Figure 5—*Dissolution of meclizine hydrochloride from a 25-mg solid gelatin capsule in simulated gastric fluid (without pepsin) at 37° using the rotating-bottle method.*

solid gelatin capsules and 25-mg tablets. The mean recovery was 100.4 and 106.0% of labeled claim with relative standard deviations of 1.6 and 4.0%, respectively.

Figure 5 shows the dissolution of meclizine hydrochloride from a 25-mg solid gelatin capsule in simulated gastric fluid (without pepsin) at 37° using the rotating-bottle method (6,7). The initial portion of the curve represents the dissolution of the drug from the shell. When the shell dissolved, the slope of the curve changed from the dissolution of meclizine hydrochloride in the lesser concentrated shell to the more concentrated

core. The core completely dissolved after about 20 min and the curve leveled off.

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Recording pH Method of Characterizing Composition and Monitoring Dissolution Profile of an Anhydride–Acid Copolymer and Its Salt Derivatives

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Abstract □ A sensitive potentiometric monitoring method was developed that permits the continuous measurement of the dissolution profiles of methyl vinyl ether–maleic anhydride–acid copolymers and salt derivatives. Three distinct rate periods were observed in the dissolution of the anhydride copolymer. The relative dissolution rate of the anhydride copolymer, expressed as percent anhydride dissolved, was independent of sample weight over the weight range studied. The acid form of the copolymer showed only one dissolution rate period, with dissolution being very rapid. The rapid initial pH decrease observed during the first stage of dissolution for a series of anhydride–acid copolymer powder samples correlated closely with the anhydride–acid ratio, permitting chemical characterization of the copolymer functionality simultaneously with the analysis of dissolution profiles. Similarly, the extent of copolymer alkaline salt conversion was inversely proportional to the initial maximum pH increase observed during the first stage of dissolution of these salts.

Mechanisms of dissolution of copolymer powder materials are discussed and compared to the dissolution of compressed disks and films reported previously.

Keyphrases □ Maleic anhydride–acid copolymers—with methyl vinyl ether, potentiometric characterization of composition and measurement of dissolution profiles □ Methyl vinyl ether–maleic anhydride–acid copolymers—potentiometric characterization of composition and measurement of dissolution profiles □ Copolymers—methyl vinyl ether–maleic anhydride–acid, potentiometric characterization of composition and measurement of dissolution profiles □ Potentiometry—characterization of composition and measurement of dissolution profiles of methyl vinyl ether–maleic anhydride–acid copolymers □ Dissolution—methyl vinyl ether–maleic anhydride–acid copolymers, potentiometric measurement of profiles

Alkyl, aryl, and alkyl vinyl ether–maleic anhydride copolymers, their hydrolyzed acids, and various ester derivatives have been recommended for various pharmaceutical applications, including use as thickeners, sus-

pension and emulsion stabilizers, topical product and cosmetic vehicles, complexing agents of iodine and other antiseptics, controlled-release matrixes, and protective, delayed-, or controlled-release coatings (1–4). Styrene,
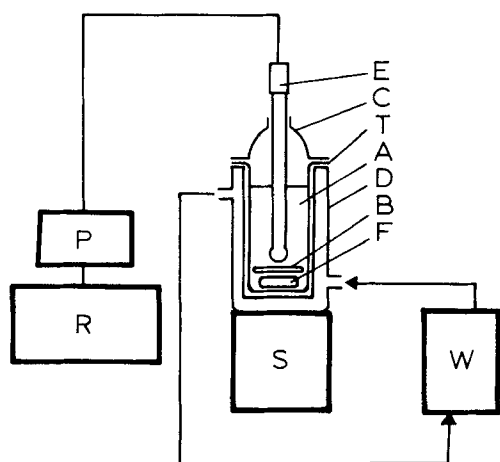
Figure 1—*Continuous pH-monitoring apparatus designed to record the dissolution processes of copolymer samples. Key: A, test solution; B, baffle plate; C, plastic cover; D, double-walled chamber; E, combination electrode; F, floating stirring bar; P, pH meter; R, recorder; S, magnetic stirrer; T, thin-walled beaker; and W, thermostat.*

Scheme I

ethylene, and various alkyl vinyl ether–maleic anhydride copolymers were studied extensively as delayed and enteric coatings (5–11), and some are now used commercially. Due to the reported low toxicity of this polymer class and its increasing acceptance in cosmetic and food applications, the importance and use of these materials in drug products probably will expand.

The dissolution of alkyl vinyl ether–maleic anhydride copolymers and ester derivatives from compressed disk and film structures, using an immersion refractometry method, was reported (12). Previously, Heyd *et al.* (13, 14) discussed the immersion refractometry method, studied the dissolution of a series of ethylene maleic anhydride and acid copolymers, and examined the surface phenomena associated with polymer dissolution. The dissolution of the anhydride copolymer as a compressed disk went through an induction period comprised of a lag time (no solute in solution), a stabilization period (rate of dissolution was nonlinear), and then a linear dissolution rate period (14). These periods were subsequently related to solvent penetration into the compressed disk and initial polymer swelling (the lag time), the formation of a hydrated layer on the disk surface and the attainment of a maximum hydrated layer thickness (the stabilization period), and a constant dissolution rate (polymer chain diffusion out of the hydrated layer probably being the rate-limiting step). Woodruff *et al.* (12) examined the effect of the degree of alkyl esterification of the alkyl vinyl ether–maleic acid copolymer and the effect of alkyl chain length of the ether substituent on dissolution properties of compressed disks. The dissolution of film structures was also characterized, and the effect of formulation factors such as the presence and concentration of plasticizers was examined.

While immersion refractometry provides a simple method of following polymer dissolution, it does not readily lend itself to continuous monitoring procedures. The method is also most applicable to polymer structures (compressed disks, matrixes, and films), but it lacks sensitivity at low polymer concentrations and has been of limited use in evaluating the dissolution characteristics of powdered polymer samples. This investigation was undertaken to develop a continuous dissolution monitoring
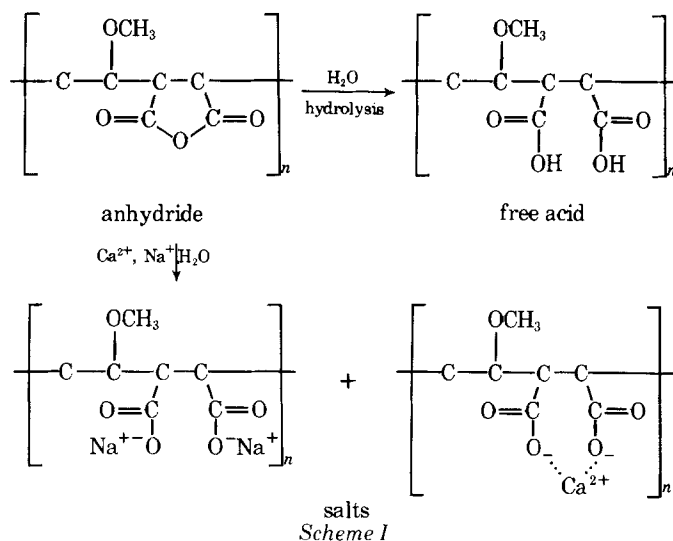
method for anhydride–acid copolymers utilizing standard laboratory equipment. Additional objectives were to study powdered polymer materials, to examine the effect of the anhydride–acid ratio and the extent of alkaline salt formation on copolymer dissolution characteristics, and to find additional methods of characterizing these copolymers as to the anhydride–acid ratio or the extent of salt formation.

EXPERIMENTAL

Materials—The free acid of the copolymer[1] (mol. wt. 1,125,000) of methyl vinyl ether and maleic anhydride (Scheme I) was prepared by completely dissolving the anhydride copolymer [assayed purity = 99.9% using potentiometric method (12)] in water to produce the totally hydrolyzed free acid, which was then lyophilized to a white dry powder. The alkaline salt of this copolymer was produced in an aqueous solution, and the resultant copolymer salt was dried utilizing lyophilization. All copolymer samples were subjected to a sieve treatment, and the fraction of each sample in the 60–100-mesh cut (150–250 μm) was used.

Continuous Potentiometric Monitoring Apparatus—Figure 1 outlines the setup for the continuous potentiometric monitoring apparatus. The changing pH of the test solution (A) was monitored continuously using a calomel–glass combination electrode[2] (E) connected to a pH meter[3] (P) equipped with a 25.4-cm chart recorder[4]. Double-deionized water (50 ml) was pipetted into the thin-walled beaker (T), which was then fitted into the double-walled chamber (D). Water, at a constant temperature (37 $\pm$ 1°) controlled by a thermostat[5] (W), was circulated through the double-walled chamber to maintain the test solution at a constant temperature. For each test, the electrode (E) was introduced into the test solution to a fixed depth of 2 cm below the surface of solution.

A 2 X 1-cm "floating" stirring bar[6] (F), equipped with baffles (B), was placed in the bottom of the beaker and operated at a constant stirring rate (455 $\pm$ 10 rpm), which was verified with a strobe light. The floating stirring bar was used to avoid the grinding or the milling of the undissolved copolymer particles by the normal stirring operation; the baffles served to furnish a more smooth and homogeneous agitation as well as a more stable reading on the pH meter. A plastic cover (C) was placed on the top of the beaker to reduce evaporation and to avoid contamination during a prolonged dissolution monitoring process.

The pH meter was calibrated with standard pH buffer solutions. The recording chart of the recorder was adjusted to give a full scale of 5 (pH 2.0–7.0) or 10 (pH 2.0–12.0) pH units for the dissolution study of the anhydride or the alkaline salt copolymer sample, respectively.

[1] General Aniline & Film Co., New York, N.Y.
[2] Sargent-Welch, McGaw Hill, Ill.
[3] LSX, Sargent-Welch, McGaw Hill, Ill.
[4] SRG, Sargent-Welch, McGaw Hill, Ill.
[5] Heto Co. (Denmark), London Co., Westlake, Ohio.
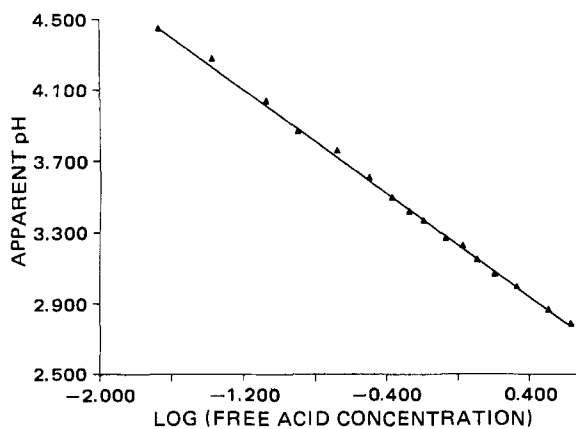[6] Spectroderm International, Inc., Fairfax, Va.

Figure 2—*Correlation of apparent pH values and logarithm values of the corresponding free acid concentrations of the copolymer standard solutions. Linear regression analysis produced a correlation coefficient of 0.998 over a concentration range of the free acid between 0.02 and 4.5 mg/ml.*

Quantitative Standardization of Copolymer Free Acid Solution—A copolymer free acid solution with an approximate concentration of 4.5 mg/ml was accurately prepared and potentiometrically titrated with a 0.1 N NaOH standard solution to determine its concentration quantitatively. An automatic titration system was used[7]. The free acid concentration was calculated as:

$$C_2 \text{ (mg/ml)} = \frac{174 \times N_1 \times V_1 \text{ (ml)}}{V_2 \text{ (ml)}} \qquad \text{(Eq. 1)}$$

where N_1 and V_1 are the normality and the amount of the sodium hydroxide standard solution consumed, respectively, and V_2 is the volume of the free acid sample solution.

RESULTS AND DISCUSSION

Correlation of Apparent pH Values with Copolymer Free Acid Concentrations in Aqueous Solutions—A series of standard copolymer free acid solutions (0.02–4.5 mg/ml) was prepared by diluting the standardized free acid solution with double-deionized water. The apparent pH value of 50 ml of each free acid solution was measured using the continuous pH-monitoring apparatus (Fig. 1) as described under *Experimental.* A linear calibration curve ($r = 0.998$) was observed when the measured apparent pH values of the free acid solutions were plotted against the logarithm of the corresponding concentrations (Fig. 2). The pH–concentration relationship may be expressed as:

$$\text{pH} = 3.2393 - 0.7382 \times \log \text{ (free acid concentration)} \quad \text{(Eq. 2)}$$

This finding coincides with the assumption (15) that the pH value of a dilute solution of a weak acid linearly correlates with the logarithm of
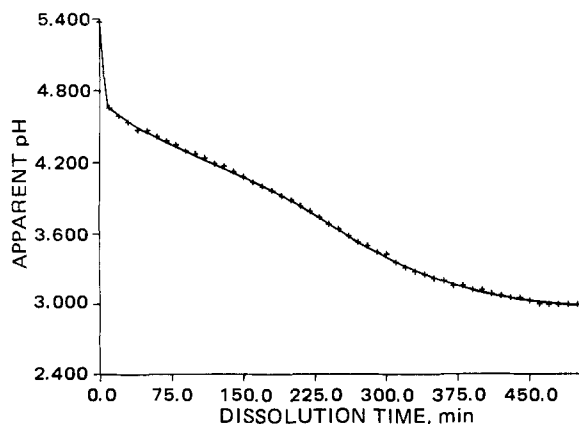

Figure 3—*The pH profile recorded during the dissolution process of the anhydride copolymer.*
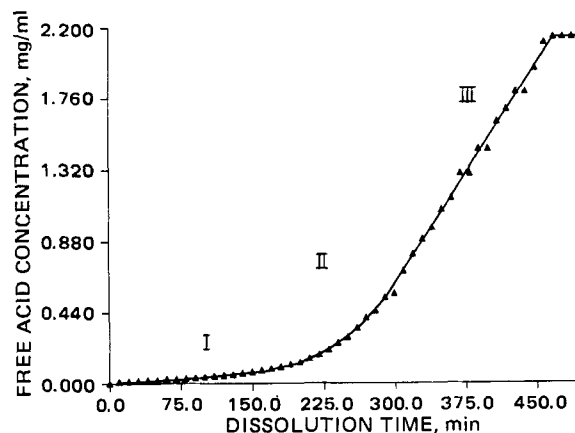
[7] Radiometer, Coppenhagen, Denmark.

Figure 4—*Dissolution profile monitoring the formation of the free acid during the dissolution process of the anhydride copolymer. Key: I, initial lag period; II, intermediate accelerating rate period; and III, final zero-order rate period.*

its respective concentration:

$$\text{pH} = 0.5 \times \text{pKa} - 0.5 \times \log \text{ (concentration)} \qquad \text{(Eq. 3)}$$

where the concentration is expressed in moles per liter. The value of the slope, 0.7382, obtained from Eq. 2 is different from the value of 0.5 of Eq. 3, because Eq. 2 expresses the concentration–pH relationship for a polyprotonic solution while Eq. 3 describes this relationship for a simple monomeric solution. For the polyacid aqueous solution, a modified form of the Henderson–Hasselbalch equation (16) was used:

$$\text{pH} = \text{pKa} - n \log \frac{(1-d)}{d} \qquad \text{(Eq. 4)}$$

where d is the degree of dissociation, pKa is the apparent dissociation constant, and n is a constant for a given set of conditions.

pH Dissolution Profile for Anhydride Copolymer—A carefully weighed sample of 100 mg of the anhydride copolymer, with a particle-size distribution ranging from 60 to 100 mesh, was added to a dissolution medium of 50 ml of double-deionized water in the sample beaker of the continuous pH-monitoring apparatus, maintained as described under. *Experimental.* The pH value of the dissolution medium was continuously recorded on the recording chart (1 pH unit = 5.08-cm scale) over 10 hr (Fig. 3).

The observed decreasing pH value was due to the increased concentration of the free acid produced in the dissolution medium as the dissolution process proceeded. An initial abrupt decrease in the apparent pH value was followed by a slow and general decrease in pH until a plateau was reached, indicating that the dissolution process was complete.

Characterization of Dissolution Process of Anhydride Copolymer—The pH profile (Fig. 3) obtained by continuously monitoring the formation of the free acid in the dissolution medium was then trans-
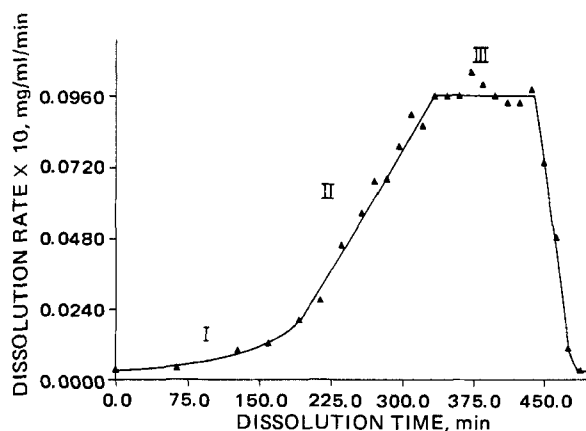

Figure 5—*Characterization of the anhydride copolymer dissolution rate process. These different periods are attributed to their different dissolution mechanisms. Key: I, wetting and penetration period; II, hydration and swelling period; and III, zero-order process period.*
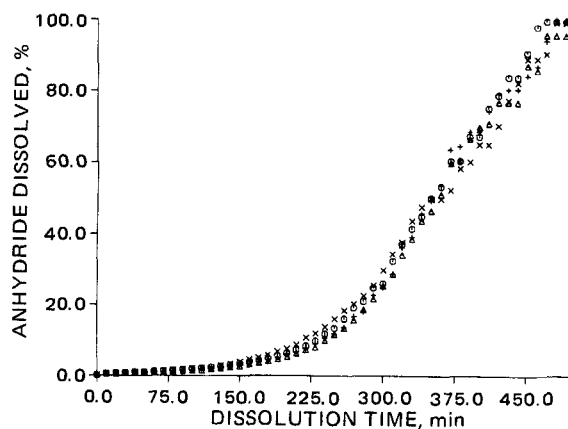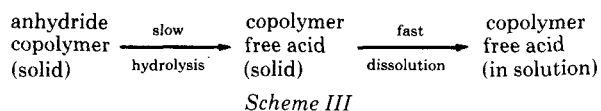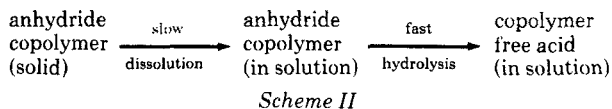
Figure 6—*Similarity of relative dissolution profiles observed for different weights of the anhydride copolymer sample. Key: O, 100 mg; △, 75 mg; +, 50 mg; and X, 30 mg.*

formed into a dissolution profile (Fig. 4). This profile correlated the formation of the free acid with the dissolution time by substituting the recorded pH values into the calibration equation (Eq. 2). The resultant dissolution profile was used to investigate the dissolution process of the anhydride copolymer powder.

Two possible mechanisms for the anhydride copolymer dissolution process are proposed, Schemes II and III. Scheme III is a more likely route for the copolymer dissolution process, where the hydrolysis reaction is the rate-limiting step.

$$
\begin{array}{ccccc}
\text{anhydride} & & \text{anhydride} & & \text{copolymer} \\
\text{copolymer} & \xrightarrow[\text{dissolution}]{\text{slow}} & \text{copolymer} & \xrightarrow[\text{hydrolysis}]{\text{fast}} & \text{free acid} \\
\text{(solid)} & & \text{(in solution)} & & \text{(in solution)}
\end{array}
$$

Scheme II

$$
\begin{array}{ccccc}
\text{anhydride} & & \text{copolymer} & & \text{copolymer} \\
\text{copolymer} & \xrightarrow[\text{hydrolysis}]{\text{slow}} & \text{free acid} & \xrightarrow[\text{dissolution}]{\text{fast}} & \text{free acid} \\
\text{(solid)} & & \text{(solid)} & & \text{(in solution)}
\end{array}
$$

Scheme III

Essentially, three different periods are observed for the dissolution process of the anhydride copolymer with respect to the formation of the free acid (Fig. 4). Period I, the initial lag period (0–180 min), is attributed to the slow process of wetting and penetration by the water molecules. Period II, an accelerating rate period, may be reflecting the hydration and swelling of the particles as well as the autocatalytic nature of the hydrolysis reaction in which the increased hydrogen-ion concentration accelerates the hydrolysis process (17). Period III is an apparent zero-order dissolution process.

The dissolution profile of the anhydride copolymer powder material correlated with reported dissolution studies of the polymer free acid film (14) and the compressed copolymer disk (12). In these studies, a similar lag time or induction period followed by an apparent zero-order dissolution process was observed.

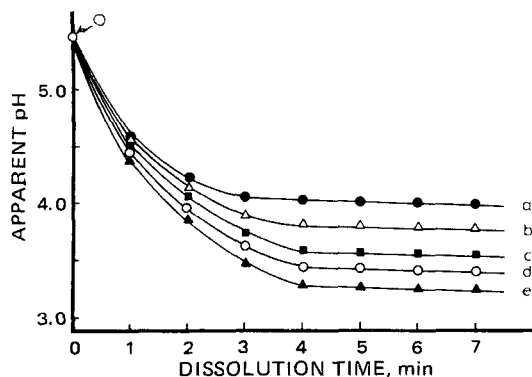The three different rate periods were further characterized by relating

Figure 7—*Comparisons of initial dissolution profiles of copolymer anhydride–free acid mixtures. Key (anhydride–free acid ratio): a, 90:10; b, 80:20; c, 60:40; d, 40:60; and e, 0:100.*
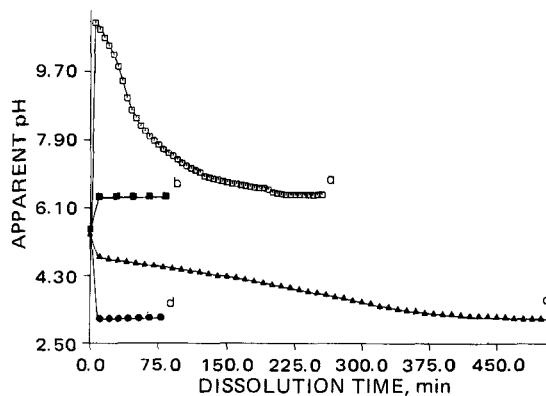

Figure 8—*Overall dissolution profiles observed for the copolymer anhydride, free acid, and salt. Key: a, mixture of the copolymer and the free alkaline salts; b, pure reacted copolymer salt; c, pure anhydride copolymer; and d, pure copolymer free acid.*

the calculated value of the initial rate of free acid formation with the dissolution time (Fig. 5). Initially, a slow dissolution rate was observed for Period I, followed by a rapidly increasing rate for Period II. The dissolution rate then reached a plateau and exhibited a constant and maximum value.

When 100-, 75-, 50-, and 30-mg powder samples of the anhydride copolymer were subjected to the dissolution test, nearly identical relative dissolution profiles were observed (Fig. 6). This result indicates that the dissolution process is essentially independent of the concentration of polymer already in solution over the concentration range studied. Figure 6 also indicates a high order of reproducibility for these recorded profiles.

Dissolution as Function of Anhydride–Free Acid Ratio—Fifty milligrams of each of a series of copolymer sample mixtures, composed of different anhydride–free acid compositions, was evaluated for dissolution characteristics as described under *Experimental*. As indicated in Fig. 7, samples containing different anhydride–free acid ratios exhibited different initial pH profiles. These profiles showed abruptly decreasing pH readings at the very beginning of the dissolution processes, followed by a much more gradual decrease in the pH values after the first 5 min (Figs. 3 and 7). In a separate experiment, the copolymer free acid completely dissolved within 5 min to give a concentration of 1.0 mg/ml.

The more abrupt drop in initial pH readings is attributed to the presence of the free acid (Fig. 8). Therefore, it is possible to determine the composition of the free acid in this mixed acid–anhydride polymer system by substituting the apparent pH reading of the dissolution medium recorded at the end of the first 5 min of the dissolution process into the calibration equation (Eq. 2) and solving for the free acid concentration. Thus, this method can be applied to the analysis of the acid–anhydride functionality of this type of polymer system. Only a very small amount of the copolymer anhydride was converted into the free acid during the first 5 min (Fig. 4). The amount of the copolymer anhydride
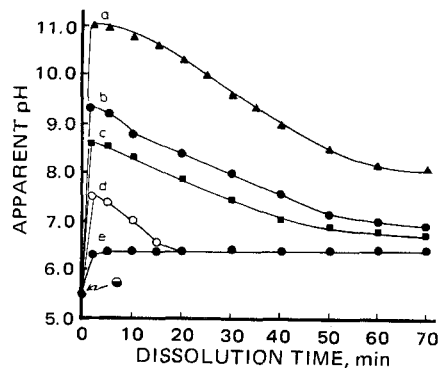

Figure 9—*Comparisons of dissolution profiles of copolymer mixtures of different anhydride–salt compositions. The half-open circle (◓) shows pH reading (5.50) prior to addition of samples. Key (anhydride–salt ratio): a, 80:20; b, 35:65; c, 25:75; d, 10:90; and e, 0:100. All samples contained identical content (29%) of alkaline salts, including both free (unreacted) and reacted salts. All profiles reached a similar plateau pH reading of 6.45 ± 0.05 toward the end of the dissolution processes.*

Table I—Correlation of the Anhydride–Salt Derivatives Ratio with the Maximum Dissolution pH Value and the Total Dissolution Time

Anhydride–Salt Derivatives Ratio[a]	Maximum pH	Total Dissolution Time, min
100/0	11.2 ± 0.1	210 ± 10
80/20	11.0 ± 0.1	180 ± 10
70/30	10.6 ± 0.1	165 ± 10
55/45	10.20 ± 0.05	140 ± 10
45/55	9.75 ± 0.05	115 ± 10
35/65	9.25 ± 0.05	95 ± 5
25/75	8.60 ± 0.05	85 ± 5
15/85	8.00 ± 0.05	55 ± 5
10/90	7.55 ± 0.05	17 ± 2
0/100	6.45 ± 0.05	1.5 ± 0.5

[a] Sample weight = 50 mg; dissolution medium = 50 ml; all samples were prepared in physical mixtures.

in a mixed anhydride–acid system is given by:

copolymer anhydride (mg) =
    50 mg − free acid concentration (mg/ml) × 50 ml   (Eq. 5)

Sample mixtures with higher free acid contents showed the greater initial pH drop.

Dissolution as a Function of Anhydride–Salt Ratio—When 50 mg of each anhydride–salt mixture was used for the dissolution study as discussed under *Experimental*, different characteristic dissolution profiles were recorded (Fig. 9). Free alkaline salts of calcium hydroxide and sodium carbonate were added to each sample mixture to maintain fixed salt concentrations. The profile of each sample abruptly rose from an initial reading of pH 5.5 to a maximum, after which the pH gradually decreased. The samples with a higher copolymer salt content exhibited a shorter dissolution process. In other words, the dissolution process of the anhydride copolymer was dramatically facilitated in the presence of

Table II—Correlation of the Total Dissolution Time and the Calculated HLB Number

Sample[a]	Total Dissolution Time, min[b]	HLB Number[c]
Copolymer salt	2	38.6
Pure copolymer free acid	5	9.8
Mixture of anhydride copolymer and free alkaline salts	210	—
Pure anhydride	540	7.3

[a] A 50-mg sample dissolved in 50 ml aqueous solution. [b] Determined as the time required to reach the plateau of the dissolution profile, which was recorded by the continuous pH-monitoring apparatus as described in the text. [c] Values were calculated for each repeating unit (Scheme 1) of the copolymers using the reported HLB group numbers (7); (COO^-Na^+) or (COO^-Ca^+) = 20; $(COOH)$ = 2.1; $(—O—)$ = 1.3; (OCH_3) = 0.5; $(C=O)$ = 0.2; and (CH) or (HCH) = 0.475. The HLB number (summation of group numbers) = +7.

alkaline salts (Fig. 8). One could, therefore, construct two working curves, correlating both the maximum pH readings and the total dissolution time values with the anhydride–acid salt ratios (Table I), to determine the anhydride–acid salt composition of an unknown sample mixture.

Four different dissolution profiles, representing the dissolution processes of the salt-catalyzed anhydride (a), the 100% totally reacted copolymer salt (b), the pure anhydride copolymer (c), and the pure copolymer free acid (d), are compared in Fig. 8. The copolymer sample that exhibited more polar functional groups as indicated by higher calculated hydrophilic–lipophilic balance (HLB) numbers (18) exhibited a faster dissolution process in aqueous solutions (Table II).

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