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Comparison and evaluation of enteric polymer properties in aqueous solutions

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Summary

Various carboxylate polymers utilized for enteric coating have been shown to differ in their dissolution rate pH profiles. Currently, little data is available to identify factors which cause these differences. For this reason, the pK_a values and dissolution rates of various phthalate containing enteric polymers were measured concurrently to clarify the relationship between these polymer properties. The pK_a values, obtained from differential plots of potentiometric titration data, were found to be dependent upon the distance between adjacent ionizable carboxylate groups on the polymers. Further analysis of the titration data, utilizing plots of pH versus $\log[(1-\alpha)/\alpha)]$, revealed an abrupt change in the nature of the acidic groups on each of the polymers which was not observed in either the titration curves or the differential plots. These changes coincided with precipitation of the polymers during the titrations. While the pK_a values of the polymers were found to influence the dissolution rate pH profiles, other polymer properties appeared equally important in determining polymer dissolution rates.

Introduction

A relatively small number of polymeric materials have been used successfully in enteric coating. These polymers are generally polyacids containing ionizable carboxylic acid groups which are either part of chemical groups attached to the polymer backbone or are attached directly to the polymer backbone. Schroeter (1965) has stated that the pH of the aqueous medium to which an enteric polymer is exposed and the pK_a value(s) of the acidic groups on the enteric polymer determine the degree of dissociation of the acid groups, and therefore, determine the solubility of the polymer.

The nature of the dissolution medium has also been found to influence enteric polymer dissolution rates. Both increasing the pH and the ionic strength of phosphate buffer solutions increased cellulose acetate phthalate (CAP) dissolution rates in the pH range of 6.0–8.5 (Hayashi et al., 1970). Furthermore, when solutions of different basic salts adjusted to pH 9.3 and pH 7.0 were used as

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the dissolution media, a linear relationship was observed between the logarithms of the dissolution rates of several enteric polymers in these solutions and the pK_a values of the various acidic components (e.g. oxalate, citrate, phosphate, and others) of the basic salts (Spitael and Kinget, 1977; Spitael et al., 1980).

While individual enteric polymers have been shown to differ in their minimum solubility pH and in dissolution rate (Spitael and Kinget, 1979), little work has been done to relate these differences to the chemical properties of the enteric polymers. In a review of enteric coating, Delporte (1970) cited a study in which an increase in the degree of phthalyl substitution for polyvinyl acetate phthalate (PVAP) increased the disintegration times of coated tablets. Noting that the polymer backbone, polyvinyl alcohol, is water-soluble, this effect was attributed to a reduction in the ease of solubilization of the polymer due to increased phthalyl substitution. Also in the Delporte article, differences in the minimum pH at which polymer dissolution occurred and differences in the dissolution rates of Eudragit L and Eudragit S were related to the degree of esterification of the methacrylic acid groups on these polymers.

In the current study, pK_a values and dissolution rate pH profiles for various phthalate containing enteric polymers were determined; and the relationship between these properties was considered.

Materials and Methods

The commercially available enteric polymers chosen for study were CAP (Eastern Chemical Products, Kingsport, TN), PVAP (Canada Packers, Toronto, Canada), and hydroxypropyl methylcellulose phthalate (HP-50 and HP-55) (Shin-Etsu Chemicals, Tokyo, Japan). The chemical compositions of the polymeric materials utilized in the study are given in Table 1. Technical grade organic solvents were used, and all other chemicals were reagent grade.

Potentiometric titration of the polymers

Five-hundred milligrams of each polymer, dried at 105°C for 2 h and cooled in a desiccator over calcium sulfate, was suspended in 70 ml of deionized water and subsequently dissolved by dropwise addition of 0.1 N sodium hydroxide solution. The polymer concentration and pH were adjusted to 0.5% w/w and 8, respectively, using deionized water and 0.1 N sodium hydroxide solution. Titrations were then performed in a covered beaker at 25°C by addition of 0.0987 N hydrochloric acid solution as the titrant until a pH of 3 was reached. Immediately following the base-to-acid titration, an acid-to-base titration was performed using 0.104 N sodium hydroxide solution as the titrant. A pH-meter (Model NX) equipped with a combination electrode (S-30072-25, general purpose type N glass, Sargent-Welch Scientific Co., Skokie, IL) and calibrated with standard buffers (pH 4.00 ± 0.01 and pH 7.00 ± 0.01, at 25°C) was used for pH measurements. Titrant additions were delayed until the pH resulting from the previous addition of titrant remained constant for 5 min. Solution agitation was accomplished with a magnetic stirrer (Magnestir Scientific Products, McGraw Park, IL) and a teflon coated stirring bar.

TABLE 1

CHEMICAL COMPOSITIONS OF THE ENTERIC POLYMERS USED IN THIS STUDY

Polymer	lot	% combined phthalyl	% combined acetyl	% free phthalic acid
Polyvinyl acetate phthalate	44481	57.0	5.6	0.50
Cellulose acetate phthalate	S-2021	33.5	21.5	2.39
Cellulose acetate phthalate	2567	32.0	22.5	1.61
Hydroxypropyl methylcellulose phthalate (HP-55)	11232	31.9		2.56
Hydroxypropyl methylcellulose phthalate (HP-50)	28023	21.3		1.05

Film preparation for dissolution rate measurements

A mixture of acetone and methanol, 50 : 50 by volume, was used to prepare 15% w/v solutions of each polymer. Portions of these solutions were spread onto the top surface of an inverted 400 ml jacketed glass beaker (Ace Glass, Vineland, NJ) maintained at 37°C. Approximately 3 ml of solution yielded films with an appropriate thickness. Dried films were removed from the glass surface and cut into 2 cm squares which were placed in a vacuum desiccator attached to a water aspirator for 3 h to assure complete dryness.

Dissolution rate measurement

Individual polymer films were weighed and placed in 200 ml of 0.04 M phosphate buffer solution maintained at 37°C in a 400 ml jacketed beaker. The films were supported by a 15-mesh nylon screen at a height of 5 cm above the bottom of the beaker. Film movement was restricted to the area above the center of the nylon screen by containing the film in a cylindrically shaped 20-mesh screen, 2.5 cm in diameter, attached to the nylon screen and extending upward slightly above the surface of the buffer solution. Agitation of the buffer solution was accomplished using a magnetic stirrer and teflon-coated stirring bar rotating at 100 rpm.

The extent of polymer dissolution was followed continuously using a double-beam spectrophotometer (Beckman DB Spectrophotometer, Beckman Instruments, Fullerton, CA) equipped with a 1 cm flow-through quartz cell and the spectrophotometer output was continuously monitored using a chart recorder. The buffer solution was sampled through a glass tube with its open end located 1 cm above the nylon screen and 1 cm outside the cylindrical screen. Sampled solution was subsequently returned to the dissolution beaker after passing through the spectrophotometer cell. The solution flow rate was maintained at 7.5 ml/min with a peristaltic pump (Model 7595 Masterflex Pump, Cole-Parmer Instruments, Chicago, IL).

Polymer films were allowed to dissolve completely during these dissolution rate measurements. Data recorded during each measurement appeared as a curve on the chart paper and represented the change in the percent of UV light transmittance with time at a wavelength of 275 nm. Complete film dissolution was evidenced by a constant transmittance for at least 5 min. Since percent light transmittance values are not linear with polymer concentration, a transformation of these values to absorbance values was necessary. The constant dissolution rate period, which was observed in each of the plots of absorbance against time, was used for calculation of the dissolution rate. A line through the points in the constant dissolution rate portion of the plot was extrapolated to intersect with lines representing zero absorbance and maximum absorbance. The time represented by the difference between the x-coordinates of these points of intersection was divided into the total film weight to obtain the dissolution rate of a film.

Results and Discussion

Ionization constant determination

While dissolving each polymer prior to an ionization constant determination, base was added slowly to prevent exposure of the polymer to a highly alkaline medium (above pH 8), in which significant hydrolysis of the phthalyl and/or acetyl bonds might occur. Each solution was allowed to stand overnight in a covered beaker to assure that full dissolution of the polymer had occurred.

A typical potentiometric titration curve for a single titration of one of the polymers is given in Fig. 1. It was assumed that small quantities of free phthalic acid and free acetic acid from the polymer samples did not affect the titration curves. Covering the titration beaker during polymer dissolution and titration also minimized carbon dioxide absorption by the polymer solution. In addition, previous work showed these titrations to be very reproducible.

Each curve appeared to have a single inflection point even though precipitation of the polymer occurred during the titration. The similarity in behavior between the forward (base-to-acid) and backward (acid-to-base) titrations indicated that precipitation and redissolution of the polymers had little or no effect on the ionization properties of the phthalate carboxyl groups. Precipitation of

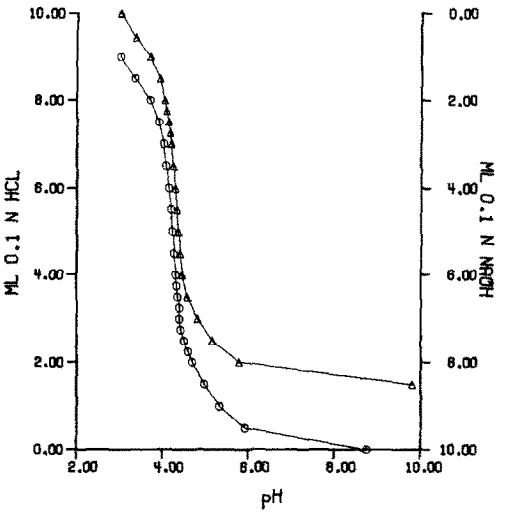

Fig. 1. Typical base-to-acid (○) and acid-to-base (△) titration curves (HP-50 lot 28023).

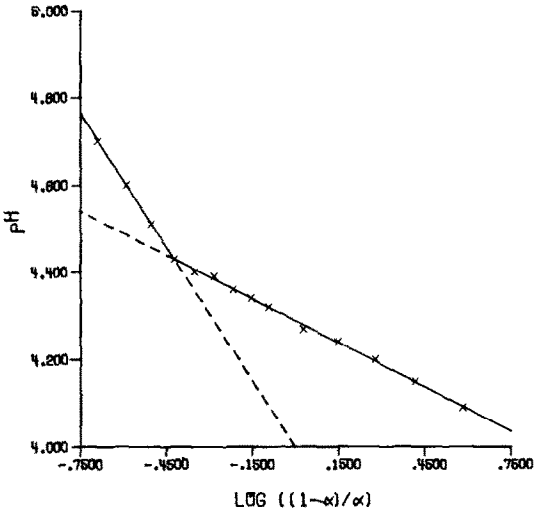

Fig. 3. Plot of pH versus $\log[(1-\alpha)/\alpha]$ for the titration of HP-50 lot 28023.

the polymers was expected, since titrations were continued below the minimum dissolution pH values for the polymers reported by Spitael and Kinget (1979).

Differential plots were prepared from the forward (base-to-acid) titration data for each polymer. A typical plot is given in Fig. 2. Although these differential plots did not exhibit single, well-defined peaks, apparent pK_a values could be obtained by estimating the midpoints of the peaks using the lower, better defined regions of each peak. PVAP had the highest apparent pK_a, 4.90, while HP-50 had the lowest, 4.20. The other polymers, HP-55 and CAP (lot 2567 and lot S-2021),

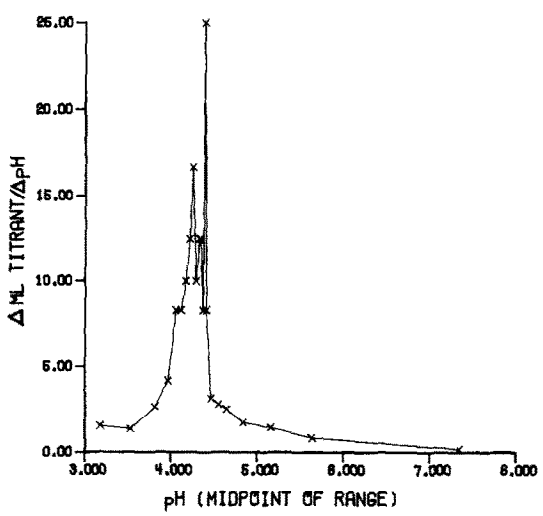

Fig. 2. Forward titration (base-to-acid) differential plot for HP-50 lot 28023.

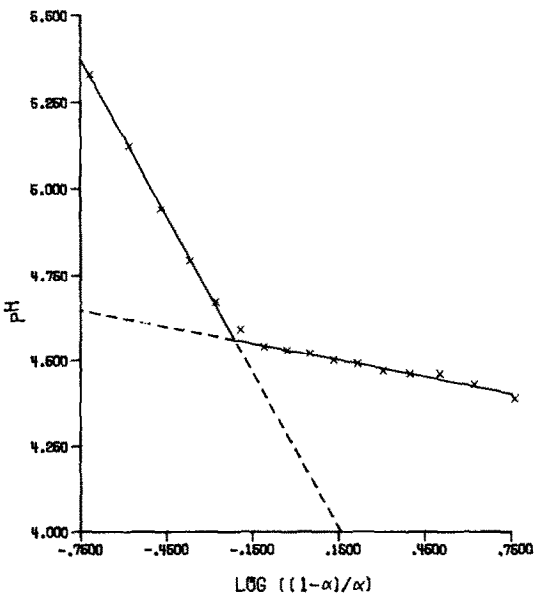

Fig. 4. Plot of pH versus $\log[(1-\alpha)/\alpha]$ for the titration of HP-55 lot 11232.

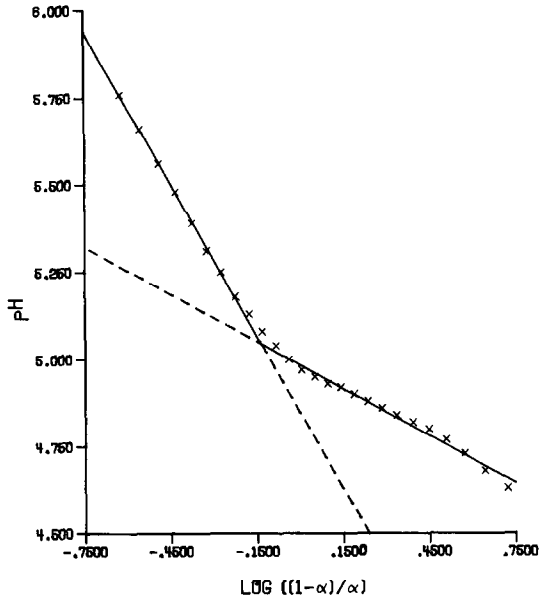

Fig. 5. Plot of pH versus $\log[(1-\alpha)/\alpha]$ for the titration of PVAP lot 44481.

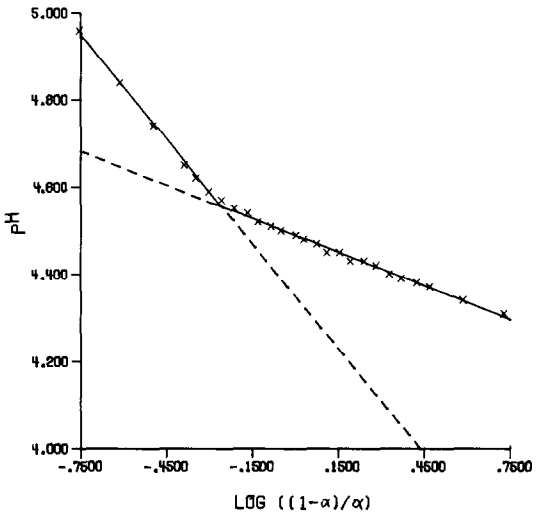

Fig. 6. Plot of pH versus $\log[(1-\alpha)/\alpha]$ for the titration of CAP lot 2567.

had apparent pK_a values of 4.49, 4.42 and 4.55, respectively.

To characterize the titration curves for certain acrylic polyacids, Katchalsky and Spitnik (1947) developed a generalized Henderson-Hasselbach relation,

$$pH = pK_a - n' \log[(1-\alpha)/\alpha] \quad (1)$$

in which pK_a represents the pH of half-neutralization, n′ represents the negative slope of the plot of pH against $\log[(1-\alpha)/\alpha]$, and α is the degree of ionization of the polyacid. For a monoprotic acid, n′ is unity and the equation appears in its usual form.

Plots of pH versus $\log[(1-\alpha)/\alpha]$, in the range of α from 0.2 to 0.8, were prepared from the forward titration data for the enteric polymers to determine values for pKa and n′ in the Katchalsky-Spitnik equation. The degree of ionization, α, was calculated from Eqn. 2,

$$\alpha = 1 - [H - (B - P)]/P \quad (2)$$

where H is the total number of milliequivalents of acid added as titrant, B is the number of milliequivalents of base used to dissolve the polymer prior to titration, and P is the number of milliequivalents of acid in the 500.0 mg sample of polymer used in the titration. P was calculated based on the polymer substitution data in Table 1. The plots are given in Figs. 3–7. While Katchalsky and Spitnik (1947) obtained single, linear plots for polymethacrylic acid as well as other polyacids, each plot for the enteric polymers was found to

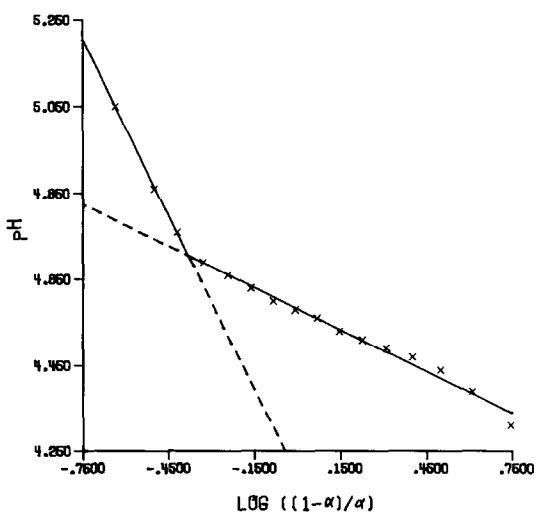

Fig. 7. Plot of pH versus $\log[(1-\alpha)/\alpha]$ for the titration of CAP lot S-2021.

TABLE 2

VALUES OF THE EMPIRICAL CONSTANTS OBTAINED FROM THE PLOTS IN FIGS. 3–7

Polymer	lot	pK_a	n'_1	pKn'_1	n'_2	pKn'_2	pH of transition in ionization behavior	pH range of polymer precipitation
Polyvinyl acetate phthalate	44481	4.90	1.46	4.85	0.45	4.98	5.04	5.18–5.00
Cellulose acetate phthalate	S-2021	4.55	1.35	4.19	0.32	4.58	4.70	4.86–4.49
Cellulose acetate phthalate	2567	4.42	0.80	4.34	0.26	4.49	4.56	4.62–4.50
Hydroxypropyl methylcellulose phthalate (HP-55)	11232	4.49	1.51	4.24	0.16	4.53	4.56	4.67–4.52
Hydroxypropyl methylcellulose phthalate (HP-50)	28023	4.20	1.02	4.00	0.33	4.29	4.43	4.43–4.32

have two linear portions and values for n′ and pK_a were designated n'_1, n'_2 and pKn'_1, pKn'_2, respectively. The line of steeper slope was given a subscript of one. The results of these determinations are summarized in Table 2, which also includes the apparent pK_a values obtained from the differential plots.

The plots in Figs. 3–7 suggest that the enteric polymer titrations were actually more complex than the titration curves and differential plots indicated. A comparison of the pH at which the transition in ionization behavior occurred on the pH versus $\log[(1-\alpha)/\alpha]$ plot, to the range of pH over which particles appeared during the titration, showed that these two values coincided for each polymer. These values are found in Table 2. Thus, the change in acid group behavior occurred following polymer precipitation. The pKn'_1 and pKn'_2 values obtained also support this hypothesis.

Much of the difference seen between the titration curves of polyacids and those of their homologs is attributed to electrical effects exerted by ionized acid groups on the polymers. This phenomenon causes the pK of a weak polyacid to increase with the increasing degree of neutralization of the acid groups (Miller, 1966). However, in the case of the enteric polymers, their precipitation during titration led to a rapid change in the microenvironment surrounding the acid groups. Inter- and intra-molecular interactions such as hydrogen bonding, steric hindrance, solvation, and charge density were increased by precipitation, leaving the carboxylic acid groups less available to the surrounding aqueous phase for ionization. Consequently, the pK_a of the available acid functionalities was raised abruptly rather than gradually as in the case with non-precipitating polyacids.

Relationship between polymer structure and apparent pK_a

It was previously mentioned that electrical effects, due to ionized groups on a polyacid, influence the ionization behavior of remaining acid groups on the polyacid. Miller (1966) explains that when a polyacid is partially ionized, negative charges are formed in the neighborhood of the dissociating carboxyl groups. These negative charges on the polymer make it more difficult for the remaining carboxylic acid groups to dissociate due to increased attraction for the hydrogen ions. This increased attraction for the remaining hydrogen ions by the partially ionized polymer is responsible for the shift in the potentiometric titration curve of the polyacid to higher pH values relative to the curve for its corresponding monomeric homolog.

Since the magnitude of these electrical effects might be expected to depend upon the distance over which they act, the distance between adjacent phthalyl groups was selected as the polymeric structural parameter for relating polymer structure to apparent pK_a. This parameter accounted for polymeric differences in both phthalyl substitution and polymer backbone structure which were found in the polymers being considered.

The distance between adjacent phthalyl groups on a polymer was calculated as the reciprocal of

TABLE 3

COMBINED PHTHALYL CONTENT OF THE ENTERIC POLYMERS EXPRESSED AS WEIGHT PERCENT, DEGREE OF SUBSTITUTION, PHTHALYL GROUPS PER UNIT DISTANCE, AND DISTANCE BETWEEN PHTHALYL GROUPS

Polymer	lot	% combined phthalyl	degree of substitution	Phthalyl groups per Å	Distance between phthalyl groups (Å)
Polyvinyl acetate phthalate	44481	57.0	0.449	0.179	5.6
Cellulose acetate phthalate	S-2021	33.5	0.796	0.146	6.8
Cellulose acetate phthalate	2567	32.0	0.752	0.138	7.2
Hydroxypropyl methylcellulose phthalate (HP-55) [a]	11232	31.9	0.639 ± 0.035 [a]	0.117 ± 0.006	8.5 ± 0.5
Hydroxypropyl methylcellulose phthalate (HP-50) [a]	28023	21.3	0.368 ± 0.019 [a]	0.069 ± 0.003	14.7 ± 0.7

[a] Hydroxypropyl and methoxyl contents were not determined for these polymer lots. Degree of substitution represents value calculated using the average of the high and low values of hydroxypropyl and methoxyl contents given as weight percentages in the specifications for the polymer. The high and low values of the range given represent the increase and decrease in degree of substitution introduced by using maximum and minimum values, respectively, for both the hydroxypropyl and methoxyl contents as allowed in the specifications. The specifications are 20–25% w/w and 18–22% w/w methoxyl and 5–10% w/w and 4–9% w/w hydroxypropyl for HP-50 and HP-55, respectively.

the quotient of the degree of phthalyl group substitution divided by the length of a monomeric unit of the polymer backbone. Conversion of the w/w composition in Table 1 to degree of phthalyl group substitution was accomplished using an equation reported by Malm et al. (1953) for CAP. Similar equations were developed for PVAP and HP-50 or HP-55. These equations are given in the appendix. The lengths of the monomeric units of the polymer backbones were obtained from models of β-D-Glucose (monomeric unit for CAP, HP-50 and HP-55) and a 6-carbon polyvinyl alcohol chain (monomeric unit for PVAP) generated on the CAMSEQ/M microprocessor-based system (Weintraub, 1979). From these models, CAMSEQ/M calculated inter-atom distances of 5.45 and 2.51 Å for the terminal atoms of the β-D-glucose and vinyl alcohol monomer units, respectively. Bond lengths and angles for modeling β-D-glucose were obtained from crystallography data (Chu and Jeffrey, 1968) while the bond lengths and angles for modeling the 6-carbon polyvinyl alcohol chain were average values provided by CAMSEQ/M. Values calculated for the degree of phthalyl group substitution, phthalyl groups per Å, and the distance between adjacent phthalyl groups for each polymer are given in Table 3.

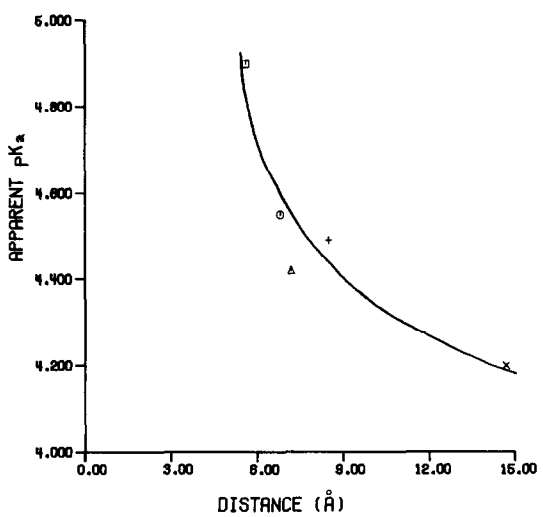

Fig. 8. Relationship between the apparent pK_a and the distance separating adjacent phthalyl groups in HP-50 lot 28023 (×), HP-55 lot 11232 (+), PVAP lot 44481 (□), CAP lot 2567 (△), and CAP lot S-2021 (○).

Fig. 8 shows the relationship found between the apparent pK_a values from the differential plots and the distances between phthalyl groups on the polymers as given in Table 3. The increase in apparent pK_a, which was seen as the distance between adjacent phthalyl groups decreased, confirmed that electrical effects influenced the ionization constants of these polymers. Apparently, as the distance between ionizable groups decreased,

the higher negative charge density on the partially ionized polymer made release of hydrogen ions more difficult. This effect produced a higher apparent pK_a.

Extrapolation of the relationship between pK_a and the distance of phthalyl group separation to higher or lower polymer substitution may be visualized by reference to Fig. 8. As substitution of phthalyl groups increases, the pK_a would be expected to increase toward infinity. On the other hand, decreasing the degree of substitution and increasing the distance between ionizable groups yields pK_a values which would be expected to asymptotically approach 3.18, the pK_a of the monomethyl ester of *o*-phthalic acid (Fieser and Fieser, 1950) which is a reasonable approximation of the polymer homolog.

Factors affecting enteric polymer dissolution rates

Fig. 9 shows dissolution rate profiles for each of the enteric polymers obtained at 37°C in 0.04 M phosphate buffers ranging in pH from 5.8 to 7.5. Each point on the graph represents the average of at least 4 determinations. The profiles were found to be similar in shape, all rising at nearly the same rate as pH increased. However, there were differences in the positioning of the profiles along the x-axis.

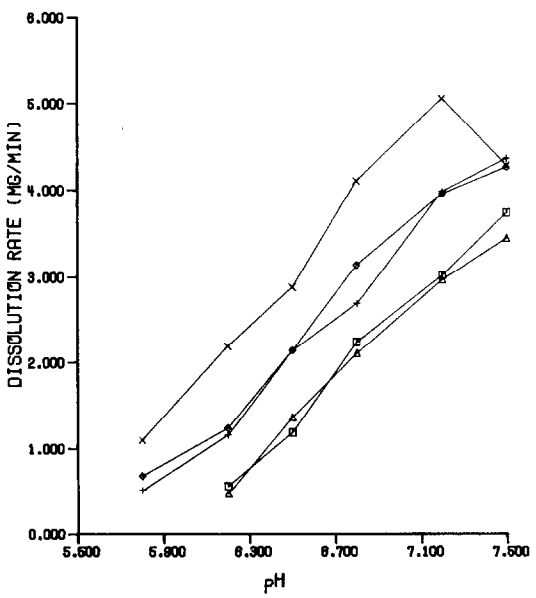

Fig. 9. Dissolution rates of the enteric polymers, HP-50 lot 28023 (×), HP-55 lot 11232 (+), PVAP lot 44481 (◇), CAP lot 2567 (△), and CAP lot S-2021 (□), in 0.04 M phosphate buffers at various pH.

Similar findings have been reported by Spitael and Kinget (1979). In studying a number of enteric polymers, including those in the current study, dissolution rate profiles in 0.066 M phosphate buffer were generated by a pH-stat method. The relative positions of the CAP, PVAP, HP-50 and HP-55 dissolution rate profiles along the x-axis were consistent with those in Fig. 9; however, the dissolution rates for a given polymer at a given pH were approximately two times greater. This difference in the dissolution rates was presumably due to the higher buffer capacity of the buffer systems used by Spitael and Kinget, since increases in dissolution rate with increased buffer capacity of the dissolving medium have been well documented for CAP (Hayashi et al., 1970; Shek, 1978; Spitael et al., 1980). Even with this difference in the measured dissolution rates, the consistency of the relative positions of the dissolution rate profiles demonstrated the usefulness of these profiles in comparing the polymers.

Two factors, polymer pK_a and polymer backbone structure, were thought to most influence the relative positioning of the polymers along the x-axis in Fig. 9, and thus, the observed differences in the dissolution rates at each given pH. The effects of the first factor, polymer pK_a, can be illustrated by comparison of the dissolution rate profiles for HP-50 and HP-55. The dissolution rate profile of HP-50 ($pK_a = 4.20$) was found to be shifted approximately 0.3–0.4 units below that of HP-55 ($pK_a = 4.47$). Interestingly, the magnitude of this shift approximates the difference in the pK_a values. Also, the shift in the dissolution rate profile, to lower pH, can be seen to produce higher dissolution rates for HP-50, relative to HP-55, at each pH except 7.5. The reason for the exception is not known.

The effect of pK_a can also be used to further explain the behavior of PVAP-coated tablets in the study reported by Delporte (1970) which was mentioned previously in the Introduction. In this study, tablets coated with various batches of PVAP

showed increasing disintegration times with increasing weight percents of combined phthalyl on the PVAP. Since an increase in weight percent of combined phthalyl logically yields a higher degree of substitution, and therefore, a smaller distance separating neighboring phthalyl groups, it can be seen from Fig. 8 that the increasing weight percents of combined phthalyl produced PVAP batches with varying pK_a values. In turn, the coating of tablets with PVAP from batches having varying pK_a values, and thus, varying polymer dissolution rates, led to the observed variation in tablet disintegration times.

While pK_a was important in determining the relative dissolution rates for polymers of the same type, variation in the structure of the backbones of the three types of enteric polymers was thought to be the primary reason for the observed differences in their dissolution rates. Removal of the combined phthalyl groups on the phthalate containing enteric polymers yields three different polymers, cellulose acetate, hydroxypropyl methylcellulose and polyvinyl acetate. The latter two polymers are water-soluble while cellulose acetate is water-insoluble. In the case of the water-soluble polymer backbones, solubility at low pH in aqueous buffers is prevented by the substitution of phthalate groups which are in an unionized form and fairly hydrophobic under acid conditions. On the other hand, substitution of phthalate groups onto cellulose acetate permits solubility in aqueous buffers at high pH by overcoming the hydrophobic nature of the backbone with ionized acid groups. Assuming that polymer dissolution is a diffusion-controlled process, these differences in the structures of the polymers, as well as the mechanisms by which their dissolution is controlled, apparently influenced the diffusion kinetics of the polymers at the interface between the polymer film and the surrounding dissolution medium, thus affecting the dissolution rates.

The extent to which dissolution rates were affected can be seen by comparing the dissolution rate profiles of the CAP polymers to those for HP-55 and PVAP in Fig. 9. Although the CAP polymers had pK_a values approximately equal to that for HP-55 and below that for PVAP, their dissolution rates were consistently lower than those of the other two polymers.

Appendix

Equations for calculating the degree of substitution for phthalyl groups on CAP, PVAP and HPMCP

CAP:

$$\text{deg. sub.} = \left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right\}\left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}} + \frac{\text{a}}{\text{MW}_{\text{a}}} + \left(\frac{100 - \text{MW}_{\text{Bph}}\left(\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right) - \text{MW}_{\text{Ba}}\left(\frac{\text{a}}{\text{MW}_{\text{a}}}\right)}{\text{MW}_{\text{B}}}\right)\right\}^{-1}$$

PVAP:

$$\text{deg. sub.} = \left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right\}\left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}} + \frac{\text{a}}{\text{MW}_{\text{a}}} + \left(\frac{100 - \text{MW}_{\text{Vph}}\left(\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right) - \text{MW}_{\text{Va}}\left(\frac{\text{a}}{\text{MW}_{\text{a}}}\right)}{\text{MW}_{\text{V}}}\right)\right\}^{-1}$$

HPMCP:

$$\text{deg. sub.} = \left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right\}\left\{\frac{\text{ph}}{\text{MW}_{\text{ph}}} + \frac{\text{m}}{\text{MW}_{\text{m}}} + \frac{\text{hp}}{\text{MW}_{\text{hp}}} + \left[100 - \text{MW}_{\text{Bph}}\left(\frac{\text{ph}}{\text{MW}_{\text{ph}}}\right) - \text{MW}_{\text{Bm}}\left(\frac{\text{m}}{\text{MW}_{\text{m}}}\right) - \text{MW}_{\text{Bhp}}\left(\frac{\text{hp}}{\text{MW}_{\text{hp}}}\right)\right](\text{MW}_{\text{B}})^{-1}\right\}^{-1}$$

where a, ph, m and hp are the weight percents of attached acetyl, phthalyl, methyl and hydroxypropyl groups, respectively, and MW_a, MW_{ph}, MW_m,

MW_{hp}, MW_{Ba}, MW_{Bph}, MW_{Bm}, MW_{Bhp}, MW_{B}, MW_{Va}, MW_{Vph} and MW_{V} are the molecular weights of an acetyl group, a phthalyl group, a methyl group, an hydroxypropyl group, an anhydroglucose unit with a single attached acetyl group, an anhydroglucose unit with a single attached phthalyl group, an anhydroglucose unit with a single attached methyl group, an anhydroglucose unit with a single attached hydroxypropyl group, an anhydroglucose unit, a vinyl unit with a single attached acetyl group, a vinyl unit with a single attached phthalyl group, and a vinyl unit, respectively.

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