International Journal of Pharmaceutics, 26 (1985) 215–226
Elsevier

IJP 00884

Evaluation of polyvinyl acetate phthalate as an enteric coating material

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(Received August 22nd, 1984)
(Modified version received May 8th, 1985)
(Accepted May 29th, 1985)

Key words: enteric coating – polyacid – polyelectrolyte – polyvinyl acetate phthalate – enteric excipient – polymer characterization

Summary

A general procedure for the evaluation of enteric coating excipients using the accepted polymeric characterization techniques of membrane osmometry, scanning electron microscopy, solubility determination and titration is described. As a model compound, the excipient functions of the enteric polyelectrolyte polyvinyl acetate phthalate (I), obtained from two sources, designated as polymer A and B, are evaluated and compared. Molecular weights determined by membrane osmometry were 61,000 and 48,000 for polymer A and B, respectively. Scanning electron photomicrographs reveal significant morphological differences between the two materials. The solubilities of A and B are different in various solvents, but their mutual solubilities in solvent coating systems were estimated from a ternary plot of their solubilities versus solvent fractional solubility parameters. The apparent pK_as of I obtained by titration are not the same for A and B, but are a function of their degree of ionization and decrease as the ionic strength of the titration solution is increased. The molar solubilities of A and B calculated from titration data at 37°C and an average ionic strength of approximately 0.06 M during the titration were 4.45×10^{-5} M and 6.48×10^{-5} M, respectively. The neutralization rates of A and B measured by a pH-stat method are equivalent and increased with increasing ionic strength. It was concluded that A and B were functional equivalents and that the characterization methods used in this study are acceptable for use as a general procedure for the evaluation of an enteric coating excipient.

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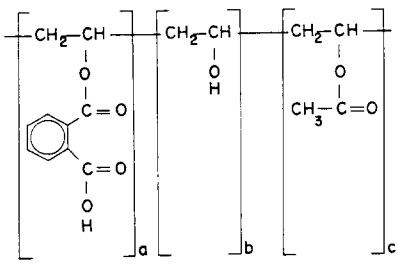
Introduction

Drug substances are usually subjected to analysis in order to characterize their physicochemical and biopharmaceutical parameters. However, these compounds are rarely administered as single entities, but are combined with various additives referred to as excipients, which permit convenient dosing or modify drug activity.

Even though it is necessary to specify the chemical makeup and purity of excipients for quality control reasons, it is their physicochemical properties that may significantly affect the manufacture, stability and bioavailability of the final product. For example, enteric coating materials are excipients whose main function is to stop the gastric release of drugs that are gastric irritants or are degraded by gastric fluids, but readily release the medicament on reaching the small intestine (Porter and Ridgway, 1982). These materials are also polyacids that are soluble in organic solvent systems.

Since the choice of an enteric coating material is critical, this study was undertaken to develop an enteric materials evaluation profile using accepted polymer characterization techniques. The experimental procedures were selected based on the end use of the material. The enteric coating substance used as a model compound for characterization and comparison in this work is polyvinyl acetate phthalate (I), obtained from two suppliers and designated as polymer A [1] and B [2].



I

Materials and Methods

Reagents and solvents. Potassium chloride [3], acetone [3], acetonitrile [3], isopropanol [3], methanol [3], methylene chloride [3], dioxide [3], alcohol USP [4], alcohol SD3A anhydrous [4], tetrahydrofuran [5], 0.1 N sodium hydroxide [6], and 0.1 N hydrochloric acid [6] were used as received.

Solubility determination. About two grams of each material was added to a 20 ml vial [7] containing about 18 ml of solvent. The mixtures were shaken periodically over

[1] Colorcon, West Point, PA. Lot 322.
[2] Canada Packers Fine Chemicals Division, Toronto, Ont., Canada. Lot 43127.
[3] Analytical Reagent, Mallinckrodt, St. Louis, MO.
[4] U.S. Industrial Chemicals, Newark, NJ.
[5] Omni Solv, EM Science, Gibbstown, NJ.
[6] Standardized, Ricca Chemicals, Arlington, TX.
[7] Vials, Screw Cap 4 Dram, Kimble, Toledo, OH.

4 h at room temperature. The samples were considered to be in solution if a single phase, clear, gel-free solution was observed after 4 h.

Density determination. The densities of A and B were determined using an air comparison pycnometer [8].

Chemical properties. Moisture, phthalyl content, free phthalic acid, and free acid (other than phthalate) were determined according to manufacturers' procedures [9,10].

Molecular weight determination. The molecular weights of A and B were determined by membrane osmometry at 37°C in tetrahydrofuran [11].

Crystallinity. The relative crystallinity of A and B was determined by powder X-ray diffraction [12].

Scanning electron microscopy. Photomicrographs of gold coated samples were obtained by employing a scanning electron microscope [13].

Titration. A 1 g sample was dissolved in 50 ml 0.1 N sodium hydroxide and 50 ml water in a 250 ml jacketed beaker [14]. This solution was titrated [15] using magnetic stirring [16], with 0.1 N hydrochloric acid until visible precipitation occurred. Additional solutions adjusted to various ionic strengths with potassium chloride were also titrated.

Neutralization rate. Films of A and B were prepared by spreading a 10% w/w solution of I over a 2 cm × 2.5 cm area defined by masking tape [17] on 7.6 cm × 2.5 cm glass slides [18]. Solvent evaporation rate was controlled during film formation by covering the slides with an inverted glass funnel. The resulting films, which were transparent and free of entrapped solvent, were dried for at least 24 h at room temperature before evaluation. Polyacid neutralization rates were determined employing a pH-stat system [15] with a 2.5 ml autoburette in a manner similar to that of Spitael (Spitael and Kinget, 1977). Experiments were done at 37°C in a 50 ml jacketed beaker with magnetic stirring, at a stirring rate of 365–375 rpm which was measured with a tachometer [19]. The beaker was sealed with a paraffin [20] sheet which contained openings for the glass slide, the pH electrode, titrant delivery tube, and nitrogen flush tube to blow nitrogen over the surface of the solution. A 40 ml sample of test solution was transferred to the beaker and allowed to come to temperature

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[8] Model 930 Pycnometer, Beckman Instruments, Irvine, CA.

[9] Specifications of Polyvinyl Acetate Phthalate, Colorcon, West Point, PA, (1975).

[10] Performed by the Analytical Research Laboratory, Warner-Lambert/Parke-Davis Pharmaceutical Research, Warner-Lambert, Morris Plains, NJ.

[11] Performed by ARRO Laboratories, Joliet, IL.

[12] Performed by ES Laboratories, Wrightstown, NJ.

[13] Model 1200B, Amray, Bedford, MA.

[14] SGA Scientific, Bloomfield, NJ.

[15] REA 160 Recording Titration System with 25 ml or 2.5 ml autoburette, Radiometer, Copenhagen, Denmark.

[16] Thermodyne, Dubuque, IA.

[17] 3 M Corporation, St. Paul, MN.

[18] Corning Glass Works, Corning, NY.

[19] Model 1891 Phototach, M. Ducommun, Warwick, NY.

[20] Parafilm, American Can, Greenwich, CT.

equilibrium with stirring. The solution was adjusted to pH 9.00 by the addition of 0.1 N sodium hydroxide. The pH-stat system was left to run until no titrant was consumed for at least 6–8 min, with the pH remaining constant. At this point, a glass slide with a film of I attached was put in the solution. Base consumption was recorded as a function of time, while the solution pH was maintained at 9.00. Additional neutralization rate determinations were made at various ionic strengths with potassium chloride as the ionic strength adjuster.

Results and Discussion

Polymer morphology (Figs. 1 and 2), density, molecular weight, relative crystallinity, and chemical composition of A and B (Table 1) are determined by the processing conditions used to produce the polymer. Thus, the differences found between A and B are dependent on the source of the material and may serve as a means of identifying suppliers of I.

Organic solvent solubility

A difference in molecular weight between A and B, and thus the number of

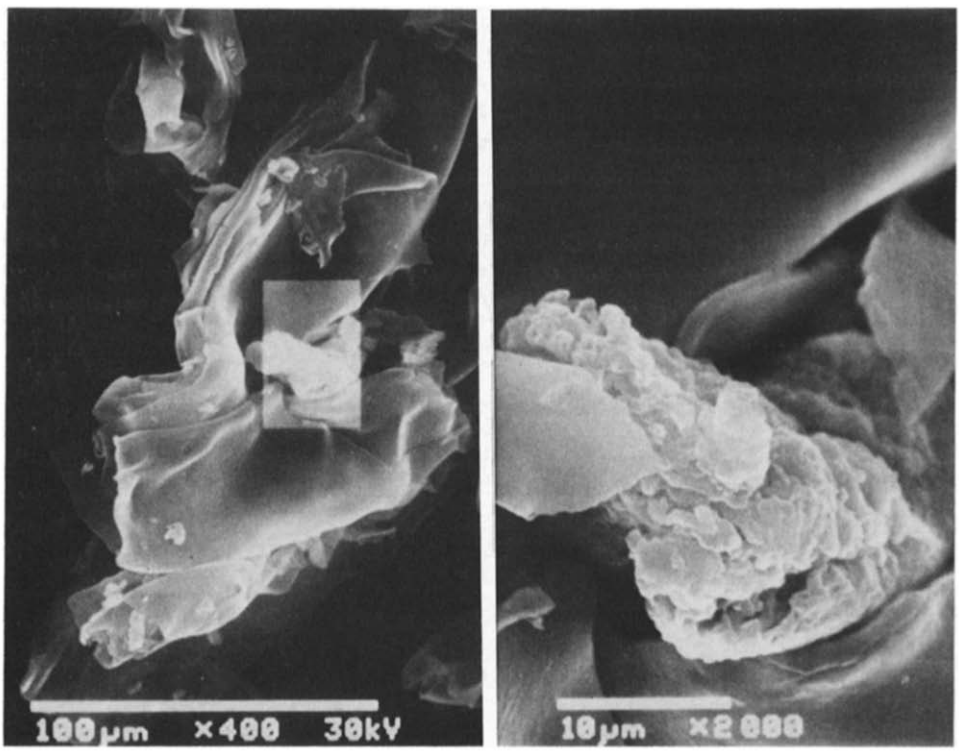

Fig. 1. Scanning electron photomicrograph of A. Highlighted area at ×400 shown at ×2000.

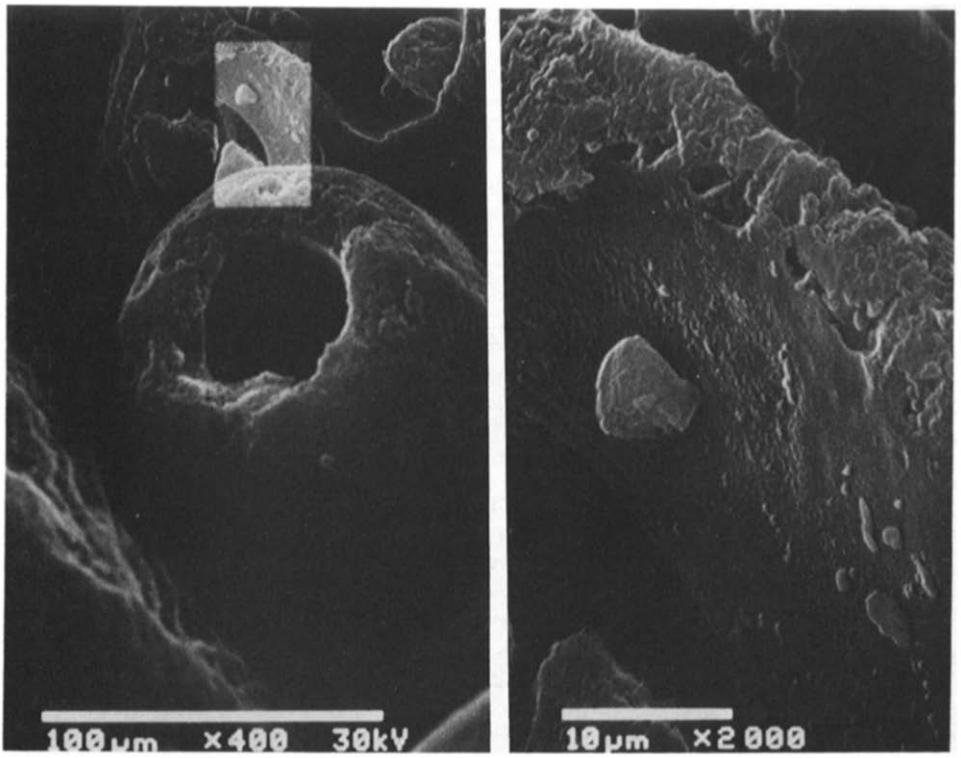

Fig. 2. Scanning electron photomicrograph of B. Highlighted area at ×400 shown at ×2000.

phthalyl groups (Table 1) present in the polymer, significantly influences the solubility of I as shown in Fig. 3, where A and B behave differently in the same solvents. Fig. 3 is a plot made of the solvating efficiency of various solvents for A

TABLE 1

POLYVINYL ACETATE PHTHALATE CHARACTERISTICS

	A	B
Acetyl content	4.9% w/w	2.9% w/w
Phthalyl content	59.5% w/w	61.6% w/w
Phthalyl groups [a]	242	197
Moisture content	3.74%	2.20%
Molecular weight [b]	60,700	47,000
Density	1.31 g/ml	1.37 g/ml
Relative crystallinity index [c]	45.9	36.9

[a] Number of phthalyl groups

$$= \frac{\text{Number average molecular weight of I} \times \text{weight fraction of phthalyl content}}{\text{Phthalyl residue molecular weight}}$$

[b] Number average molecular weight.

[c] Ratio of crystalline area: amorphous area in X-ray diffraction scan.

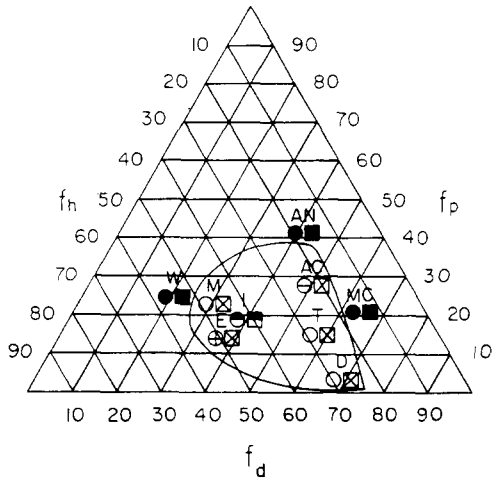

Fig. 3. Solubility of A and B in acetone (AC), acetonitrile (AN), dioxane (D), ethanol (E), isopropanol (I), methanol (M), methylene chloride (MC), tetrahydrofuran (T), and water (W) versus the relative intensity of dispersion (f_d), dipolar (f_p) and hydrogen bonding (f_h) forces, where ○, ⊕, ⊖, ◓ and ● denote soluble, almost soluble, two layers, slightly soluble and insoluble for Polymer A (circle); and ⊠, ◨ and □ denote almost soluble, slightly soluble and insoluble for Polymer B (square), respectively.

and B versus the fractional solubility parameters (Eqn. 1) of the solvent (Gardon and Teas, 1976), where X represents dispersion, polar or the hydrogen bonding component of the solvent solubility parameter (δ).

$$f_X = \frac{\delta_x}{\delta_d + \delta_p + \delta_h} \times 100 \tag{1}$$

This plotting method not only distinguishes between A and B, but can be used to select a common solvent system for I. This is advantageous for the pharmaceutical manufacturer, for, if a common solvent can be found for I, an alternate material is then available that does not require formulation modification.

For example, in Fig. 3 a boundary line which generally separates efficient solvents for A and B from nonsolvents was drawn by inspection. If tie lines can be drawn between solvents and nonsolvents of A and B that pass through the outlined area of solubility, some combination of any two nonsolvents may dissolve both types of I. This was readily demonstrated by the solubility of A and B in cosolvent systems of acetone–ethanol (1 : 1), acetone–methanol (1 : 1), methylene chloride–methanol (1 : 1) and isopropanol–water (3 : 1).

Titration

The evaluation of the potentiometric properties of I is important because it functions as an enteric coating material via pH-dependent solubility. The titration of I can be described by Eqn. 2:

$$pH = pK_0 + \log\frac{\alpha}{1-\alpha} + \Delta pK \tag{2}$$

where pK_0 is the negative logarithm of the intrinsic ionization constant characteristic of the single ionizable group on the polymer at zero degree of ionization and α is the degree of ionization. All deviations from monomeric titration behavior are incorporated in the last term of Eqn. 2 (Bloys, 1978). This term, ΔpK, represents the increase in electrical free energy of the polyion and its atmosphere on increasing the polyion charge by one unit.

The unique solution properties of polyacids such as I compared to simple acids are due to the proximity of the charges on the polymer chain. The large potential present during the titration of I holds oppositely charged counterions near the chain. These counterions interact with the polymer in two ways: some condense onto the charged sites of I, while the remainder are in the ionic atmosphere that surrounds the chain (Manning, 1972; Manning and Holtzer, 1973). Thus, when the counterions of a solution containing I are increased, such as the existence of food in the gastrointestinal tract while a dosage form coated with I or any polyacid is present, the effective charge density of I will be lowered due to counterionic condensation and the titration curve will shift towards lower pH (Fig. 4). Since the titration curve of a polyacid is independent of molecular weight (Arnold and Overbeek, 1950), the observed differences between the curves of A and B at approximately equal ionic strengths are due to the unequal number of phthalyl groups present on their chains (Table 1).

More information about I can be gained from the titration curves by rewriting

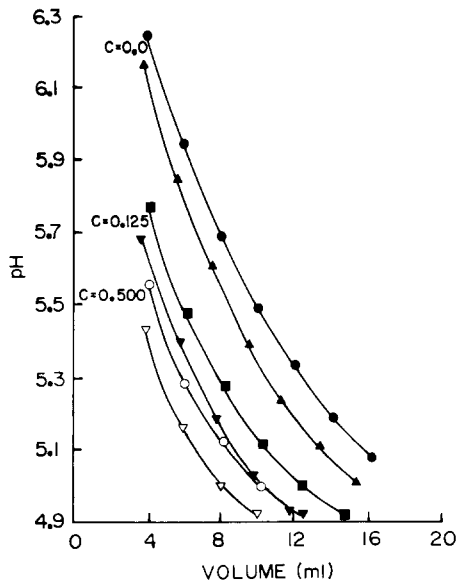

Fig. 4. The effect of ionic strength on the back titration curves of A and B. Key: (▲) A, 0.059 M (±0.002); (▼) A, 0.163 M (±0.003); (▽) A, 0.486 M (±0.009); (●) B, 0.058 M (±0.002); (■) B, 0.164 M (±0.003); and (○) B, 0.487 M (±0.009). Values are solution mean ionic strength during titration ±S.D. C equals molar concentration of added potassium chloride before start of titration with 0.1 N HCl.

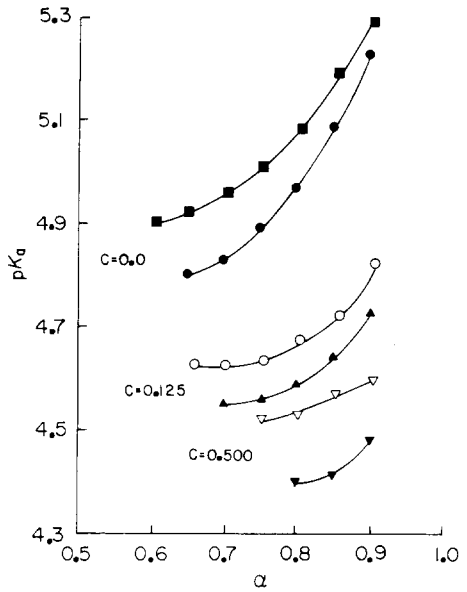

Fig. 5. The dependence of the apparent ionization constants of A and B on their degree of ionization and solution ionic strength. Key: (●) A, 0.059 M (±0.002); (▲) A, 0.163 M (±0.003); (▼) A, 0.486 M (±0.009); (■) B, 0.058 M (±0.002); (○) B, 0.164 M (±0.003); and (▽) B, 0.487 M (±0.009). Values are solution mean ionic strength during titration ±S.D. C equals molar concentration of added potassium chloride before start of titration with 0.1 N HCl.

Eqn. 2.

$$pK_a = pH - \log\frac{\alpha}{1-\alpha} \tag{3}$$

where pK_a is the apparent pK composed of pK_0 and ΔpK. A plot of pK_a vs α (Fig. 5) illustrates the dependency of the pK_a on the degree of ionization of I and solution ionic strength. The observed differences between A and B in Fig. 5 parallel those of Fig. 4. In addition, Fig. 5 readily demonstrates that the potentiometric properties of I or any enteric coating that is a polyacid is solely dependent upon its ionic environment.

Aqueous solubility

Since I functions as an enteric material by being pH-sensitive, it is important that its pH–solubility profile be well defined. The solubility of the unionized portion of I formed during back titration can be calculated from the fraction unionized multiplied by the total concentration. Therefore, the intrinsic molar solubility S_0 of I is given by:

$$S_0 = \frac{V_e N}{V_p(10^{pH_p - pK_p} + 1)} \tag{4}$$

TABLE 2

AQUEOUS SOLUBILITY OF A AND B

Ionic strength		pH of precipitation		Intrinsic solubility $\times 10^5$ M	
A	B	A	B	A	B
0.060 [a]	0.060 [a]	5.07	5.08	4.45	6.48
0.162 [a]	0.161 [a]	4.92	4.91	3.89	5.77
0.268 [a]	0.265 [b]	4.97	4.92	3.33	5.07
0.483 [a]	0.479 [b]	5.00	5.00	2.70	4.31

[a] Average of three determinations.
[b] Average of two determinations.

where pH_p, V_p and pK_p are solution pH, total solution volume and polyion pK_a at the point of precipitation, respectively. Using Eqn. 4, the intrinsic solubility of B was found to be 1.5 times more than that of A at comparable ionic strengths (Table 2). Solubility curves were constructed employing the following equation:

$$S = S_0\left(1 + \frac{K_a}{[H_3O^+]}\right) \tag{5}$$

where S is the molar solubility and K_a is the ionization constant. The ionization constant was calculated from Eqn. 3 as a function of the hydronium ion concentration for each point on the curve. Data for the solubility profiles were computed because equilibration of I with buffer systems in the pH range of interest was unattainable without exceeding the buffer capacity of a suitable buffer. On a molar basis, B is more soluble than A (Fig. 6). The effect of added electrolyte on the solubility of I is readily apparent in that the calculated solubility curves are shifted towards the left (higher solubility at lower pH). However, the solubility shift seems to approach a limit after a critical amount of electrolyte has been added due to counterion condensation on I.

Neutralization rate

The dissolution (neutralization) rate of an enteric coating excipient should be useful as a material quality control measure. The dissolution rate constants of several polymeric enteric coating materials were determined using a pH-stat method (Spitael and Kinget, 1977; Spitael and Kinget, 1979; Spitael et al., 1980). The log of the dissolution rate constant was found to be linearly related to the pK_a of the conjugate acids of the salts used in the dissolution media. These results were reported to be consistent with general base catalysis in which both proton transfer and dissolution of the polyelectrolyte are enhanced (Spitael and Kinget, 1977; Spitael and Kinget, 1979; Spitael et al., 1980). It has also been suggested that polymer dissolution is related to the buffer capacity of the various salts and not to catalytic activity (Shek, 1978). Still other workers found that an increase in pH and ionic strength led to

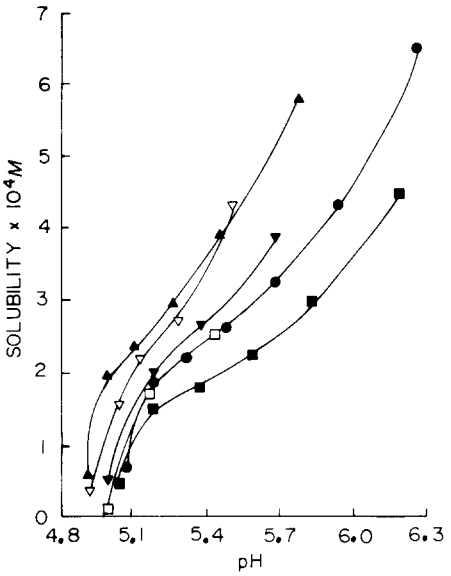

Fig. 6. Effect of pH and ionic strength on the solubility of A and B. Solubility curves were calculated using Eqn. 5. The ionization constants were calculated from the titration curves. Key: (■) A, no salt; (▼) A, 0.125 M; (□), A, 0.500 M; (●) B, no salt; (▲) B, 0.125 M; and (▽) B, 0.500 M. Values are the molar concentration of added potassium chloride before the start of titration from which the ionization constants were calculated.

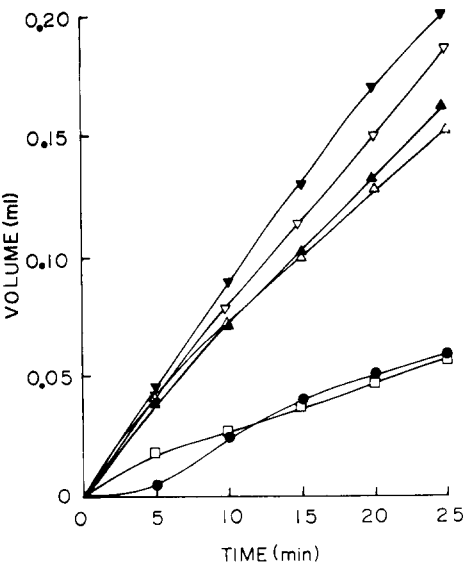

Fig. 7. Consumption of 0.1 M NaOH versus time at 37°C for A and B cast on a glass slide at a constant pH 9.00. Key: (●) A, no salt; (▲) A, 0.125 M; (▼) A, 0.500 M; (□) B, no salt; (△) B, 0.125 M; and (▽) B, 0.500 M.

increased dissolution of a polyelectrolyte (Hayashi et al., 1970). In order to ensure complete ionization of I, a pH of 9.00 was chosen for the pH-stat neutralization method. This was also the lowest constant pH at which the pH-stat apparatus could be stabilized without buffer addition. The addition of potassium chloride to the dissolution media dramatically increases the neutralization rate of I (Fig. 7). The salt addition causes a decrease in the ionization constant, thus making I a stronger acid due to counterion condensation onto I. The neutralization curves, like the solubility curves, exhibit a large shift with the addition of 0.125 M potassium chloride. Further salt addition, however, does not lead to proportional increases in the neutralization rate. Though A and B have somewhat different physical properties, their neutralization rates are similar (Fig. 7).

Conclusion

In this study, an enteric material evaluation profile was developed using accepted polymer characterization methods. A and B were found to be functional equivalents based on their similar titration, pH–solubility and neutralization curves. Although A and B conformed to the same phthalyl content specifications on a weight to weight basis, their solubilities were different in commonly used coating systems due to molecular weight differences. This study also demonstrated that the ionic strength of the dissolution medium plays an important role in the functioning of an enteric polyacid. Thus it must be emphasized that successful in vitro performance is no guarantee of the intended in vivo response, because the counterion milieu of the gastrointestinal tract may vary greatly with food intake.

Acknowledgements

The authors are indebted to I. Ghebre-Sellassie and U. Iyer for their comments and suggestions.

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