Dissolution of Salicylic Acid and Polyvinylpyrrolidone from Compressed Mixtures

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The present study was initiated to describe quantitatively the dissolution mechanism of a polyphase mixture of drug and water-soluble polymer. The release pattern of both salicylic acid and polyvinylpyrrolidone (PVP) was described quite well by the theoretical model for the dissolution of two noninteracting phases. The PVP dissolution rates from various mixtures, as determined by a weight-loss method, were in excellent agreement with a model describing dissolution of nonbarrier solid. The dissolution rates of salicylic acid over a wide composition range were essentially invariant but lower than the intrinsic dissolution rate of salicylic acid.

THERE IS considerable pharmaceutic interest in the dissolution of drugs from solid mixtures. The various mathematical theories and physical models presented in the reports of T. Higuchi (1–3) and the more recent efforts of W. I. Higuchi (4, 5) form the basis for much of the current research on diffusion-controlled dissolution phenomena.

A recent report from this laboratory was concerned with the dissolution of drugs dispersed in polyvinylpyrrolidone (6). The observed dissolution phenomenon was not consistent with the anticipated release rate of solute from a hydrophilic matrix (2). Hence, the present study was initiated to describe quantitatively the dissolution mechanism of a polyphase mixture of drug and polyvinylpyrrolidone (PVP).

The release pattern of both salicylic acid and the hydrophilic polymer from compressed mixtures was described quite well by the theoretical model for the dissolution of two noninteracting phases (5). These findings are of particular interest in that: (*a*) there is evidence of significant physical-chemical interaction between salicylic acid and PVP (7), (*b*) the PVP/salicylic acid solubility ratio probably exceeds the limit suggested by Higuchi (4), and one might anticipate that dissolution would adhere to the models developed for solute release from an inert matrix, and (*c*) a previous report by Lapidus and Lordi (8) demonstrated that the release of chlorpheniramine maleate from a compressed hydrophilic methylcellulose matrix follows the theoretical relationships proposed for solid drugs in solid matrices (2) rather than the models proposed for simple polyphase mixtures (5).

EXPERIMENTAL

Determination of Dissolution Rates—Salicylic acid and PVP,[1] each with a particle size <250 μ, were blended thoroughly, in various ratios, in a mortar. The blend was then compressed at 10,000 lb. load for 10 sec. on a laboratory model Carver hydraulic press using a 1.2 cm. (0.5-in.) flat-faced punch and die. Tablet thickness was about 5 mm.

Initial dissolution rates[2] were determined by the rotating disk method (9, 10) using 250 ml. of 0.1 *N* HCl at 37° and 100 r.p.m. One-milliliter samples were withdrawn at various times and diluted with 0.1 *N* HCl. Salicylic acid concentration was determined spectrophotometrically at 303 mμ using a Beckman DB-G recording spectrophotometer. Preliminary studies indicated no need to correct for PVP interference at this wavelength under the experimental conditions.

The initial dissolution rate of PVP was estimated by measuring weight loss of the tablet as a function of time, and correcting the weight loss for the previously observed dissolution rate of salicylic acid. Tablets of the desired composition were prepared as described above and the dissolution rate studies were run in a manner similar to that described for salicylic acid with the following exceptions. At selected time intervals the stirring was stopped, the Plexiglas holder was withdrawn from the dissolution medium, and the holder surface wiped with a tissue. The entire unit was placed in an oven at 45° for 5 min. and then immediately weighed on a Mettler H-15 balance. After weighing, the Plexiglas unit was returned to the dissolution apparatus and the procedure repeated at appropriate intervals.

Preliminary studies indicated that further drying for 1 hr. beyond the 5-min. period resulted in minimal weight loss (about 4 mg./hr.) as compared to the initial weight loss of residual water (about 130 mg./hr.). Moreover, the apparent retention of water after the 5-min. drying period was independent of the total length of time the disk was exposed to the dissolution medium. This additional dehydration essentially reflects the loss of the normal moisture content of the PVP rather than the penetration of dissolution fluids into the matrix. Drying of disks of pure PVP under identical conditions for 1 hr. showed a rate of loss of about 3 mg./hr. Hence, penetration of water into the tablet (beyond a surface phase) does not occur to a significant extent. These

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[1] Plasdone K 29-32, average mol. wt. 40,000, was generously supplied by the General Aniline and Film Corporation, New York, N. Y.

[2] The term "initial dissolution rate" in this context indicates steady-state dissolution under essential sink conditions.

data also indicate that the weight-loss method provides a valid measure of the dissolution of PVP.

Solubility Studies—Salicylic acid solubility was determined in a series of aqueous solutions of PVP in 0.1 *N* HCl. In each case, 200 mg. of salicylic acid was added to 20 ml. of solution contained in 25-ml. culture tubes. The tubes were sealed, placed in a Metabolyte shaker (New Brunswick Scientific Co., N. J.), and equilibrated at 37°. The solutions were sampled periodically by means of a filter pipet, diluted, and assayed for total salicylate to determine equilibrium. Under the conditions of the study, PVP gave no spectral interference.

A limited study was conducted on the behavior of salicylic acid in PVP solution as a function of time according to the method of Bates *et al.* (11). A 2.5-Gm. quantity of salicylic acid was added to 250 ml. of 2% PVP solution in 0.1 *N* HCl at 37°. The system was stirred at 100 r.p.m. by means of a Teflon blade. Samples were withdrawn at various intervals and assayed for total salicylic acid.

RESULTS

The initial dissolution rates of both PVP and salicylic acid followed apparent zero-order kinetics in accord with the experimental conditions of constant dissolution surface area and apparent sink conditions. Representative plots at various compositions are shown in Figs. 1 and 2. The PVP data in Fig. 1 were corrected for an initial time lag to yield a zero intercept in each case.

The use of the weight-loss method manifested a lag of 2 to 3 min. before the occurrence of apparent zero-order kinetics. The initial time lag may reflect a surface hydration phenomenon (a presteady-state condition), and the mild drying employed between sampling was apparently insufficient to dehydrate completely the tablet surface, since the lag is noted initially but not between drying periods.

Figure 3 shows the dissolution rates of PVP and salicylic acid as a function of the composition of the biphasic mixture, as determined from the apparent zero-order dissolution rate plots. At each composition studied the dissolution rate of salicylic acid is essentially constant and somewhat lower than the intrinsic dissolution rate of salicylic acid. The dissolution rate of PVP was found to increase with increasing proportions of PVP in the mixture.

The results of the solubility studies at 37° are presented in Fig. 4. These findings must be considered preliminary in that an exceedingly long period was required for apparent equilibrium. The early sampling period provided results which indicated a decreased apparent solubility of salicylic acid at low PVP concentrations. Apparent solu-

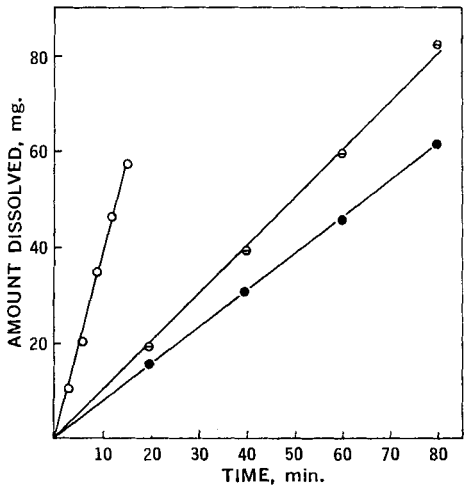

Fig. 1—Apparent zero-order dissolution rates of PVP from compressed mixtures of varying composition. Key: PVP:salicylic acid ratio, w/w. ○, 5:1; ⊖, 3:1; ●, 1:1. Each plot is corrected to origin.

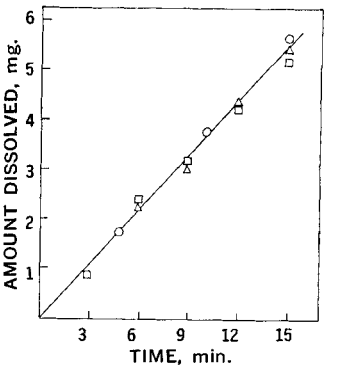

Fig. 2—Apparent zero-order dissolution rates of salicylic acid from compressed mixtures of varying composition. Key: PVP:salicylic acid ratio, w/w. □, 10:1; Δ, 3:1; ○, 1:2. Each plot is corrected to origin.

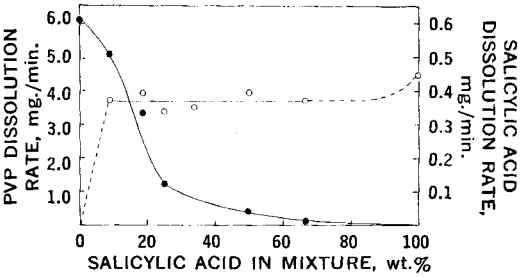

Fig. 3—Dissolution rates of salicylic acid and PVP as a function of mixture composition. Key: ○, salicylic acid; ●, PVP. Each data point represents the average of 2–4 determinations.

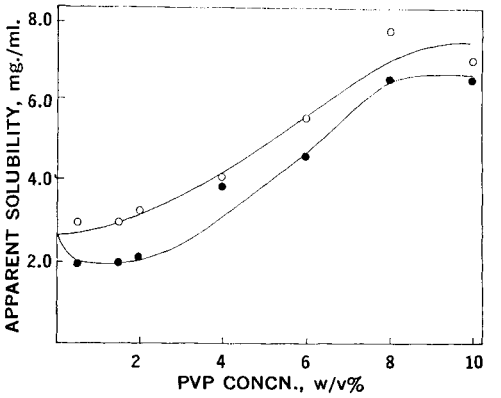

Fig. 4—Apparent solubility of salicylic acid in various concentrations of PVP in 0.1 N HCl. Key: ○, after 336 hr.; ●, after 48 hr.

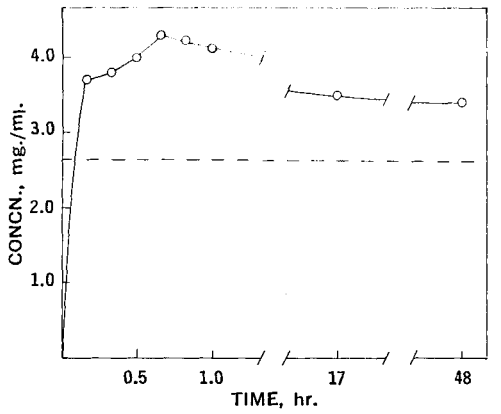

Fig. 5—Dissolution of salicylic acid in 2% PVP solution in 0.1 N HCl. Key: ———, intrinsic solubility of salicylic acid.

TABLE I—COMPOSITION OF "COMPLEXES" ISOLATED FROM 2% PVP SOLUTION AT 37°

Determination	Molar Ratio (PVP Repeating Unit/Salicylic Acid) Stirrer Solid	Bulk Solid
1	1.81	0.68
2	1.87	0.69

bility increased with time at each PVP level and "equilibrium" appeared to be established after about 2 weeks. The equilibrium solubility plot indicates a continuous increase in apparent solubility of salicylic acid as a function of PVP concentration up to about 8%. Twenty-four hours after incubation, no crystalline salicylic acid was observable in any tube. Each tube contained an amorphous, plastic precipitate.

The concentration of salicylic acid in 2% PVP solution as a function of time is shown in Fig. 5. A maximum occurs at about 40 min. and thereafter the concentration of drug in solution decreases. After 48 hr., stirring was stopped and two distinct amorphous solid phases were observed. No crystalline salicylic acid was noted. One phase was a transparent glass material concentrated about the stirring shaft (in the region of the system where the vortex had existed). The second phase was an opaque amorphous material occurring at the bottom of the flask. A sample of each solid phase was dried to constant weight and the stoichometry determined by chemical assay. The composition of each phase is reported in Table I.

DISCUSSION

The PVP and salicylic acid dissolution rate data were consistent with the models recently presented to describe the dissolution rate behavior of polyphase mixtures (5). The PVP data were in agreement with the simplest of these models which describes the dissolution of nonbarrier solid from a mixture of two noninteracting solid phases.

For a two-phase mixture of components A and B, Higuchi (5) has proposed the following model. Upon exposure to solvent, A and B dissolve initially at rates proportional to their solubilities and diffusion coefficients. If the ratio of amounts in the mixture, *i.e.*, N_A/N_B, exceeds the ratio of the product of diffusion coefficient (D) and solubility (C^0), *i.e.*, $D_AC^0_A/D_BC^0_B$, then after a short time, component B will become depleted from the solid–liquid interface region of the dissolving solid. Consequently, a surface layer of pure component A is formed.

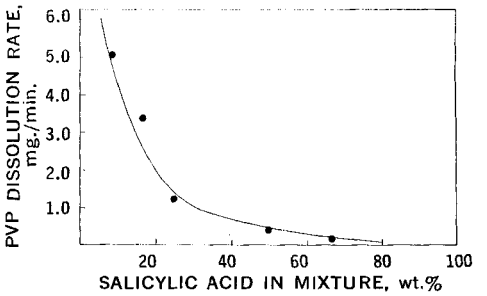

Fig. 6—Comparison of theoretical and experimental dissolution rates of PVP as a function of mixture composition. Key: ——, theoretical; ●, experimental.

Estimates of the magnitude of the ratio of diffusion coefficients and solubilities of PVP and salicylic acid (SA) indicate that $D_{SA}C^0_{SA}/D_{PVP}C^0_{PVP} < 0.1$. Hence, in mixtures with $N_{SA}/N_{PVP} > 0.1$, PVP would be expected to behave in a manner similar to component B described above.

Accordingly, when $N_A/N_B > (D_AC^0_A)/(D_BC^0_B)$, the dissolution rate of component B from the mixture is described by the following equation (6):

$$(DR)_B = \frac{N_B}{N_A}(DR)^0_A \qquad \text{(Eq. 1)}$$

where $(DR)^0_A$ is the intrinsic dissolution rate of component A.

Figure 6 shows a comparison of the theoretic dissolution curve of PVP *versus* mixture composition, as determined from Eq. 1 and the experimental data. Good agreement is observed despite the fact that solubility studies suggest significant interaction of PVP with salicylate. Apparently the formation of complex in the diffusion layer contributes little to the overall dissolution rate of PVP from the nonbarrier phase. The diffusion of the complex will be discussed in greater detail below.

The physical model employed to describe the PVP dissolution rate predicts that the dissolution rates of salicylic acid over the composition range studied should be constant and equal to the intrinsic dissolution rate of salicylic acid, since this component represents the barrier phase. As shown in Fig. 3, the dissolution rates of salicylic acid over a wide composition range is essentially invariant but somewhat lower than the intrinsic dissolution rate of salicylic acid. The regression line fitted to the six data points gave a slope of essentially zero ($\sim 10^{-4}$). The data provide no indication of the contribution of a salicylate–PVP complex to the dissolution process. In fact, the results are somewhat lower than those predicted by the noninteracting model.

Although the dissolution rate studies of various PVP–salicylic acid mixtures provide little evidence for the existence of solution interaction, the solubility data indicate definite interaction of PVP and salicylic acid. The nature of the complex is not clear at present but probably could be represented by PVP–$(SA)_n$ where n is a variable depend-

ent upon the PVP concentration and temperature. The maximum value of n is likely to be in the order of 360. This would be consistent with a complex containing one salicylic acid molecule bound to each vinylpyrrolidone repeating unit. Previous studies (12) of the interaction of phenol with PVP report a value for bound phenol of 0.94 moles $L.^{-1}$/equiv. of PVP $L.^{-1}$ corresponding to a 1:1 complex of phenol with the repeating unit.

Significant existence of a 1:1 complex with the vinylpyrrolidone repeating unit in the salicylic acid system is unlikely except at very low concentrations of PVP (<0.5%). The formation of the 1:1 complex may be limited by the poor solubility and precipitation of less substituted complexes at 37°. The initial increase in apparent solubility noted in Fig. 5 may be due to the formation of soluble complexes of PVP–$(SA)_n$ where n has a relatively low order of magnitude. It is likely that n increases with time and the resulting higher molecular weight complexes precipitate from solution.

The complex isolated from the stirrer shaft probably represents precipitated complex. The bulk complex was found to have a salicylic acid:vinylpyrrolidone repeating unit ratio exceeding unity, which suggests the possible physical inclusion of unbound, undissolved salicylic acid. The apparent absence of undissolved salicylic acid from the stirrer solid may reflect the turbulent conditions in the vortex which would minimize the presence of drug particles. Further studies are in progress to characterize more clearly the PVP–salicylic acid interaction.

Regardless of the nature of the complex which exists in the diffusion layer during dissolution, it would appear likely that the large molecular weight and presumably small diffusion coefficient of the complex precludes a significant contribution of this species to the diffusion process. Since the complex species is expected to contribute little to the dissolution phenomenon, the dissolution of PVP and salicylic acid from the biphasic mixture adheres to a simple model developed for two noninteracting phases rather than the more complex case where the phases demonstrate solution interaction.

The decreased dissolution rate of salicylic acid from the barrier phase of the mixtures, as compared to the intrinsic dissolution rate of salicylic acid may reflect the increased viscosity in the diffusion layer of the dissolving solid due to the presence of high concentrations of PVP. The diffusion coefficient and hence the dissolution rate of the drug is an inverse function of viscosity in the diffusion layer. The presence of PVP in the diffusion layer would, therefore, tend to decrease the dissolution rate of the drug. Alternatively, a film of a high-molecular weight PVP–salicylic acid complex may form at the interface and depress the salicylic acid dissolution rate while minimally affecting the more rapidly dissolving PVP.

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Keyphrases

Salicylic acid–PVP—compressed mixtures
Dissolution rates—salicylic acidP–VP
PVP determination—weight-loss method
UV spectrophotometry—analysis, salicylic acid
Solubility—salicylic acid–PVP