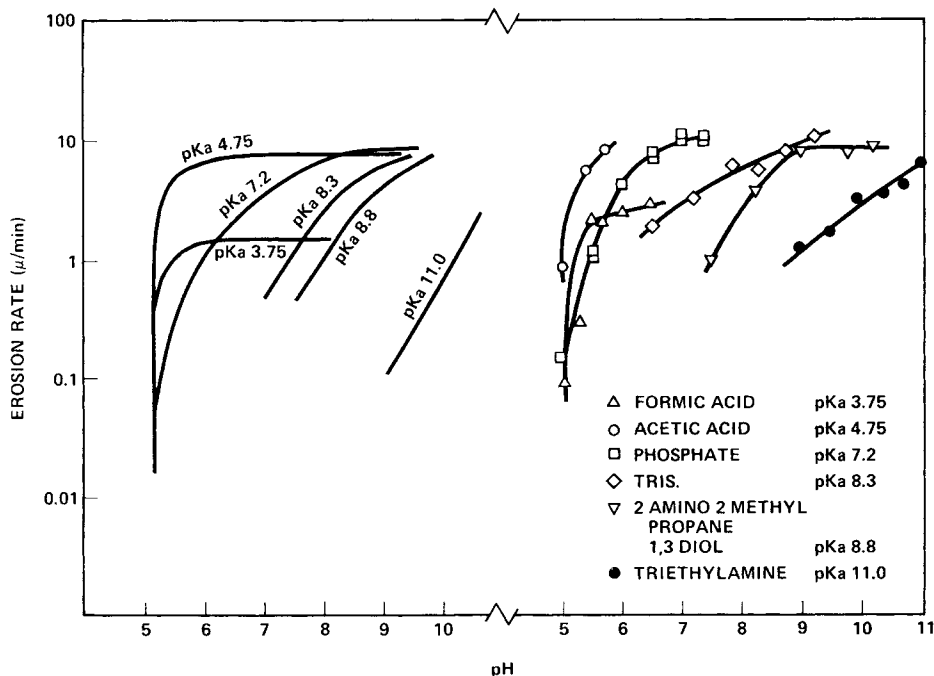
Fig. 16. Calculated and observed erosion rates for n-butyl half-ester of methyl vinyl ether–maleic anhydride copolymers in various $0.1M$ buffer solutions.

various buffer solutions. Clearly, the rate is highly dependent on the pH of solution, slowing to almost zero as the pH of the bulk solution approaches the pH of dissolution of the polymer. However, at all pH values, the erosion rate as shown by the slope of the lines is constant. Another way of showing pH dependence of the erosion process is to plot the erosion rate versus pH as shown in Figure 12 for the three different half-ester polymers. All curves have the same form, and as predicted by eq. (10) no polymer erosion occurs at or below the dissolution pH, although erosion rapidly increases above this pH and finally reached a plateau about 2 pH units above the dissolution pH.

Equation (10) can be used to predict actual erosion rates. Thus, buffer concentration B_T, buffer dissociation constant K_B, pH of dissolution of polymer H_d, and dissociation constant K_a of the acid are known, and the diffusion coefficient of the buffer ion and of the hydrogen ion can be estimated from tables with reasonable accuracy. The only adjustable parameter, then, is the boundary layer thickness, which for the purposes of this calculation has been assumed to be $100 \, \mu$.

Figure 13 shows the results of substituting these values into eq. (10) and calculating polymer erosion rate as a function of pH for the five-carbon half-ester. Although for this particular polymer the agreement between calculated and observed erosion rate is excellent, other half-esters show poorer agreement. However, considering the complexity of the model and the number of parameters in eq. (10) that have to be estimated, the qualitative agreement between theory and experiment is encouraging and adds credence to the validity of the erosion model.

Effect of Buffer Concentration. From the model illustrated in Figure 11

and from eq. (10), it is clear that the concentration of buffer in the erosion medium plays a substantial role in the erosion process. Figure 14 shows the erosion of the n-butyl ester in different phosphate buffer solution concentration. In the 0.1 molar buffer solution the erosion rate reaches a plateau at a maximum value of ~10 μ/min. And as the buffer concentration was decreased, the erosion rate also decreased; in 0.08 molar buffer the erosion rate reached a plateau at a maximum of ~3 μ/min. This effect shows the substantial contribution of buffering ion on the rate of removal of hydrogen ion and hence the erosion rate of the polymer.

Effect of Stirring. Because the rate-determining step in the erosion process involves diffusion of ions across a boundary layer, the erosion rate is stirring rate dependent. Figure 15 shows the erosion rate of the n-butyl half-ester plotted versus stirring speed. At high stirring speeds the thickness of the boundary layer surrounding the polymer film is small, and hence the rate of diffusion of ions across it is rapid, thus leading to a rapid erosion rate. As the stirring speed is reduced, the thickness of the boundary layer increases, and with it the erosion rate decreases. When the stirring rate approaches zero, the erosion process virtually stops.

Effect of Buffer pK_a. The effect of the buffering species pK_a on the erosion rate of these polymers is a parameter whose importance might have been overlooked had it not been for eq. (10), which predicts a considerable effect in solutions under conditions where the majority of hydrogen ions being transferred across the boundary layer are associated with buffers. Consider the n-butyl half-ester with a pH of dissolution of 5.2 and phosphate buffer with a pK_a of 7.2. At the surface of the eroding polymer virtually all of the phosphate buffer is in the protonated form, whereas in the bulk solution the fraction in the protonated form will decrease with increasing pH. At pH 7.2 half the buffer is in the protonated form, and the buffer cycle is working at half of its theoretical maximum rate. At pH 8.2 most of the buffer ions are in the unprotonated form, and the buffering cycle is working at its maximum efficiency. Hence, the erosion rate reaches its plateau value. With multivalent buffering ions such as phosphate and tris buffers, the situation is somewhat more complex than the above argument suggests but the essential result is the same, namely, the erosion rate reaches its plateau value at about one pH unit above the pK_a of the buffer.

Figure 16 shows calculated and experimental curves for the butyl half-ester eroding in various 0.1 molar buffer solutions. The range of pH in which any one buffer can be used is limited by the liberation of hydrogen ions by the eroding polymer. However, it is clear that the calculated and experimental curves have the same form, and despite the complexity of the model the quantitative agreement is good.

The calculated and experimental curves for formate buffer of pK_a 3.75 are particularly interesting. The pK_a of this buffer is below the pH at the polymer surface so that even at the polymer surface most of the buffer is in the unprotonated form. Thus, when the buffer cycle is working at its maximum efficiency, that is, when most of the buffer in the bulk solution is in the B^- form, the rate of hydrogen ion removal (and hence erosion rate) is not as large as with the same concentration of higher pK_a buffers.

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