Dissolution Rates of High Energy Sulfathiazole–Povidone Coprecipitates II: Characterization of Form of Drug Controlling Its Dissolution Rate *via* Solubility Studies

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Abstract □ Solubility studies were made to characterize the form of sulfathiazole controlling the rate of dissolution exhibited in previously reported dissolution rate studies of sulfathiazole coprecipitated with povidone. The aqueous solubility of the high energy form of sulfathiazole obtained using sulfathiazole–povidone coprecipitates was determined in the presence of polymer in solution. Its aqueous solubility in the absence of polymer was determined by extrapolation. The solubility value was much greater than either the supercooled melt or the crystalline forms of sulfathiazole. Stabilization of these sulfathiazole solutions supersaturated with respect to the more stable crystalline form was achieved by the addition of sufficient polymer to the solution to prevent nucleation of the crystalline form. The concentration of polymer required to prevent nucleation of the crystalline forms was much higher than the previously reported concentrations required to inhibit crystal growth of sulfathiazole. The ratio of the solubility value obtained for the coprecipitated sulfathiazole as compared with its crystalline form I was in agreement with the ratio of their dissolution rates obtained in the plateau regions of the dissolution rate experiments reported previously. The extrapolated aqueous solubility values in the absence of povidone were obtained as a function of temperature and were utilized to obtain thermodynamic parameters. The difference in the heat of solution of the two forms of sulfathiazole from the slope of the van't Hoff plots of the extrapolated solubility values was 1618 cal/mole, in excellent agreement with the literature value. The free energy, enthalpy, and entropy at 27° for the coprecipitated drug relative to its crystalline form I were 1125 cal/mole, 8439 cal/mole, and 24 eu, respectively, indicating the high degree of molecular randomness and lack of structure in these high energy systems. These results provide strong evidence for the presence of an amorphous state of sulfathiazole as the controlling phase of both the solubility and dissolution rate experiments involving the high energy form of sulfathiazole obtained by coprecipitation with povidone.

Keyphrases □ Sulfathiazole–povidone coprecipitates—dissolution rates, solubility studies, compared to supercooled melt and crystalline forms of sulfathiazole, thermodynamic parameters □ Dissolution rates—sulfathiazole–povidone coprecipitates, compared to supercooled melt and crystalline forms of sulfathiazole, thermodynamic parameters □ Solubility studies—sulfathiazole–povidone coprecipitates, dissolution rates, compared to supercooled melt and crystalline forms of sulfathiazole, thermodynamic parameters

A previous article (1) showed that the dissolution rates of sulfathiazole could be significantly increased by coprecipitating the drug with povidone. As suggested in that report and subsequently shown (2), these results are generally applicable to other drugs and coprecipitating agents. Other workers also have reported (3–8) increased dissolution rates of drugs by the method of coprecipitation.

Numerous reasons have been presented to explain these observed increases in dissolution rates including glass solutions (6), solid solutions (8), decreased particle size (9), eutectic mixtures (10), and colloidal dispersions (11). Although the previous study (1) led to the postulation of a model that was consistent with all of the results obtained, the specific form of the drug in the solid sulfathiazole–povidone coprecipitate responsible for increasing its dissolution rate was not determined. This study was initiated primarily to investigate this aspect of these coprecipitates. Obviously, this information is essential for a complete understanding of the mechanism operative in these systems.

The importance of increasing the dissolution rates of poorly soluble drugs to obtain better therapeutic results cannot be overestimated. Furthermore, a proper understanding of these systems may also permit the formulator to increase the apparent solubility of a given drug as well as its dissolution rate. Although the dissolution rate of a drug in a solvent will increase if its apparent solubility in that solvent is increased, the reverse is very often not true. For example, if a more soluble form of the drug readily reverts to a less soluble form, the dissolution rate of the drug can still be increased by utilizing the more soluble form if the reversion rate is not too rapid, but a stable apparent solubility can be achieved only if the reversion can be completely prevented.

EXPERIMENTAL

Materials—Sulfathiazole[1] was recrystallized from 95% ethanol prior to use. Povidone[2] (average molecular weight of 10,000) was used as received.

Preparation of Different Forms of Sulfathiazole—Crystalline forms I and II of sulfathiazole were obtained by crystallization from 95% ethanol and 1-propanol, respectively (12). The glassy state (supercooled melt) of sulfathiazole was prepared by heating crystalline sulfathiazole on a hot plate[3] at a controlled temperature to prevent any charring, followed by rapid cooling of the melt.

The povidone coprecipitates of sulfathiazole, used in the solubility determination, were prepared by the alcohol evaporation method described previously (1).

The different forms of sulfathiazole were characterized by obtaining their X-ray diffraction[4] patterns (12) using the nickel filter and copper K alpha I radiation.

Solubility Determinations—A weighed excess quantity of the drug or coprecipitate was placed in a 5-ml test tube for each system studied, and 3 ml of the solvent (distilled water or povidone solution) was added at zero time. The test tube was sealed by using a screw cap[5] and placed on a rotating device[6] immersed in a constant-temperature water bath. Duplicate samples were withdrawn and filtered through a Swinney adapter syringe assembly as a function of time, and the filtrate was analyzed for both sulfathiazole and povidone.

[1] Merck and Co., Rahway, N.J.
[2] PVP K-15, GAF Corp., Easton, Pa.
[3] Kofler, Reichert Co., Austria.
[4] Siemens Crystaloflex IV counter-tube X-ray diffractometer.
[5] Lined with Teflon.
[6] Ernest B. Menold Co., Lester, Pa.

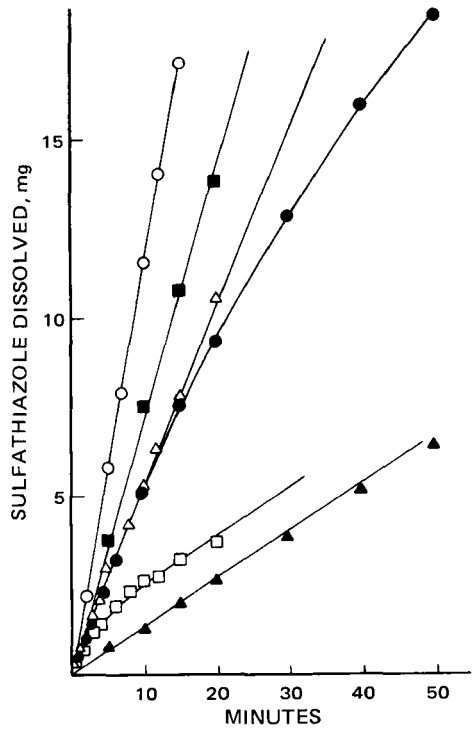

Figure 1—*Effect of sulfathiazole crystalline Form I to povidone ratio on the release profile of sulfathiazole from tablets made from 95% alcohol coprecipitated mixture. Key: ○, 1:3 ratio; ■, 1:2 ratio; △, 1:1.5 ratio; ●, 1:1 ratio; □, 1.5:1 ratio; and ▲, 1:0 ratio.*

Sulfathiazole was analyzed using its UV absorption peak at 282 nm[7]. The polymer was analyzed by means of the refractive index difference[8] between the solution and its solvent after subtracting the contribution due to the sulfathiazole present. The contribution of sulfathiazole was calculated by multiplying its concentration (determined from its UV absorbance) by its refractive index parameter (1). The concentration of the polymer was then obtained from its calibration curve of the refractive index difference *versus* povidone concentration.

RESULTS AND DISCUSSION

Previous work on dissolution rates of sulfathiazole as a function of the povidone weight fraction of the coprecipitate showed that the concentration of drug as a function of time was linear for coprecipitates containing high polymer weight fractions (1). The coprecipitates containing low polymer weight fractions, however, showed a continual decrease in slope, which then became linear as a function of time (Fig. 1). For these coprecipitates in which curvature appeared, both the initial and limiting slopes were determined. The relative rates of dissolution of tablets containing coprecipitates as compared to those containing pure crystalline drug were plotted *versus* the povidone weight fraction in the solid coprecipitate (Fig. 2).

At low polymer weight fractions, there were two plateaus. One plateau, obtained from the limiting slopes of the concentration *versus* time plot, was designated as the limiting rate of dissolution for that system (solid line in Fig. 2). It was reasoned that the drug at the surface of the coprecipitate tablet in this region had to be that of the crystalline form I, since the limiting rate of solution was equal to that exhibited by a pure tablet of the crystalline form I of the drug.

At that time, it was also postulated that the initial rate of dissolution exhibited at the higher plateau (dashed line in Fig. 2) in this region also could be represented by the dissolution rate of a tablet composed of a pure drug but in a higher energy form. This higher energy form, however, could not be crystalline because all known crystalline forms of sulfathiazole would have yielded much lower

[7] Cary 14 UV–visible recording spectrophotometer.
[8] Brice-Phoenix differential refractometer (model BP-2000V).

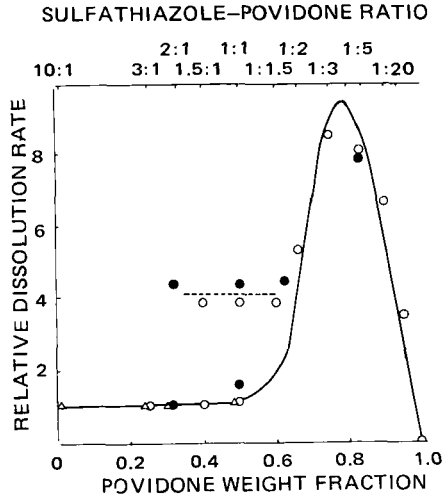

Figure 2—*Comparison of theoretical and experimental relative release rates of sulfathiazole compared to a 1:0 crystalline form I as a function of the povidone weight fraction in tablet. Key: ●, 95% alcohol coprecipitated mixtures; ○, aqueous coprecipitated mixtures; △, mechanical mixtures; - - -, rates calculated from initial slopes (Fig. 1); and —, rates calculated from final slopes (Fig. 1). The curves were empirically drawn. For the theoretical curves, the reader is referred to Fig. 20 of Ref. 1.*

dissolution rates. As a result, it was hypothesized that at initial times the surface of the tablet was composed of a high energy form of the drug, which reverted in solution to the crystalline form I with the passage of time. This hypothesis explained why the initial and limiting rates of drug dissolution yielded a release rate that was independent of the polymer weight fraction in this region (less than a 3:2 ratio of povidone to drug).

An equally compatible explanation would be that both forms were initially present. However, due to its higher dissolution rate, the higher energy form was rapidly depleted from the surface, leaving only the crystalline form on the surface. This process resulted in the composition of the outer layer being effectively transformed to one containing only the crystalline drug. It should be emphasized that this reversion only occurred at the lower povidone weight fractions; for this reason, coprecipitates in this region should not be expected to yield useful dosage forms. This region, however, due to its invariant reproducible release rates, is excellent for study to develop a better understanding of the system.

Solubility of Different Forms—It was of interest to define the physical state of the drug, whether it was another polymorph, a complex, or some other form. The first experiments utilized solubility determinations of each different known form in the presence of povidone. The concentration of drug in solution of the various forms of sulfathiazole was measured as a function of time rather than simply at equilibrium, because important information not otherwise available is often obtained in this way.

Figure 3 shows the concentration of drug in 7% povidone solution in the presence of excess solid drug as a function of time at 37°. The lower curve shows that the concentration of drug rapidly

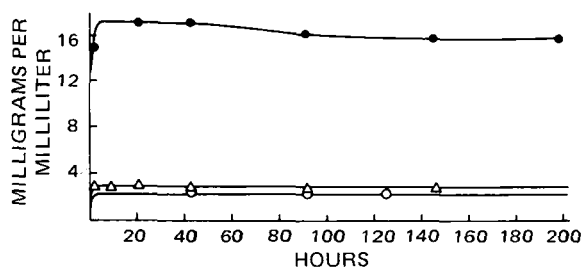

Figure 3—*Concentrations of different forms of sulfathiazole in 7% povidone solutions in the presence of excess solid (drug) as a function of time at 37°. Key: ○, sulfathiazole form I; △, sulfathiazole form II; and ●, sulfathiazole–povidone coprecipitate (1:2).*

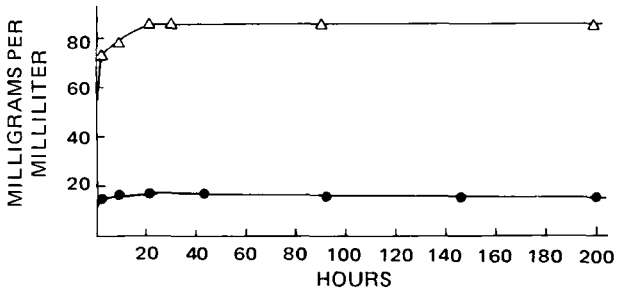

Figure 4—*Release of sulfathiazole and povidone in solution from a sulfathiazole–povidone coprecipitate (1:2) as a function of time at 37°. Key: ●, sulfathiazole; and △, povidone.*

reached a plateau level in the presence of excess crystalline form I of the drug. The same type of behavior was exhibited by the crystalline form II of sulfathiazole, except that the plateau was higher. This finding is interesting, because sulfathiazole crystalline form II has been shown to revert very rapidly in water (12). The higher apparent solubility exhibited by the crystalline form II indicated that the polymer must inhibit its reversion in water to a more stable form and strongly suggested that the solubility of the crystalline form II might be measurable in aqueous solutions under these conditions. Povidone inhibition of sulfathiazole crystal growth was reported previously (13) and, therefore, supported this possibility.

Since povidone solutions were apparently necessary to prevent the reversion of crystalline form II, studies with crystalline form I also were made in solutions of the polymer for a comparison of their activities in solution (Fig. 3). The uppermost curve in Fig. 3 shows the results obtained using the povidone coprecipitate of sulfathiazole. In this case, the concentration of drug rapidly increased, reached a peak, and then decreased slightly to a plateau. Since povidone has a high aqueous solubility, all of the polymer incorporated in the coprecipitate should have dissolved in these solubility experiments. If this expectation was true, the solid that was in apparent equilibrium with the drug solution must have been composed of only drug.

To investigate this aspect, it was decided that the solubility experiments should include measurements of the concentration of the polymer as well as drug in solution as a function of time (Fig. 4). As shown in Fig. 4, the sulfathiazole in solution again reached a plateau. The polymer also behaved in a similar manner, since its concentration in solution increased rapidly as a function of time and reached a plateau value.

The quantity of polymer in solution was calculated using the plateau concentration in solution, and this procedure confirmed the expectation that all of the polymer incorporated in the coprecipitate was indeed in solution. This finding indicated that, within experimental error, only drug and no povidone was present in the apparently equilibrated solid phase. Therefore, it would appear that the drug solution was indeed in apparent equilibrium with pure solid drug, eliminating the possibility, at least in these solubility experiments, that a polymer complex of the drug was the controlling solid phase causing the apparent increased solubility.

Effect of Polymer on Solubility—It was decided to study the solubility of sulfathiazole as a function of the povidone concentration in solution. In this way, the contribution of polymer complexation to the apparent drug solubility can be separated from that due to the free drug. The two lower curves of Fig. 5 show the solubilities of crystalline forms I and II as a function of the polymer concentration in solution at 37°. The apparent solubility of both forms exhibited a linear relationship as a function of the polymer concentrations in solution over the polymer concentration range studied. This finding strongly suggests that extrapolation of the data to 0% polymer should yield the solubility of the respective form of the drug in water in the absence of povidone. To check this possibility, the crystalline form I data were extrapolated to 0% polymer. A value for its solubility of 0.81 mg/ml was obtained, in excellent agreement with the experimentally determined value in water (Fig. 5).

It seemed reasonable to assume at this point that the crystalline form II data also could be extrapolated to obtain its correct solubility in water. This value cannot be obtained by any direct methods due to the rapid transformation to its more stable form (crystalline form I). This extrapolation yielded a solubility of 1.22 mg/ml, 1.5 times higher than the value for the crystalline form I at 37°. It was reported previously (12, 14) that the relative dissolution rate of the crystalline form II as compared to the crystalline form I was 1.7 times higher at 30° in nonaqueous solvents. If one considers the effect of temperature, the latter two ratios are within extrapolation and experimental error.

The dissolution rate technique assumes that the chemical potentials are dependent only on the activity of the respective solids; that is, the diffusion layer, diffusion coefficient, and degree of solvation in solution are constant for both systems. Interestingly, the solubility ratios of form II to form I obtained by these different methods yielded a ratio that showed excellent agreement with the values obtained by direct measurements (1) of the relative dissolution rates in povidone solutions. The measurement of solubility by extrapolation involves fewer assumptions and should provide more reliable value than the other methods; this technique should be used when applicable.

These results indicated that it would be worthwhile to use this approach to study the sulfathiazole–povidone coprecipitate system. Therefore, the apparent solubility of coprecipitated drug as a function of povidone in water was determined by measuring both the drug and polymer concentrations in the presence of excess solid when the system reached an apparent equilibrium. For this purpose, coprecipitates containing different ratios of drug to polymer were used. The final concentration of polymer in solution was only a function of the polymer weight fraction in the solid coprecipitates and the amount of solid coprecipitate added to the solvent, since all of the polymer in solution was provided by the coprecipitate and no attempt was made to control the polymer concentration in solution by the addition of exogenous povidone.

The ratios of drug to polymer in the solid coprecipitate used were 1:1.5, 1:2, 1:3, and 1:4. The data plotted in Fig. 6 show the results of such a study made at 37°. As expected, the solubility using coprecipitated drug was substantially higher than with either crystalline drug and increased with increasing polymer concentration in solution. These data were obtained using a wide range of drug to

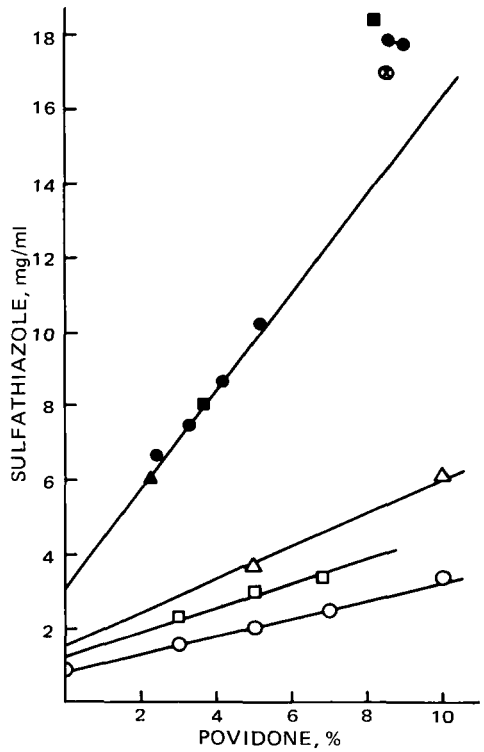

Figure 5—*Solubilities of different forms of sulfathiazole as a function of povidone concentrations in solution at 37°. Key: ○, sulfathiazole form I; □, sulfathiazole form II; △, supercooled melt of sulfathiazole; ▲, 1:1.5 sulfathiazole–povidone coprecipitate; ●, 1:2 sulfathiazole–povidone coprecipitate; ■, 1:3 sulfathiazole–povidone coprecipitate; and ⊕, 1:4 sulfathiazole–povidone coprecipitate.*

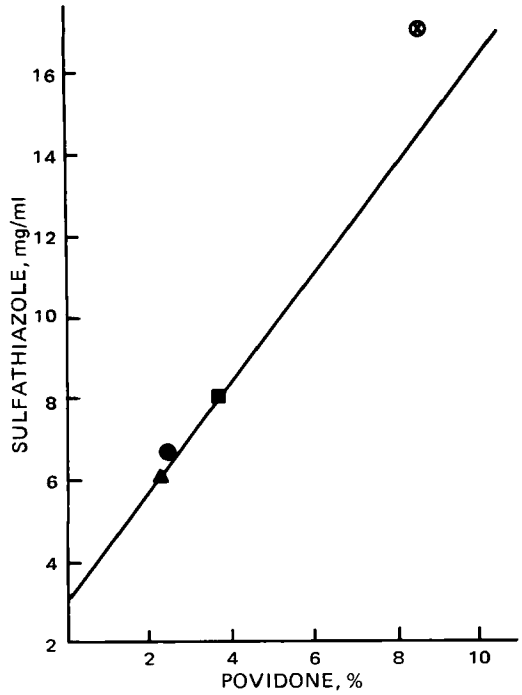

Figure 6—*Apparent solubility of sulfathiazole coprecipitated with different povidone weight ratios as a function of povidone concentrations in solution at 37°. Key: ▲, 1:1.5 sulfathiazole–povidone coprecipitate; ●, 1:2 sulfathiazole–povidone coprecipitate; ■, 1:3 sulfathiazole–povidone coprecipitate; and ⊕, 1:4 sulfathiazole–povidone coprecipitate.*

polymer weight ratios in the coprecipitate, and the final povidone concentration in the solution varied from 2.3 to 8.5%.

If the apparent relationship shown in Fig. 6 for the coprecipitated sulfathiazole is valid, the same curve should be obtained if the drug to polymer weight ratio in the coprecipitate is kept constant and the apparent solubility of the drug is determined in solutions containing varying initial concentrations of povidone. The studies were made using a 1:2 drug to povidone coprecipitate; as expected, the data points showed excellent agreement with those obtained using different coprecipitates. The results of all solubility experiments using coprecipitates were plotted in Fig. 5 to facilitate comparison of the data.

To verify further that the results were independent of the drug to polymer weight ratio of the coprecipitate used, a coprecipitate containing a 1:3 drug to polymer weight ratio was used to determine the apparent drug solubility at the higher polymer concentration in solution. Figure 5 shows that the same results were obtained regardless of the weight ratio of drug to polymer used in the coprecipitate. These latter results also could have been obtained by using the same coprecipitate but controlling the final povidone concentration in solution by simply varying the solid to solvent (water) ratio. Although there appear to be higher orders of interactions between drug and polymer at the higher polymer concentrations in solution contributing to the overall drug solubility, the data points at the lower povidone concentrations strongly suggest that a linear relationship would be applicable in this range of polymer concentrations.

Solubility of Unstable Forms in Absence of Polymer—Having established the validity of the solubility profile of the high energy form of the coprecipitated drug, it seemed reasonable to assume that if the linear portion of these data is extrapolated to 0% povidone, the aqueous solubility of the high energy form of the drug in the coprecipitate can be obtained. This extrapolation (Fig. 5) yielded a solubility of 3.06 mg/ml for the high energy form of sulfathiazole, about 3.8 times greater than that of its crystalline form I.

The solubility of the high energy form in water in the absence of povidone could not be obtained directly for two reasons. First, the high energy form would revert too rapidly to a crystalline form. Second, the coprecipitate itself contains povidone which, of course, would be released simultaneously with the drug when the coprecipitate is added to water. Furthermore, the extrapolation method utilized here allows one to use equilibrium solubility rather than dissolution rate data to obtain this solubility. This fact is very important because the extrapolated solubilities of the different solid forms of sulfathiazole then can be used as a measure of their relative activities.

Correlation to Dissolution Rate Data—This factor of 3.8 is equal to the ratio of the limiting and initial rate plateaus seen in Fig. 2. This evidence strongly supports the hypothesis that pure drug during dissolution is on the surface of the tablet containing the lower polymer weight ratios. This excellent agreement between the solubility and dissolution rate experiments also provides strong evidence that the high energy form of the drug dictating the solubility value exhibited in these solubility experiments is identical to the form controlling the initial dissolution rates of tablets compressed from coprecipitated sulfathiazole at the lower polymer weight fractions (Fig. 2).

These conclusions infer that the amount of polymer at tablet surfaces (containing lower povidone weight fractions) is negligible during the dissolution rate experiments. This implication also can be justified by an alternative approach. Since these experiments showed that the presence of increasing concentration of polymer significantly increased the solubility of sulfathiazole, it would be reasonable to state that increasing the concentration of povidone at the tablet surface would also increase the apparent dissolution rate of the drug. Therefore, increasing the amount of povidone compressed in the tablet would be expected to increase the polymer concentration at the surface and thereby increase the apparent dissolution rate of the drug.

It is seen in Fig. 2, however, that the rates of solution of tablets containing low polymer weight fractions show the same rate of dissolution, despite an increasing weight fraction of povidone incorporated in the tablet. This finding strongly suggests that at low polymer weight fractions the concentration of polymer at the surface is indeed insignificant and that the drug is not present as, or interacting with polymer to form, a polymer complex, dispersion, *etc.*, at the tablet surface in these experiments. This reasoning lends further support to the concept of a pure drug layer existing during dissolution at the surface of tablets containing low povidone weight fractions.

Studies with Supercooled Melts—To investigate this possibility further, a supercooled melt of sulfathiazole was prepared. Sulfathiazole was melted on a hot stage at a controlled temperature to prevent charring, and then the melt was quickly frozen. This process produced a transparent solid which appeared to be in the "glassy state." This material was powdered, and an X-ray diffractogram of the powder was obtained. The diffraction pattern showed no evidence of crystallinity and suggested that the drug may be amorphous and may correspond to the high energy form of the drug present in the coprecipitate. Therefore, the apparent solubility of this form of sulfathiazole was determined as a function of the povidone concentration in solution (Fig. 5).

Although the resultant solubilities were higher than those obtained for the crystalline form I or form II, they were significantly lower than those obtained for the coprecipitate. This finding indicated that the specific form of the drug obtained in this way did not correspond to any of the previous forms encountered, including the high energy form found in the coprecipitate. Since the amorphous state is generally defined in terms of a lack of crystalline structure, it is possible to produce amorphous states containing varying degrees of structuring that are not crystalline. The lower solubility of the powder obtained by supercooling as compared with that of the coprecipitated drug implied that it contained a higher degree of structuring than the high energy form of the drug present in coprecipitates. Therefore, sulfathiazole may be highly structured in the molten state.

Mathematical Analysis of Solubility *versus* Polymer Concentration Curves—The solubility curves of the different forms found in Figs. 5–7 can be analyzed since they should all follow the following relationship:

$$S_t = \sum_{i=1}^{i=n} \sum_{j=0}^{j=m} K_{i,j} S_x^i \%_p^j \qquad \text{(Eq. 1)}$$

where S_t is the total apparent solubility of drug; S_x is the concentration of the free drug at equilibrium in the presence of excess solid for each form X of the drug; $\%_p$ is the percent povidone in so-

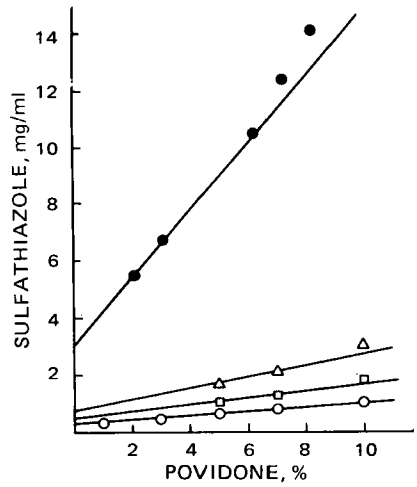

Figure 7—*Solubilities of different forms of sulfathiazole as a function of povidone concentrations in solution at 17°. Key:* ○, *sulfathiazole form I;* □, *sulfathiazole form II;* △, *supercooled melt of sulfathiazole; and* ●, *sulfathiazole–povidone coprecipitate.*

lution; i and j are the stoichiometry of the drug and polymer, respectively, in the complex; and K_{ij} is the corresponding stability constant. For a system limited to a 1:1 complex, Eq. 1 becomes:

$$S_t = S_x + K_{1,1}S_x\%_p \qquad \text{(Eq. 2)}$$

Equation 2 predicts that a straight line relationship will be obtained with an intercept of S_x and a slope of $K_{1,1}S_x$. Thus, the ratios of the intercepts obtained with two forms of sulfathiazole will be equal to the ratio of their respective slopes. Within experimental error, one sees that the curves for the different forms in Figs. 5 and 7 follow this relationship reasonably well and provide further evidence in support of the proposed relationships.

Dissolution Plots—Even though its magnitude is small (≈7%), it is worthwhile commenting on the possible reasons for the overshoot peak in the solubility curve for the high energy form shown in Fig. 3. There are a number of possible explanations but no definitive evidence. One explanation which may be applicable is the nonhomogeneity of the amorphous phase of sulfathiazole. Evidence presented in this report indicates that it is possible for an amorphous solid to have a varying degree of structure. It would not be unreasonable, therefore, to assume that a fraction of the coprecipitated drug may have less structure than the bulk of the amorphous solid. If this assumption is true, the less structured fractions would be expected to exhibit a higher solubility and dissolution rate. As a result, the less structured fractions would preferentially dissolve.

If the fraction of the less structured components initially present was sufficiently large and its dissolution rate sufficiently rapid relative to the more structured components, a slight oversaturation of the solution would result with respect to the more structured amorphous components remaining in the solid phase. This would cause the concentration in solution to overshoot the final controlling solubility. Needless to say, if this explanation is applicable, the range of degree of structuring initially present in the solid would only need to be small since the overshoot is very small.

It is also possible that the peak in the sulfathiazole concentration is due to different rates of solution of the polymer and drug. Figure 4 shows that the polymer exhibits a slower rate of equilibrium than the drug. If so, the polymer concentration at the surface of the solid particles would initially decrease at a slower rate than that of the drug. During this initial period, the higher polymer concentration at the surface of the solid would permit the drug, because of complexation, to continue dissolving despite the concentration of the bulk of the solution being at or above the saturation point. After this initial period, however, the polymer concentration at the surface would decrease to its bulk solution concentration, requiring that the excess drug return to the solid phase. If this explanation is true, the drug supersaturation is not sufficient for nucleation of new particles in the bulk. Since the overshoot shown in Fig. 3 is only of the order of 7%, one should not expect nucleation to occur in the presence of solid drug particles.

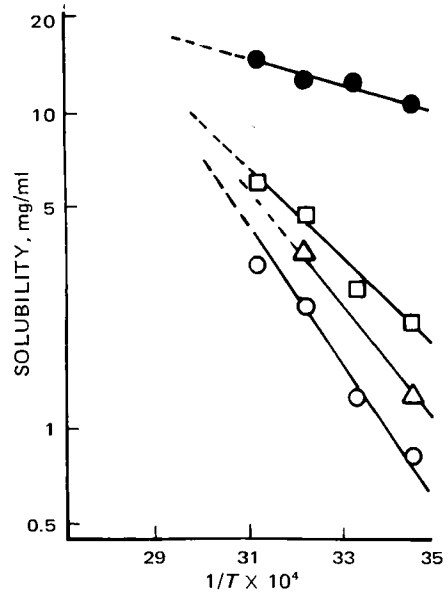

Figure 8—*Van't Hoff plots of the solubilities of the different forms of sulfathiazole in 7% povidone solution. Key:* ○, *sulfathiazole form I;* △, *sulfathiazole form II;* □, *supercooled melt of sulfathiazole; and* ●, *sulfathiazole–povidone coprecipitate.*

Thermodynamic Parameters—The reproducibility of these experiments suggests that further evidence regarding the form of the drug in the coprecipitate could be obtained by obtaining the thermodynamic parameters of the various forms. Therefore, the apparent solubility of the various forms of the drug as a function of the povidone in solution was determined as a function of the temperature. Figure 7 shows the results obtained at 17°. Plots similar to Figs. 5 and 7 were also obtained at 27 and 47°.

A van't Hoff plot of the sulfathiazole solubility was made for each percent povidone solution utilized. A typical plot is shown in Fig. 8. Although the plots yield apparently linear curves, permitting enthalpies to be calculated from their slopes, the enthalpies so obtained are difficult to interpret due to the large number of possible species involved. For this reason, it is difficult to extract from these data the enthalpy of the individual processes. Nevertheless, the linearity of all van't Hoff plots of the different forms of sulfathiazole in the different percent polymer solutions strongly indicates that these solubilities are not due to a chemical kinetic barrier existing between the solid and solution phases but are due to a balance of their chemical potentials.

Since all plots of solubility *versus* povidone concentrations were

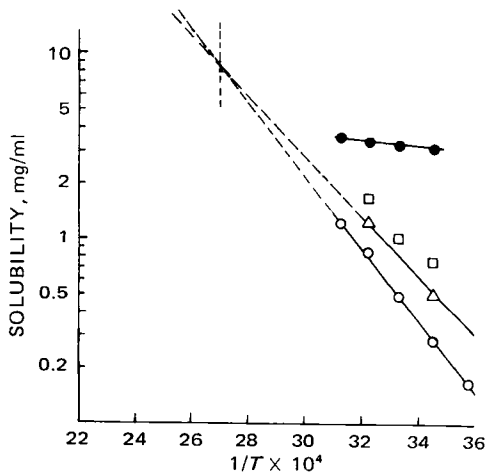

Figure 9—*Van't Hoff plots of the aqueous solubilities of the different forms of sulfathiazole obtained by extrapolation of solubility* versus *povidone concentration plots. Key:* ○, *sulfathiazole form I;* △, *sulfathiazole form II;* □, *supercooled melt of sulfathiazole; and* ●, *sulfathiazole–povidone coprecipitate.*

Table I—Free Energy Values Calculated for the Different Forms of Sulfathiazole Relative to the Crystalline Form I at 27°

Solid Form	S°_X/S°_I	$\Delta F^{27^{\circ}}_{I,X}$, cal/mole
Crystalline form II	1.70	316
Glassy state form	2.06	431
Coprecipitated form	6.60	1125

reasonably linear (*e.g.*, Figs. 5 and 7), one should be able to extrapolate the curves of 0% polymer to obtain the apparent solubility of the respective form of the drug in water at a particular temperature. These solubilities would then permit the thermodynamic parameters for each form of the drug to be obtained in the absence of polymer, without the complications due to the presence of complexes.

The equations needed to calculate the thermodynamic parameters can be obtained (15) by considering the following processes, $S_{\text{solid } I} \rightleftarrows S_{\text{solution}}$, and $S_{\text{solid } X} \rightleftarrows S_{\text{solution}}$. One can utilize the thermodynamic parameters obtained from solubility experiments to calculate the corresponding parameters for the two solids.

Free Energy—Since the ratio of the activities[9] of the solids are equal to the ratios of their respective solubilities (assuming that the activity coefficient in solution remains constant) at a given temperature, one can calculate the free energy for the different forms of sulfathiazole relative to the crystalline form I from:

$$\Delta F^{T}_{I,X} = RT \ln \frac{S^{\circ}_X}{S^{\circ}_I} \qquad \text{(Eq. 3)}$$

The calculated free energies for 27° are listed in Table I. The free energy of the coprecipitated drug is more than three times higher than that of the crystalline form I and justifies the term "high energy form" used previously to describe the form of the coprecipitated drug.

Enthalpy—The van't Hoff plot using the solubilities obtained by extrapolation to 0% polymer is shown in Fig. 9. As previously stated, the heat of solution for each form is calculable from this plot because only one species of sulfathiazole is involved in the solution phase. The enthalpies calculated from these slopes are given in Table II.

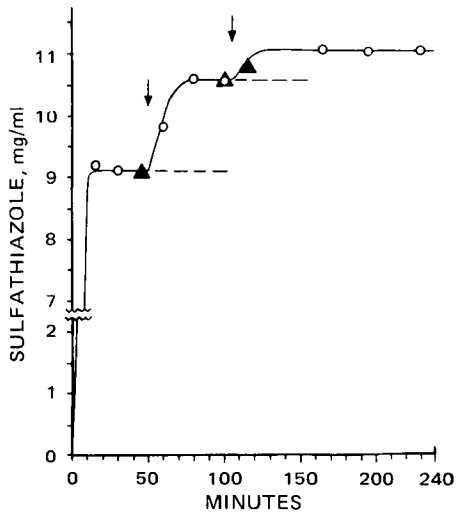

Figure 10—*Effect of incremental additions of 1% povidone to apparently equilibrated drug solutions in two different vials in the presence of excess coprecipitated drug. The time of each incremental addition of 1% polymer is indicated by an arrow. The concentration of povidone was initially 4%; it was increased to 5% after the first addition of polymer and finally was increased to 6% with the second addition. Key: —, observed sulfathiazole concentration as a function of time; - - -, expected curve if subsequent addition of povidone was not made;* ○, *vial A; and* ▲, *vial B.*

[9] If one follows the generally accepted convention for solids, this ratio should be referred to as the ratio of the fugacities rather than the activities. The authors, however, preferred the term activities in this context due to the more obvious extension of the relative properties of the solids to that of their saturated solutions such as rates of solutions and absorption.

Table II—Heats of Solution of the Various Forms of Sulfathiazole

Solid Form	Heat of Solution, cal/mole	Heat of Transition, cal/mole
Crystalline form I	9244	—
Crystalline form II	7626	1618
Glassy state form	5632	3612
Coprecipitated form	805	8439

Theoretically, the curves of the crystalline forms I and II should intersect at their transition temperature. For this reason, the curves in Fig. 9 were arbitrarily drawn through the experimental points so that the curves of forms I and II intersected at the transition temperature, which was previously reported (14) in the literature as 94.5°. Figure 9 shows that, despite this restriction, the agreement of the slopes of the drawn curves with the data points was excellent.

This result strongly indicates that the solubilities obtained by extrapolation are, in fact, thermodynamic values of the solubility in water for both forms. This viewpoint was supported by the fact that the solubility of the crystalline form I obtained by extrapolation to 0% polymer corresponds, as expected, to that obtained by direct measurement. The validity of the extrapolated solubility values of the crystalline form II cannot be tested directly due to its rapid reversion in the absence of povidone. It can be confirmed, however, by an indirect approach using the difference of the heat of solution of the two forms and comparing this value with the literature value determined by a different method.

The value of this difference was calculated from the heat of solution of the two forms determined from the slopes of their respective van't Hoff plots and found to be 1618 cal/mole, in excellent agreement with the previously reported value of 1744 cal/mole (14) obtained from dissolution rates in 95% alcohol. Surprisingly, the data obtained using the supercooled melt was relatively high and yielded 5632 cal/mole as the heat of solution. This relatively high enthalpy confirms the earlier postulation that the supercooled melt was highly structured. On the other hand, the heat of solution for the coprecipitated drug was unexpectedly small, only about 805 cal/mole. This finding indicates that the enthalpy of the coprecipitated drug is approximately 8 kcal/mole higher than that of the crystalline form I and is a clear indication of the lack of structure in the coprecipitated sulfathiazole.

These results are summarized in Table II. The large enthalpic differences between the crystalline and high energy forms shown in Table II strongly suggest that the higher solubility and dissolution rates of the high energy form may be due to the relatively small cohesive and adhesive forces present in the coprecipitated drug.

Entropy—The previous discussion suggests that the molecules of the coprecipitated sulfathiazole in the solid state are more random than those of the glassy state since it has less structure. Since entropy is a measure of the randomness of a system, the entropy difference between the crystalline form I and the other forms of sulfathiazole were calculated (Table III) using:

$$\Delta S_{I,X} = \frac{\Delta H_{I,X} - \Delta F_{I,X}}{T} \qquad \text{(Eq. 4)}$$

Table III confirms that the greater degree of randomness existing in the coprecipitated sulfathiazole (expressed as its entropy) relative to the other forms is indeed very high.

Reversibility of Coprecipitate Solubility System—The data

Table III—Entropy Values Calculated for the Different Forms of Sulfathiazole Relative to the Crystalline Form I at 27°

Solid Form	$\Delta S_{I,X}$, eu
Crystalline form II	4.3
Glassy state form	10.6
Coprecipitated form	24.4

strongly support the postulation that the solubilities reported in this article are equilibrium values. Nevertheless, the importance of future experiments dictated that this postulation should be put on as firm a base as possible. If these solubilities were the result of a kinetic barrier between phases, they would not be reversible. Not only would the opposite be true for two phases in equilibrium, but one of the best tests for equilibrium is to demonstrate the reversibility of the system.

Since the previous solubilities were determined from a solution in which the drug was previously at a higher concentration, it was only necessary to test the approach to the same equilibrium value from a lower concentration of drug in solution to establish reversibility. The solubility experiment shown in Fig. 3 was repeated. After apparent equilibration, more povidone was added. If a kinetic barrier was maintaining a supersaturated solution of drug, no effect on the apparent solubility of the drug should be observed due to the addition of more polymer. If, however, the concentration of drug in solution was due to an equilibrium process, the apparent solubility of the drug should increase with additional povidone as predicted by the previous data shown in Fig. 5.

The results of this experiment are shown in Fig. 10. The concentration of drug in solution did increase, and the coprecipitated drug dissolved rapidly until it reached a plateau. At this point, all of the polymer of the coprecipitate had dissolved, but part of the drug remained undissolved as a suspended solid. After the plateau was clearly established, a sufficient amount of pure povidone (*i.e.*, containing no drug) was added to increase its concentration from 4 to 5% polymer. As expected, the solubility of the drug was increased. After a plateau was established for a second time, 1% more povidone was again added. The concentration of sulfathiazole again increased until all of it dissolved to produce a crystal clear solution.

This result clearly demonstrated that the solubility value previously obtained was controlled by an equilibrium process and was not influenced by any kinetic factors. As expected, the values of the drug concentrations at the new equilibria after each addition of povidone corresponded closely to the solubility predicted by the solubility curve of the high energy form (Fig. 5) at the corresponding polymer concentration in solution.

CONCLUSIONS

A number of important points and conclusions should be emphasized regarding the results of this study involving high energy drug coprecipitates. The evidence presented strongly confirms the original postulate that the dissolution rate of tablets containing high energy drug coprecipitates at lower povidone weight fractions is controlled by a layer of solid drug on the tablet surface. It also adds credence to the postulate that when reversion occurs, the layer of high energy drug solid is replaced by a layer of the crystalline form of the drug.

These studies showed that a solution of an unstable form of a drug that is supersaturated with respect to a more stable form of the drug can be stabilized by the addition of a sufficient concentration of another agent. For sulfathiazole, this result was successfully accomplished by adding a sufficient concentration of povidone. In addition, these studies showed that higher concentrations of povidone were required to prevent nucleation as compared to the concentration of polymer required to inhibit crystal growth (13).

The applicability of high energy forms could be severely limited unless reliable methods are available for their identification and analysis. Melting points, IR absorption, differential thermal analysis, thermal gravimetric analysis, differential scanning calorimetry, and X-ray diffractograms often can be useful for this purpose.

If one is to utilize fully the potential of higher energy forms, however, one needs to characterize their solution behavior as well. The solubility and thermodynamic parameters can be useful for this purpose but often are not available due to instability of the solid phase. This study illustrated the use of a third component, povidone, which stabilized the higher energy forms of sulfathiazole in order to determine the solubility of the otherwise physically unstable higher energy forms of the drug. The effect of the stabilizing agent was eliminated by determining the solubility of the higher energy form as a function of the concentration of the stabilizing agent in solution. Extrapolation of the resultant curve to zero concentration of the stabilizing agent yields the desired solubility.

This study also provided strong evidence for the presence of an amorphous state of sulfathiazole as the controlling phase of both the solubility and dissolution rate experiments involving the high energy form which was obtained by coprecipitation with povidone. Other possibilities such as drug–polymer complexes, molecular or colloidal dispersions, and solid solutions are not controlling in these systems.

Although previous studies utilizing coprecipitates showed that higher dissolution rates could be obtained, it had not been shown that a higher solubility measured by the equilibrium method could be obtained. This study clearly demonstrated that high energy forms of a drug made by the coprecipitation technique can be used to provide metastable solutions of a drug which are significantly supersaturated with respect to the stable crystalline form. For sulfathiazole, this supersaturation ratio was approximately 3.8 at 37°.

Although higher dissolution rates are due to a higher solubility of the high energy forms involved, the implication that higher solubilities can also be achieved is not necessarily true. It can be easily shown that rapidly reverting systems of high energy forms can be successfully utilized to obtain faster dissolution rates, particularly from dissolving powders, but they may not show higher solubility values due to rapid reversion during equilibrium solubility studies. Needless to say, rapidly dissolving systems that revert can be used to obtain higher blood levels of poorly soluble drugs only if administered as a solid dosage form. Very often, a solid dosage form cannot be used. For this reason, effectively increasing the apparent solubility of many drugs could significantly increase their usefulness in therapeutic situations as compared to increasing only their dissolution rates.

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