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DISSOLUTION CHARACTERISTICS OF BENZOIC ACID AND SALICYLIC ACID MIXTURES IN REACTIVE MEDIA

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ABSTRACT

The dissolution rates of mixtures of the two acids, benzoic acid and salicylic acid were determined in a phosphate buffered medium. Dissolution properties from compressed discs under sink conditions were essentially linear. Plots of dissolution rate versus compact composition deviated from the two component models for both non-interacting and interacting components. Dissolution rates, particularly for benzoic acid at intermediate weight fractions, were lower than predicted by the theory for two non-interacting components. These lower than expected rates were explained in terms of the physicochemical changes occurring in the microenvironment at the solid liquid interface.

INTRODUCTION

The kinetics of dissolution for pure materials in non-reactive media have been extensively investigated[1,2] and dissolution models developed which consider diffusion as the driving force for mass transfer from the solid to the liquid phase.[3] According to the film theory a stagnant liquid film of calculable width is postulated to exist adjacent to the dissolving solid surface. Under sink conditions dissolution rate (J) is directly proportional to the equilibrium solubility (C_s) the diffusion coefficient (D) and inversely proportional to the film thickness (h):

$$J = \frac{DA}{h} C_s \qquad 1$$

where A is the surface area.

However, in reactive media deviations from equation 1 are observed.[4,5] Consequently the film theory has been modified to take into account the species generated during dissolution and their diffusion coefficients.[6,9] These studies together with those of Serajuddin and Jarowski have highlighted the self buffering action in the diffusion layer of the dissolving ionizable solute.[10,11] An analysis of the dissolution of pure acidic and basic compounds as a convective diffusion process rather than a stagnant film diffusion only process has also been reported recently.[12]

Models of dissolution from multicomponent soluble systems have received less attention despite the fact that solid dosage forms invariably contain multiple soluble components. The dependence of dissolution rate on the proportion of the components present in a compact was reported by Nelson.[13] Higuchi, Mir and Desai[14] extended the film theory to quantify the dissolution rate of benzoic acid and salicylic acid mixtures of varying composition i.e. two non-interacting solids, in an essentially non-reactive medium. A model was also developed to quantify the dissolution rates observed when components interact to form a soluble complex in solution. These models have been used and expanded by other authors to examine a variety of drug-drug and drug excipient mixtures, particularly solid dispersion systems.[15-20]

In this report we have examined the dissolution properties of benzoic acid-salicylic acid mixtures in buffered media.

THEORY

On exposure to dissolution medium both components of a two component mixture (x,y) will tend to dissolve at rates proportional to their solubilities and diffusion coefficients. One phase will generally become depleted at the solid-liquid interface because N_x/N_y may not be equal to D_xC_{sx}/D_yC_{sy} where N_x and N_y are the original amounts of x and y in the mixture. Consequently a surface layer results composed of only one of the components. If the surface phase is x then the dissolution rate G_x per unit surface area is given by

$$G_x = \frac{Jx}{A} \approx \frac{D_x}{h} C_{sx} \qquad 2$$

and

the dissolution rate of the receding component y is given by

$$G_y = \frac{D_y C_{sy}}{h + \frac{\tau}{\varepsilon}(s_1 - s_2)} \qquad 3$$

$$G_y = \frac{D}{h} C^{\circ}_y \qquad 4$$

where τ is the tortuosity, ε the porosity, (s_1-s_2) is the thickness of the porous layer formed at the solid-liquid interface and C°_y is the concentration of y at the outer solid-liquid interface. In the steady state equation 3 becomes[14]

$$G_y = \frac{N_y}{N_x} G_x \qquad 5$$

Only at the critical mixture case defined by

$$\frac{N_x}{N_y} = \frac{D_x C_{sx}}{D_y C_{sy}} \tag{6}$$

will no porous layer form at the surface and both components will dissolve at a rate equal to that of each pure component.

In the case where the components are ionizable the situation is more complex. For two acids dissolving in a diprotic buffered medium the initial dissolution rates will be given by:-[7-9]

$$G_X = G_{HX} + G_H + G_{OH} + G_B + G_{BH_2} \tag{7}$$

$$G_Y = G_{HY} + G_H + G_{OH} + G_B + G_{BH_2} \tag{8}$$

where

$$G_{HX} = D_{HX}\,[HX]_o/h \tag{9}$$

$$G_{HY} = D_{HY}\,[HY]_o/h \tag{10}$$

$$G_H = D_H([H^+]_o - [H^+]_h)/h \tag{11}$$

$$G_{OH} = D_{OH}([OH^-]_h - [OH^-]_o)/h \tag{12}$$

$$G_B = D_B([B]_h - [B]_o)/h \tag{13}$$

$$G_{BH_2} = D_{BH_2}([BH_2]_h - [BH_2]_o)/h \tag{14}$$

where the subscripts o and h identify concentrations at the disc surface/boundary layer and boundary layer/bulk medium interfaces respectively. The situation in a monobasic buffered medium is represented diagrammatically in Fig. 1(a). This schematic diagram also represents the continuous situation in the boundary layer at the critical mixture ratio. For all other ratios, as time progresses, a porous layer of one component should form at the surface resulting in a boundary layer (l) within the disc. The thickness of this layer and the time to reach steady state will vary with the

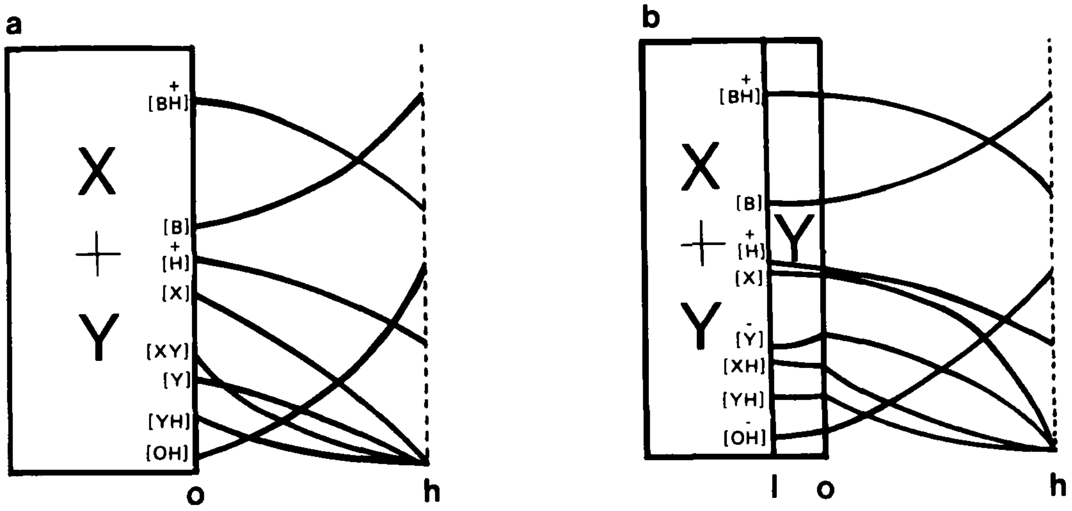

FIGURE 1

Diagrammatic representation of a mixture of two acids (X and Y) dissolving into a reactive medium with a diffusion layer of thickness h. The situation at the critical mixture ratio is illustrated in (a). The situation when the recession of the boundary layer of X is more rapid than that of Y is illustrated in (b).

proportions of the components in the disc. The situation when x becomes depleted at the surface is represented in Fig. 1(b). The species gradients will change in the aqueous boundary layer. Furthermore gradients will also develop within the porous disc layer. The depletion of one acid component (e.g. x) from the surface of the disc may, depending on the component solubilities and pKa's, give rise to a higher pH at the outer disc surface (o) and hence a higher dissolution rate for the surface component than that observed at the critical mixture ratio. Thus the dissolution rate of the surface component will not be constant in the weight fraction range up to the critical mixture ratio, as suggested by Eq. 2 for non-interacting mixtures, but rather will decrease, the magnitude of the effect being greatest at the critical mixture ratio.

Serajuddin and Jarowski have shown that the pH of a saturated solution represents the pH at the surface of the dissolving solid, i.e. $pH_{(h=o)}$. Consequently good approximations of equations 7 and 8 are

$$G_X = \frac{D_X}{h} C_{sx(h=o)} \qquad 15$$

and

$$G_Y = \frac{D_Y}{h} C_{sy(h=o)} \qquad 16$$

where $C_{sx(h=o)}$ and $C_{sy(h=o)}$ are the total solubilities of x and y respectively. In the case of a mixed disc of x and y, at the critical mixture ratio, the pertinent pH and solubilities will be those for the medium saturated with both components. These solubilities may also be used in equation 6 to estimate the critical mixture ratio. At compositions other than the critical mixture ratio, the depletion of one component from the disc surface (e.g. y), may result in an increase in the surface pH and consequently a higher solubility and limiting dissolution rate for the surface component (i.e. G_X). As a first approximation, an estimate of the surface concentration of y may be obtained by combining equations 4 and 5, i.e.

$$C^o_y = \frac{h\, N_Y}{D\, N_X} G_X \qquad 17$$

The fall in concentration of y at h = o may thus be determined and used to recalculate values of $C_{sx(h=o)}$ and G_X. Using an iterative procedure an estimate of the increased dissolution rate of x (G_X) may be calculated for each disc composition.

MATERIALS AND METHODS

Solubility Determinations

Solubilities of benzoic acid and salicylic acid (analytical grade) were determined at 37°, in a range of pH's as previously described.[7] Solubilities were also determined in isotonic phosphate buffer[21] (pH 7.34). Equilibrium was achieved within 48 hrs and samples filtered through 0.2 μm membrane filters (Gelman Sciences Inc.). On dilution, samples were assayed by U-V spectroscopy (Shimadzu UV.160).

Dissolution Rate Method

Dissolution profiles were determined from compressed discs of drug mounted in paraffin wax as previously described.[22] Powders were ground to a sub 210μ particle size before use. The pH of the dissolution medium was monitored using a pH meter (PHM82 Radiometer) and when pH control was required a pH-stat (Radiometer) was employed.

Microscopy

Photomicrographs of disc surfaces and broken edges were obtained using a Scanning Electron Microscope (Hitachi S520).

RESULTS AND DISCUSSION

The total solubility of a monoprotic weak acid [HX] in aqueous media is given by

$$S = [HX]_o + \frac{K_a[HX]_o}{[H^+]} \qquad 18$$

TABLE 1

Measured intrinsic solubility $[HX]_o$ and Ka values for salicylic acid and benzoic acid at 37°C.

Compound	$[HA]_o$, M	Ka	pKa	r*
Salicylic Acid	1.87×10^{-2}	1.47×10^{-3}	2.83	0.9965
Benzoic Acid	3.73×10^{-2}	1.84×10^{-4}	3.74	0.9988

* Correlation coefficient from plot of s versus $^1/[H^+]$.

Thus, from a plot of S versus $^1/[H^+]$, the pKa and intrinsic solubility $[HX]_o$ may be determined. The values obtained for benzoic acid and salicylic acid are summarized in Table 1. From these estimates the relationship between solubility and pH for both acids is plotted in Fig. 2.

The intrinsic solubility and pKa of salicylic acid are lower than those of benzoic acid. Consequently at pH's below 3 benzoic acid is more soluble, while at higher pH's salicylic acid will be the more soluble component. The dissolution profiles of benzoic acid and salicylic acid obtained in phosphate buffer (pH 7.34) at 37°C are shown in Fig. 3(a and b). The dissolution profiles of the acids from pure component discs were of a similar magnitude, the rate for pure salicylic acid being slightly lower than that of benzoic acid. The pH of the dissolution media was measured during the dissolution experiments and negligible (<0.01 pH units) change in pH from the starting pH of 7.34 was observed. Sink conditions prevailed throughout the experiments.

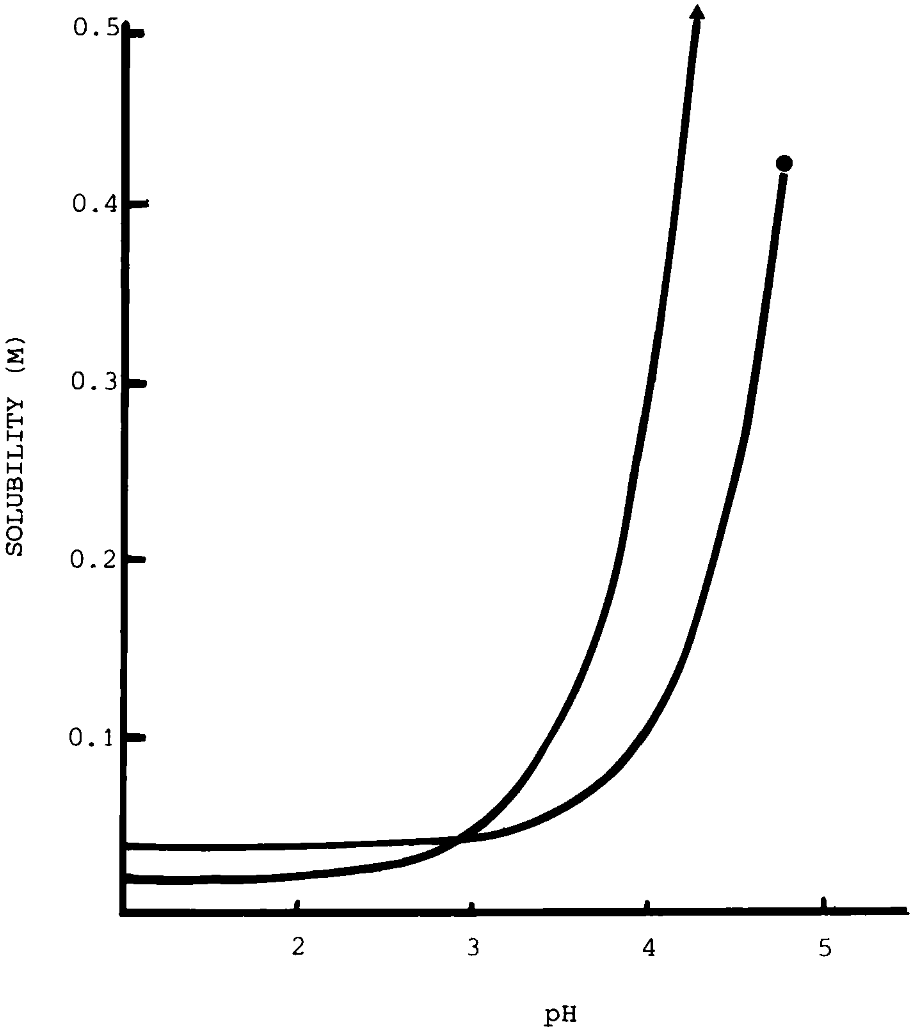

FIGURE 2

Solubility versus pH profiles for benzoic acid ●, and salicylic acid ▲.

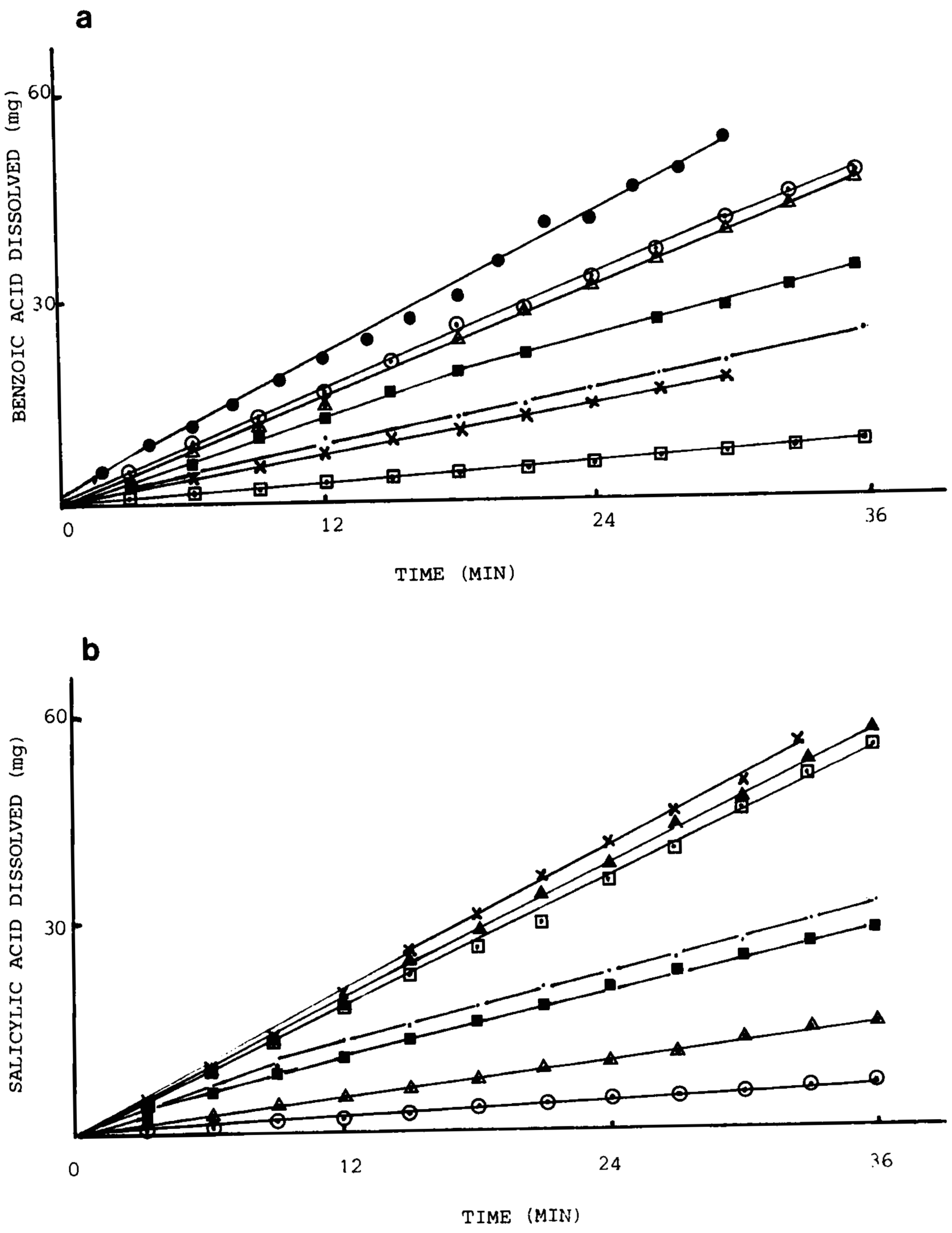

FIGURE 3

Dissolution profiles for benzoic acid (a) and salicylic acid (b) mixtures dissolving in phosphate buffer, pH 7.3.

Key: ● pure benzoic acid, ▲ pure salicylic acid, salicylic acid: benzoic acid □ 6:1, X 3:1, . 3:2, ■ 1:1, △ 1:3 and O 1:6.

TABLE 2

Measured saturation solubilities and pH's of phosphate buffered media containing salicylic acid and benzoic acid.

Component in Buffer	Salicylic Acid Solubility (M)	Benzoic Acid Solubility (M)	pH (filtrate)
Salicylic Acid	0.073	-	3.41
Benzoic Acid	-	0.099	4.32
Salicylic Acid and Benzoic Acid	0.083	0.035	3.38

Dissolution rates in reactive media are a function of the pH at the solid-liquid interface rather than the pH of the bulk medium. An estimate of the surface pH was obtained by measuring the pH of media samples saturated with the respective acid. These solubilities and pH's are summarized in Table 2. Salicylic acid, the stronger acid, reduced the buffer pH to the largest extent, i.e. from 7.34 to 3.41 in contrast to 4.32 in the case of pure benzoic acid.

In Figure 4 the limiting dissolution rates for each component are plotted versus disc composition. The salicylic acid rates remained relatively constant as the salicylic acid content decreased towards the critical mixture ratio, i.e. in the range where salicylic acid is expected to be the surface phase controlling dissolution. Photomicrographs taken of the disc surface and edge of a 75:25 salicylic acid:benzoic acid disc are shown in Fig. 5. The porous nature of the disc surface indicating dissolution and recession of benzoic acid is evident.

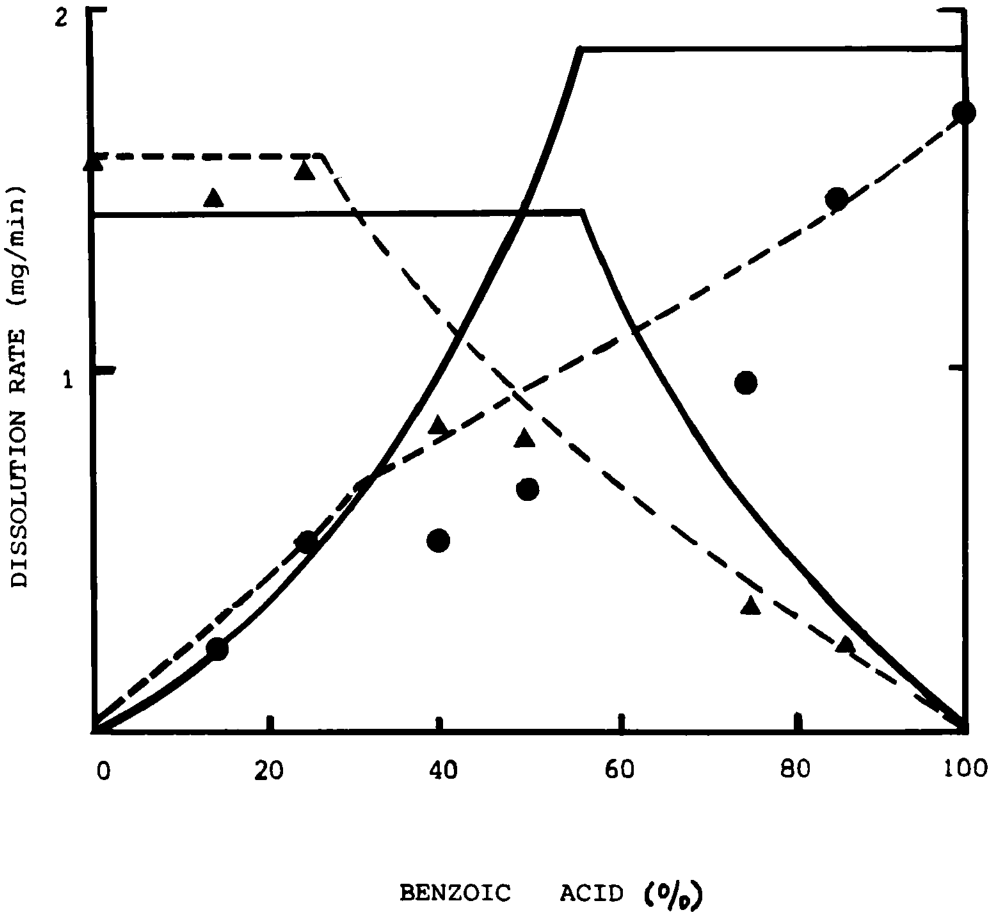

FIGURE 4

Relationship between limiting dissolution rate and composition. Salicylic acid: ▲ , benzoic acid: ● . The continuous curves represents prediction from the non-interacting component model. The dashed line includes a contribution from the pH effect (see text).

In the composition range where benzoic acid is the controlling phase, the expected plateau in the benzoic acid dissolution rate versus composition plot was not observed, the rate declining as the benzoic acid content of the disc decreased. To illustrate this deviation from theory equations 2 and 5 were used to construct theoretical curves of rate versus composition. The pure component solubilities in the buffer were used for the calculation (Fig. 4). The diffusion coefficients of salicylic acid and benzoic acid employed were 11.32×10^{-6} and $12.36 \times 10^{-6}\ \mathrm{cm^2\ sec^{-1}}$ respectively. The diffusion layer thickness for the method was determined previously to be 62×10^{-4} cm[23]. The experimentally determined pH of the dissolution medium when saturated simultaneously with both acids was 3.38 (Table 2), i.e. lower than that for the individual acids. This pH corresponds to the surface pH at the critical mixture ratio and to the initial surface pH at other mixture ratios. From the solubility curves in Fig. 2 it is evident that the fall in pH due to the presence of the second acid should decrease the solubility and hence dissolution rate of benzoic acid by about 70%. However the effect of benzoic acid on salicylic acid solubility will be slight, i.e. a decrease of 6%. Experimentally, salicylic acid solubility in the presence of benzoic acid increased slightly. The presence of increasing concentrations of salicylic acid was found to decrease the pH and equilibrium solubility of benzoic acid (C_s) in phosphate buffer. Using a simplex search procedure for function minimization[24], the data was fitted by:

$$C_s = 0.0234\ (1 + 10^{\mathrm{pH}\ -3.84}) \qquad 19$$

Using the saturated solubilities of each acid in the presence of the other (Table 2), the critical mixture ratio was calculated from

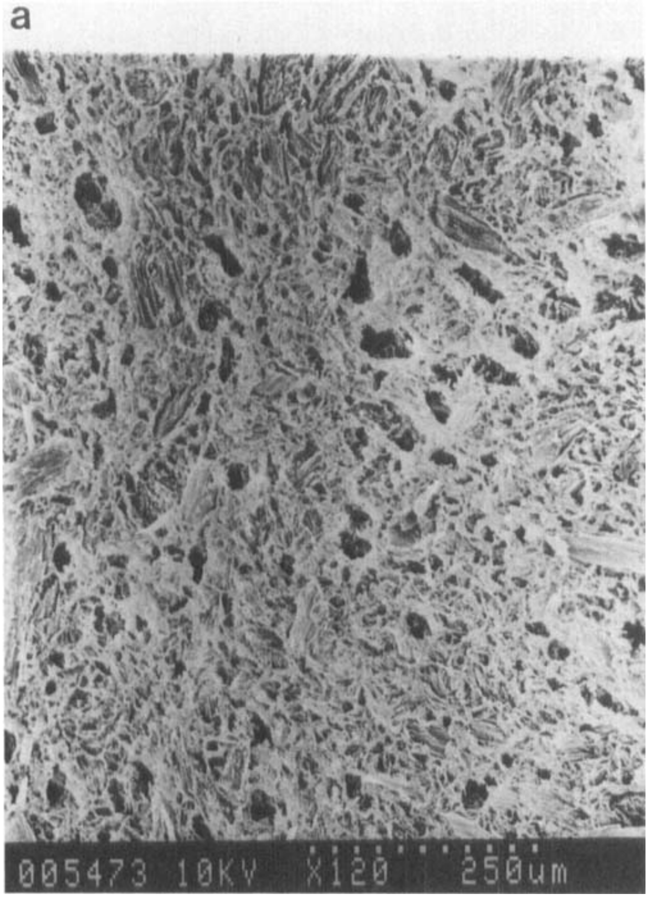

FIGURE 5

Photomicrographs of the surface (a) and broken edge (b) of a 75:25 salicylic acid:benzoic acid disc following dissolution. In (b) the disc surface to the left was exposed to the dissolution medium.

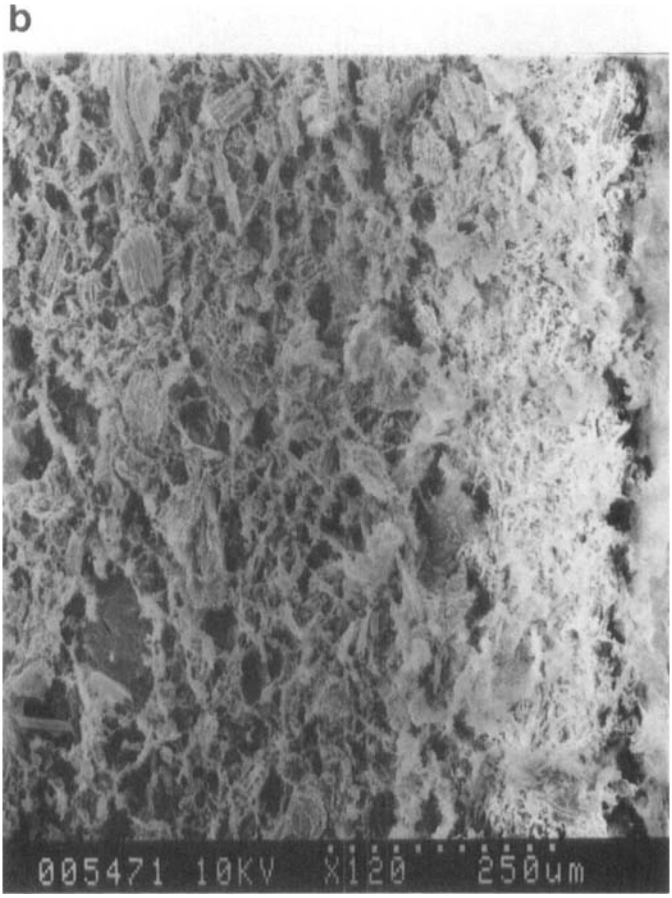

FIGURE 5 CONTINUED

Eq. 6. The value obtained was 0.41; significantly different from 1.3 the corresponding value based on saturation solubilities in the absence of the second acid. The shift in critical mixture ratio to a lower benzoic acid disc content, reflects the suppression of benzoic acid dissolution by salicylic acid and the resultant extension of the range of weight fraction over which benzoic acid is the phase controlling dissolution. Equations 15-19 were used to estimate the change in benzoic acid dissolution rate due to the recession of salicylic acid from the surface, i.e. the weight fraction range where benzoic acid is the surface phase controlling dissolution. In the weight fraction range where salicylic acid is the controlling phase, salicylic acid dissolution rate was considered to be independent of the benzoic acid surface concentration. These assumptions were used to approximate the relationship between dissolution rate and disc composition. The calculated values are included in Fig. 4 as the dashed lines. The relationships obtained reflect the shift in critical mixture ratio and the decrease in benzoic acid dissolution rates observed experimentally. However the experimental values are systematically lower than predicted. Work is continuing on a wider range of systems to better quantify these interrelationships.

Shah and Parrott investigated the dissolution rate of aspirin -salicylic acid mixtures in water and observed deviations from the values predicted by the two component model for non-interacting components.[15] They suggested that the deviations were probably caused by small local variations in composition. It is likely that the surface pH effects outlined in the current model also contributed to the lower rates observed by these authors.

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