Dissolution Kinetics of a Three-Component Solid II: Benzoic Acid, Salicylic Acid, and Salicylamide

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Abstract □ The dissolution rates of each component in compressed spheres consisting of three components were measured under sink conditions. The observed dissolution rates of benzoic acid, salicylic acid, and salicylamide compare favorably to the predicted dissolution rates according to a previously presented kinetic model.

Keyphrases □ Benzoic acid—dissolution kinetics of a three-component solid, salicylic acid, salicylamide □ Salicylic acid—dissolution kinetics of a three-component solid, benzoic acid, salicylamide □ Salicylamide—dissolution kinetics of a three-component solid, benzoic acid, salicylic acid

A dissolution model has been presented to describe the 13 dissolution behaviors of three-component, nondisintegrating solids (1). In continuing the study of dissolution phenomena the dissolution rates of benzoic acid, salicylic acid, and salicylamide from compressed spheres were determined and compared to calculated dissolution rates in order to examine the suitability of the suggested dissolution model.

EXPERIMENTAL

Preparation of Spheres—Twenty grams of each composition was prepared by blending the appropriate amounts of 60/80-mesh size fraction of benzoic acid[1], salicylic acid[2], and salicylamide[3] for 15 min in a V-blender[4]. By means of a hydraulic press[5] fitted with a spherical punch and die set, each composition was compressed at a force of 2268 kg into spheres having a diameter of 1.273 ± 0.005 cm. The compositions were selected according to a scheme previously described (1).

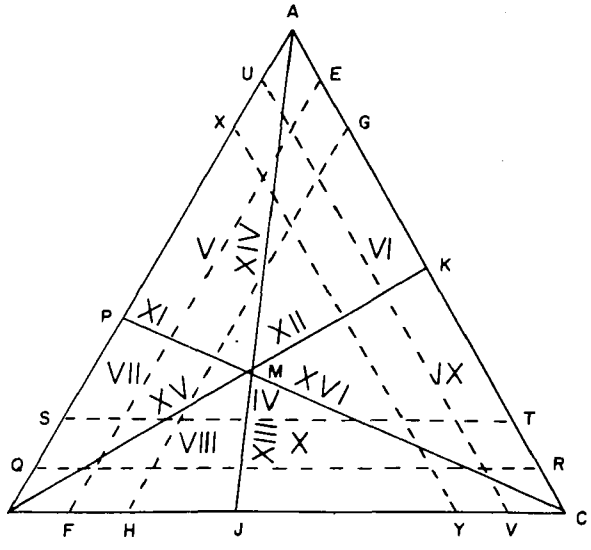

Figure 1—*Composition diagram for mixtures of benzoic acid, salicylic acid, and salicylamide showing the regions corresponding to the 13 dissolution behaviors and their relation to the compositions selected for investigation according to the scheme in Fig. 1 of Ref. 1.*

[1] ACS, Fisher, lot no. 783313.
[2] USP, J. T. Baker, lot no. 43397.
[3] Sigma, lot no. 106C-0409.
[4] Patterson-Kelly.
[5] Carver press, model C.

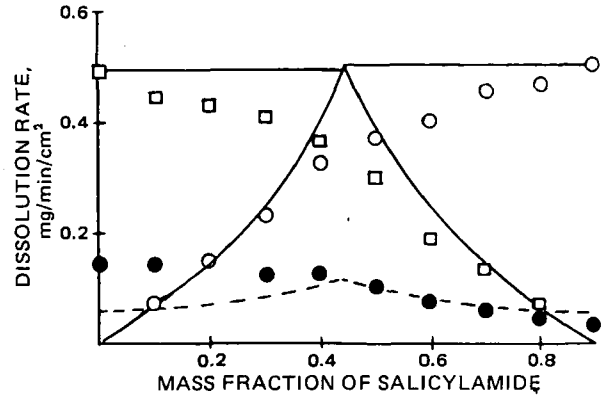

Figure 2—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.1 benzoic acid corresponding to line UV of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

Dissolution Rate—The dissolution rate was determined in distilled water at 25 ± 0.1° at 300 rpm, as described previously (2, 3), under conditions where the concentration of the solutes did not exceed 5% of solubility.

Solubility—Solubility measurements were made at 25 ± 0.1° as reported earlier (4). The solubilities of benzoic acid, salicylic acid, and salicylamide are 3.428 ± 0.064, 2.239 ± 0.027, and 2.511 ± 0.018 mg/ml, respectively.

Analytical Procedure—The absorbance of each sample was measured at 269.5, 298, and 329 nm. The standard curve of each component at each wavelength exhibited a Beer's law relationship. From these plots the nine molar absorptivities were calculated (Table I). As previously described (1) the concentration of each component in solution was obtained by the solution of simultaneous equations. The method was tested with seven solutions containing known concentrations of the three components. The percent determined by the analytical procedure ranged from 98.9 to 101.8% of the known concentration. The concentration was converted to amount dissolved in order to express a dissolution rate.

RESULTS AND DISCUSSION

A detailed discussion of a model for dissolution of a three-component solid has been presented (1). The 13 dissolution behaviors at various compositions are identified by the Roman numerals in Fig. 1. For the system investigated, A represents salicylic acid, B represents benzoic acid, and C represents salicylamide.

Dissolution rates (R) were measured at 25° under sink conditions at various compositions. The solubilities (C_s) were experimentally measured. When the dissolution of a nondisintegrating pure solid occurring in a nonreactive medium at sink conditions is diffusion controlled, the dissolution rate may be expressed (2):

$$R = \frac{DC_s}{h} \qquad \text{(Eq. 1)}$$

Table I—Molar Absorptivities of Benzoic Acid, Salicylic Acid, and Salicylamide

Wavelength, nm	Molar Absorptivity		
	Benzoic Acid	Salicylic Acid	Salicylamide
269.5	578	680	195
298	0	3,522	1,477
329	0	256	5,632

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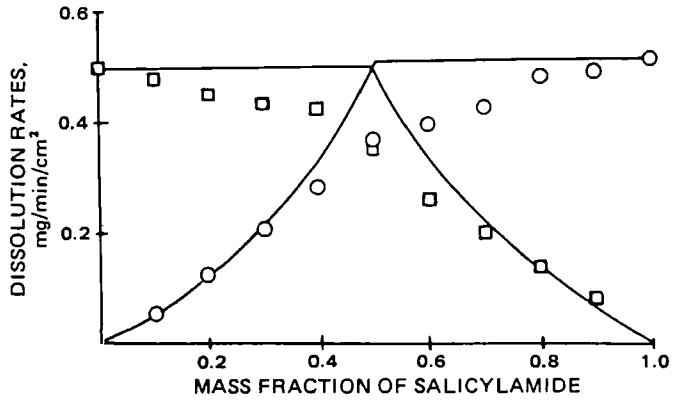

Figure 3—*Comparison of experimental dissolution rates of the components of salicylic acid and salicylamide mixtures corresponding to line AC of Fig. 1 and the smooth curves representing the theoretical rates. Key: (□) salicylic acid; and (○) salicylamide.*

where h is the effective diffusion layer thickness. The diffusion coefficient of salicylamide was reported (1) to be 1.12×10^{-5} cm²/sec. The only unknown term in the equation is h, which may be calculated by rearrangement and substitution of experimental values for salicylamide:

$$h = \frac{1.12 \times 10^{-5} \times 2.51}{0.505/60} = 0.0033 \text{ cm} \quad \text{(Eq. 2)}$$

Using this value of h, the diffusion coefficients of benzoic acid and salicylic acid were calculated to be 1.19×10^{-5} and 1.21×10^{-5} cm²/sec, respectively.

The critical composition (Case IV at point M of Fig. 1) at which the three components coexist at the solid–liquid interface may be expressed:

$$\frac{N_A}{N_B} = \frac{D_A C_A}{D_B C_B} \quad \text{(Eq. 3)}$$

$$\frac{N_A}{N_C} = \frac{D_A C_A}{D_C C_C} \quad \text{(Eq. 4)}$$

and

$$\frac{N_B}{N_C} = \frac{D_B C_B}{D_C C_C} \quad \text{(Eq. 5)}$$

where N is the mass fraction of a component, and C is the solubility of that component. Since:

$$N_A + N_B + N_C = 1 \quad \text{(Eq. 6)}$$

substitution of the values of diffusion coefficient and solubility of the components into any two combinations of Eqs. 3, 4, or 5 with Eq. 6 and solution of the simultaneous equations permit the calculation of the mass fraction of each component. The critical mass fractions are 0.425 benzoic acid, 0.293 salicylamide, and 0.282 salicylic acid.

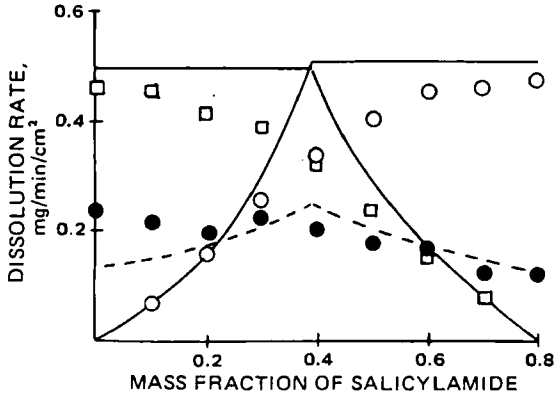

Figure 4—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.2 benzoic acid corresponding to line XY of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

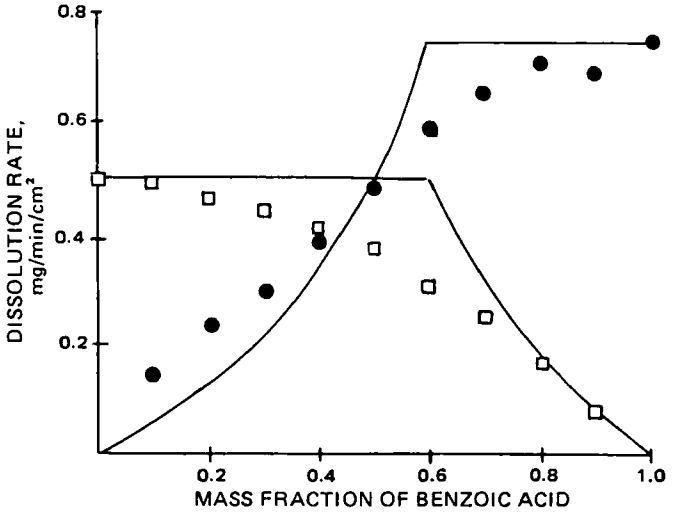

Figure 5—*Comparison of experimental dissolution rates of the components of salicylic acid and benzoic acid mixtures corresponding to line AB of Fig. 1 and the smooth curve representing the theoretical rates. Key: (□) salicylic acid; and (●) benzoic acid.*

Similarly, by use of the values of solubility and diffusion coefficient and appropriate equations (5), the critical mass fractions for two-component mixtures were calculated. The critical mass fractions are 0.40 salicylic acid and 0.60 benzoic acid, 0.59 benzoic acid and 0.41 salicylamide, and 0.49 salicylic acid and 0.51 salicylamide.

Using these critical compositions for two- and three-component mixtures, Fig. 1 was constructed to show the regions that represent the 13 dissolution behaviors. By considering Fig. 1 and by then using appropriate equations, the theoretical dissolution rates were calculated for dissolution behavior in the various regions of the diagram.

For Case IV dissolution behavior at the critical composition of the three components and boundaries recede at the same rate, and the dissolution rates may be calculated by Eq. 1. The dissolution rates of benzoic acid, salicylic acid, and salicylamide are 0.742, 0.493, and 0.505 mg/min/cm², respectively.

A constant mass fraction of 0, 0.1, and 0.2 benzoic acid and varying mass fractions of salicylic acid and salicylamide are represented by lines AC, UV, and XY, respectively, in Fig. 1. In considering line UV at point U there is a two-component solid for which salicylic acid is the surface layer, and the dissolution behavior is expressed by Case II behavior in which:

$$\frac{N_A}{N_B} > \frac{D_A C_A}{D_B C_B} \quad \text{(Eq. 7)}$$

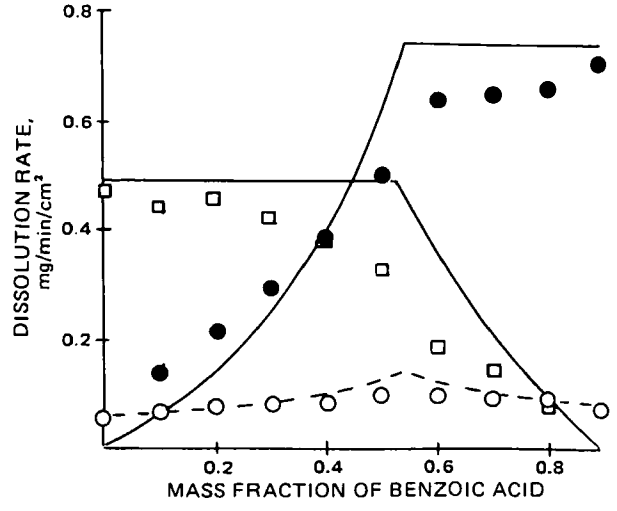

Figure 6—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.1 salicylamide corresponding to line EF of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

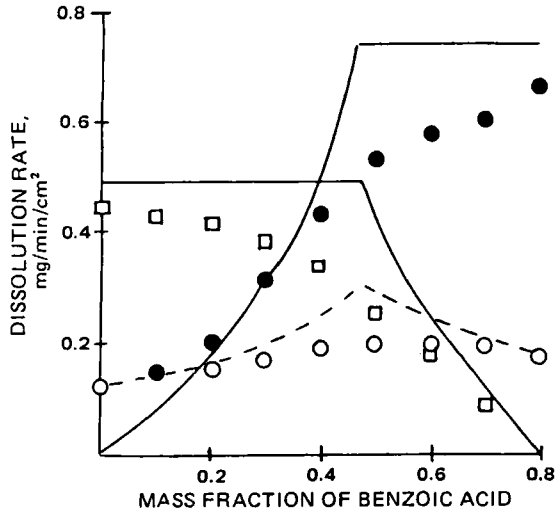

Figure 7—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.2 salicylamide corresponding to line GH of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

and the dissolution rate of salicylic acid according to Eq. 1 is 0.493 mg/min/cm², and the dissolution rate of benzoic acid is:

$$R_B = \frac{N_B}{N_A} R_A \qquad \text{(Eq. 8)}$$

$$R_B = \frac{0.1}{0.9} \times 0.493 \qquad \text{(Eq. 9)}$$

$$= 0.055 \text{ mg/min/cm}^2$$

Since the mass fraction of salicylamide is progressively increased along line UV, the dissolution behaviors are expressed by Case V in region APM, Case XIV on line AM, Case VI in region AMK, Case XII on line MK, Case IX in region KMC, Case XVI on line MC, and Case X in region MCJ. At point V there is a two-component solid for which:

$$\frac{N_C}{N_B} > \frac{D_C C_C}{D_B C_B} \qquad \text{(Eq. 10)}$$

and the dissolution rate of salicylamide according to Eq. 1 is 0.511 mg/min/cm², and the dissolution rate of benzoic acid is:

$$R_B = \frac{N_B}{N_C} R_C \qquad \text{(Eq. 11)}$$

$$R_B = \frac{0.1}{0.9} \times 0.511 \qquad \text{(Eq. 12)}$$

$$= 0.057 \text{ mg/min/cm}^2$$

In Case V dissolution behavior, salicylamide dissolves faster than benzoic acid and salicylic acid, and the boundary of salicylamide recedes into the solid. Benzoic acid dissolves faster from the solid surface than salicylic acid, so that the dissolving boundary of benzoic acid recedes within the solid leaving a surface layer of salicylic acid. This dissolution behavior occurs under the conditions that:

$$\frac{N_A}{N_B} > \frac{D_A C_A}{D_B C_B} \qquad \text{(Eq. 13)}$$

$$\frac{N_A}{N_C} > \frac{D_A C_A}{D_C C_C} \qquad \text{(Eq. 14)}$$

and

$$\frac{N_B}{N_C} > \frac{D_B C_B}{D_C C_C} \qquad \text{(Eq. 15)}$$

Since salicylic acid is always on the surface at compositions represented by Eqs. 13–15, its dissolution rate (R_A) is calculated by Eq. 1 is 0.493 mg/min/cm². The benzoic acid must diffuse through the layer of salicylic acid and the liquid diffusion layer, and its dissolution rate (R_B) is:

$$R_B = \frac{N_B}{N_A} R_A \qquad \text{(Eq. 16)}$$

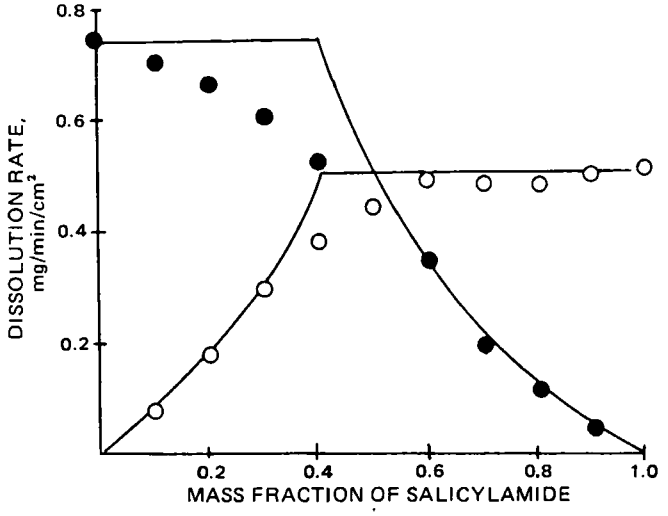

Figure 8—*Comparison of experimental dissolution rates of the components of benzoic acid and salicylamide mixtures corresponding to line BC of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; and (○) salicylamide.*

For example, at mass fractions of 0.1 benzoic acid, 0.88 salicylic acid, and 0.02 salicylamide, the dissolution rate of benzoic acid (R_B) is:

$$R_B = \frac{0.1}{0.88} \times 0.493$$

$$= 0.056 \text{ mg/min/cm}^2 \qquad \text{(Eq. 17)}$$

The salicylamide must diffuse through the layer of benzoic acid and salicylic acid, the layer of salicylic acid, and the liquid diffusion layer, and its dissolution rate (R_C) is:

$$R_C = \frac{N_C}{N_A} R_A \qquad \text{(Eq. 18)}$$

At mass fractions of 0.1 benzoic acid, 0.88 salicylic acid, and 0.02 salicylamide, the dissolution rate of salicylamide (R_C) is:

$$R_C = \frac{0.22}{0.88} \times 0.493$$

$$= 0.011 \text{ mg/min/cm}^2 \qquad \text{(Eq. 19)}$$

Case VI, IX, and X in Fig. 1 describe dissolution behaviors similar to Case V; however, the order of dissolving and the receding of the boundaries are different with different mass fractions of salicylic acid and salicylamide along line UV. The dissolution rates may be calculated by the same reasoning used for Case V dissolution behavior.

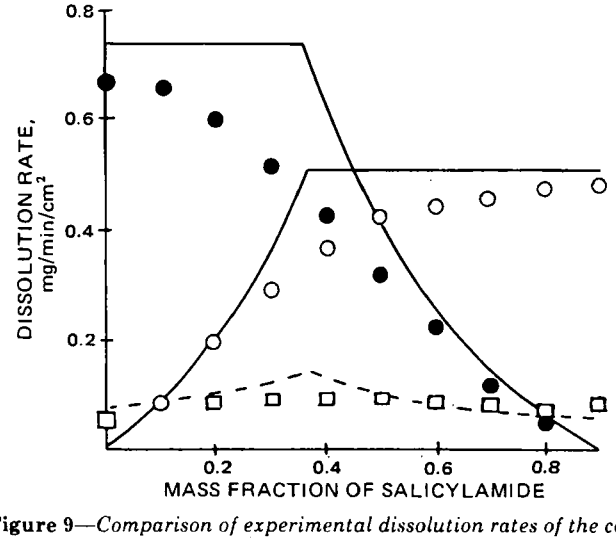

Figure 9—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.1 salicylic acid corresponding to line QR of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

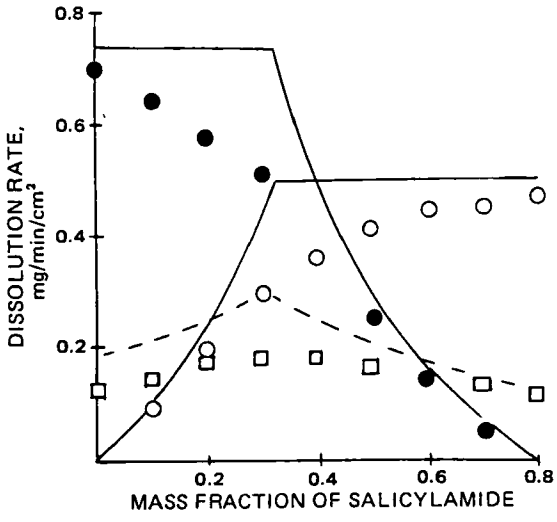

Figure 10—*Comparison of experimental dissolution rates of the components of benzoic acid, salicylic acid, and salicylamide mixtures with a constant mass fraction of 0.2 salicylic acid corresponding to line ST of Fig. 1 and the smooth curves representing the theoretical rates. Key: (●) benzoic acid; (□) salicylic acid; and (○) salicylamide.*

In Case XIV dissolution behavior on line AM, both benzoic acid and salicylamide dissolve faster than salicylic acid so that the boundaries of benzoic acid and salicylamide recede at the same rate and coexist at the same boundary leaving a surface layer of salicylic acid. Case XIV dissolution behavior occurs under the condition that:

$$\frac{N_A}{N_B} > \frac{D_A C_A}{D_B C_B} \quad \text{(Eq. 20)}$$

$$\frac{N_A}{N_C} > \frac{D_A C_A}{D_C C_C} \quad \text{(Eq. 21)}$$

and

$$\frac{N_B}{N_C} = \frac{D_B C_B}{D_C C_C} \quad \text{(Eq. 22)}$$

The dissolution rate equations for Case XIV dissolution behavior are:

$$R_A = \frac{D_A C_A}{h} \quad \text{(Eq. 23)}$$

$$R_C = \frac{N_B}{N_A} R_A \quad \text{(Eq. 24)}$$

and

$$R_C = \frac{N_C}{N_A} R_A \quad \text{(Eq. 25)}$$

At mass fractions of 0.831 salicylic acid, 0.1 benzoic acid, and 0.069 salicylamide, the dissolution rate of salicylic acid as calculated by Eq. 23 is 0.493 mg/min/cm². The dissolution rate of benzoic acid according to Eq. 24 is:

$$R = \frac{0.1}{0.831} \times 0.493 = 0.056 \text{ mg/min/cm}^2 \quad \text{(Eq. 26)}$$

and the dissolution rate of salicylamide according to Eq. 25 is:

$$R = \frac{0.069}{0.831} \times 0.493 = 0.041 \text{ mg/min/cm}^2 \quad \text{(Eq. 27)}$$

Case XVI dissolution behavior is similar to Case XIV except that the order of dissolving and the receding of the boundaries are different with their respective mass fractions of salicylic acid and salicylamide. The dissolution rates may be calculated by the same reasoning used for Case XIV dissolution behavior.

In Case XII dissolution behavior benzoic acid dissolves leaving a surface layer of salicylic acid and salicylamide under the conditions that:

$$\frac{N_B}{N_A} < \frac{D_B C_B}{D_A C_A} \quad \text{(Eq. 28)}$$

$$\frac{N_B}{N_C} < \frac{D_B C_B}{D_C C_C} \quad \text{(Eq. 29)}$$

and

$$\frac{N_A}{N_C} = \frac{D_A C_A}{D_C C_C} \quad \text{(Eq. 30)}$$

The dissolution rates as calculated by use of Eq. 1 are 0.493 and 0.511 mg/min/cm² for salicylic acid and salicylamide, respectively. The dissolution rate of benzoic acid is:

$$R_B 2 = \frac{N_B}{N_A} R_A \quad \text{(Eq. 31)}$$

$$R_B = \frac{0.1}{0.46} \times 0.493 = 0.107 \text{ mg/min/cm}^2 \quad \text{(Eq. 32)}$$

Thus, along line UV from point U to point V the nine dissolution behaviors and the calculation of the dissolution rates of the components at each composition have been considered as shown in Fig. 2. Similarly, the dissolution rates of benzoic acid, salicylic acid, and salicylamide are shown at various compositions with a constant mass fraction of 0 and 0.2 benzoic acid along lines AC and XY in Figs. 3 and 4, respectively.

The dissolution rates of benzoic acid and salicylic acid at various compositions along line AB are shown in Fig. 5. The dissolution rates of benzoic acid, salicylic acid, and salicylamide are shown at various compositions with a constant mass fraction of 0.1 and 0.2 salicylamide along lines EF and GH in Figs. 6 and 7, respectively.

The dissolution rates of benzoic acid and salicylamide at various compositions along line BC are shown in Fig. 8. The dissolution rates of benzoic acid, salicylic acid, and salicylamide are shown at various compositions with a constant mass fraction of 0.1 and 0.2 salicylic acid along lines QR and ST in Figs. 9 and 10, respectively.

The agreement of the theoretical dissolution rates with the experimental data is satisfactory. The greatest variance occurs in the vicinity of the critical composition at which the experimental dissolution rates are slower. The model neglects the amount of the components that remained as solutions in the pores of the layers. This may contribute to the variance. Variance may also be caused by lack of uniformity of the blend and the limits of the analytical method at small mass fractions of a component.

CONCLUSION

The dissolution rates of each component of benzoic acid, salicylic acid, and salicylamide compacts were measured and compared to theoretical dissolution rates based on a previously described model. On initially presenting the model a similar comparison was made for ethylparaben, phenacetin, and salicylamide compacts (1). The agreement between the experimental and calculated dissolution rates for both systems support the suitability of the model.

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