Determination of Solubility of a Metastable Polymorph

By GEORGE MILOSOVICH

A method based on dissolution rate measurement was developed to obtain solubility data for rapidly reverting solid states. Experimental tests of the method showed it to be valid. Solubility and thermodynamic data for sulfathiazole II and I in 95 per cent alcohol were obtained. Other applications of the method are discussed.

RECENT LITERATURE reports (1–3) have demonstrated the feasibility of using metastable polymorphic crystal forms to improve the pharmacologic performance of drug compounds possessing low water solubility. Several drugs are presently marketed in their metastable polymorphic forms. Stability problems associated with such products have also been noted (1).

Both increase in drug absorption rate and physical instability are functions of the increased solubility of the metastable state. In order to study such systems it is advantageous to have solubility data on each solid state, preferably at several temperatures. Usual methods for solubility determination are not suitable for many polymorphic forms because reversion can occur during the time period necessary for the measurement. Such is the case for the phenacetin, diphenylsulfone, and sulfathiazole systems. Data reported by Higuchi and Shefter (4) on dissolution from solvate forms also show reversion occurring during the experimental time period, the concentration in solution passing through a maximum with time. It was the purpose of this investigation, therefore, to develop a method suitable for the determination of the solubility of metastable solid states that rapidly revert.

Because the relatively long experimental time required for an equilibrium solubility measurement increases the probability for nucleation and growth of more stable forms, it was felt that the desired data would have to be obtained in the shortest possible time period. Also, it is known that nucleation probability is a function of the size of the physical system, supersaturation increasing with decrease in volume of solution. These considerations suggested a procedure based on a measurement of dissolution rate since such data can be obtained in time periods less than 1 minute (5) with minimum volume of supersaturated solution due to the limited boundary region in contact with the dissolving solid.

Received June 3, 1963, from the College of Pharmacy, University of Michigan, Ann Arbor.

Accepted for publication August 7, 1963.

This study was partially supported by an equipment grant from the Horace H. Rackham School of Graduate Studies, University of Michigan, Ann Arbor.

Presented to the Scientific Section, A.PH.A., Miami Beach meeting, May 1963.

The Nernst equation (6) relates the rate of concentration increase to solubility for a dissolving solid

$$\frac{dC}{dt} = \frac{SD}{V\delta}(C_s - C_t) \qquad \text{(Eq. 1)}$$

where S is the area of the dissolving interface, D is the diffusion coefficient of the solute in the solvent, V is the volume of solvent, δ is the thickness of the diffusion layer, and C_s and C_t are concentrations at saturation and at time, t, respectively. Equation 1 reduces to

$$\frac{dW}{dt} = \frac{SD}{\delta} C_s \qquad \text{(Eq. 2)}$$

for the experimental condition that $C_s \gg C_t$ and V constant. Since D is a property of the solute molecule and the solvent, it is independent of solid-state form. S and δ can be maintained constant by suitable control of the experiment. If these conditions obtain, the rate of dissolution is directly proportional to solubility, and the solubility of higher energy states can be calculated from dissolution rate data and solubility data of the most stable form. Thus $dW/dt = KC_s$.

EXPERIMENTAL

Sulfathiazole U.S.P. was chosen as the model compound for use in this investigation. It can be obtained in at least two crystal forms, I melting at 174–175° and II melting at 200–201°. The II→I system is enantiotropic, I being the lower energy state at room temperature. Form I was obtained by slow recrystallization from warm alcohol. Form II was obtained by heating form I to 180° where form I melted and form II crystallized. The particle sizes of these states were reduced to approximately the same range by mortar and pestle. Normal solubility determinations showed both forms to have the same solubility, indicating that the higher energy state reverted to form I during the experiment. This was confirmed by X-ray diffraction measurements.

To conduct the dissolution rate experiments under conditions of constant surface area and constant δ the apparatus shown in Fig. 1 was built from aluminum and stainless steel. The sample holder was a $^3/_8$-in. hardened steel die obtained from a rotary tablet press. The surface of the die was ground to remove the tapered shoulder. The stirrer

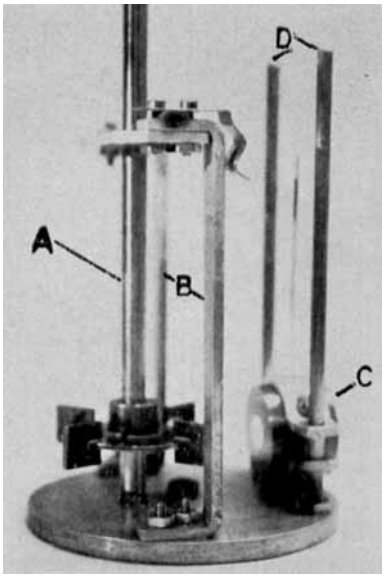

Fig. 1.—Apparatus used to determine dissolution rate under conditions of constant S and δ. Key: A, stirrer shaft; B, baffles; C, rotary tablet die and holder; and D, aluminum support rods for positioning the die.

was driven with a Bodine model B2246E-06 300 r.p.m. constant speed motor. Previous experiments using a variable speed motor showed 300 r.p.m. to be well within the range for diffusion control (a prerequisite for Eq. 2). The sample was prepared by compressing approximately 300 mg. of powder in the die between a $^3/_8$-in. punch and a hardened steel block using a Carver press. One surface of the formed tablet was flush with the die face, and the opening in the opposite face was corked. This procedure has the advantage over similar ones reported in the literature (7, 8) that a good tablet is not necessary so long as the surface is uniform. The apparatus was mounted in a 1-L. stainless steel beaker which was partially emersed in a constant temperature water bath. Dissolution was measured using the method of Niebergall and Goyan (5). Because of the limited surface available for dissolution, a "good" solvent was necessary so that sufficient sulfathiazole would dissolve in a short time period for assay. Ninety-five per cent v/v alcohol was chosen as the solvent for this study.

Since a rapid flow rate was desired, the solution was returned to the beaker to maintain the volume and agitation constant. At the beginning of an experiment, 500 ml. of solvent was added to the beaker, and the circulating pump was started. A 65-ml. quantity of solvent was contained in the pump and the flow lines to make the total volume 565 ml. The stirrer was started, and the temperature within the beaker was monitored until it became constant. At that time the recorder was balanced to 0 and 100% transmission; the sample was introduced by sliding the die holder down the two alignment rods. Figure 2 shows a typical recording obtained from these experiments. The per cent transmission data were converted to absorbance and then to concentration using a standard Beer-Lambert plot of known concentrations. Corrections were made for solvent expansion at temperatures above 25°.

RESULTS

Effect of Compression Pressure.—Dissolution data obtained from a tablet have meaning only if it is assumed that the tablet dissolves as though it were a single crystal. It was felt that if the dissolution rate from a tablet were independent of compression pressure this assumption would be valid. Figure 3 shows data obtained from a pressure series using lubricated (die walls swabbed with an ether solution of stearic acid) and unlubricated dies. While the lubricated die series showed the expected pressure independence, it is interesting to note the greater variation and apparent increase in dissolution rate with pressure for the unlubricated series. This latter effect will be reported in more detail in a future publication. In further support of the validity of using tablet surfaces for dissolution experiments, rate data were determined using tablets made from different particle sizes of sulfathiazole I. No size effect was observed. The conclusion was that as long as lubricated dies were used the tablet surface could be assumed to behave as a single crystal. Subsequent experiments were conducted with surfaces compressed under 21,000 p.s.i. pressure.

Effect of Solid State.—Dissolution rates were determined for each of the two crystal forms of sulfathiazole at six temperatures. Table I shows the data obtained from these experiments.

Figure 4 shows an absorbance *versus* time plot for form II at 29.8°. The change in slope occurring between 40–60 seconds demonstrates reversion of

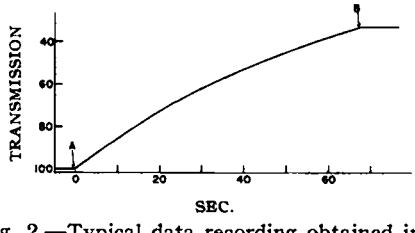

Fig. 2.—Typical data recording obtained in this study; form II, 48.8°C. Key: A, tablet added; B, tablet removed.

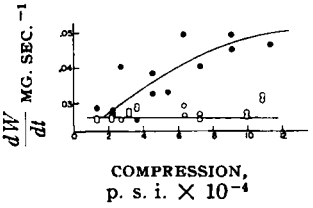

Fig. 3.—Effect of compression on dissolution rate of tablet surfaces. Key: ●, unlubricated die wall; ○, lubricated die wall.

TABLE I.—DISSOLUTION RATE AND SOLUBILITY DATA FOR SULFATHIAZOLE I AND II IN 95% ALCOHOL

Temp., °C.	Dissolution Rate, mg. cm.$^{-2}$ sec.$^{-1}$		Solubility, Gm./1000 Gm. Solvent	
	Form I	Form II	Form I	Form II
59.1	.185	.239	31.50	40.7
48.8	.102	.145	19.80	28.1
39.4	.0598	.0913	14.00	21.4
29.6	.0355	.0597	9.93	16.7
24.1	.0237	.0413	8.15	14.2
20.4	.0201	.0371	7.10	13.1
14.5	...	...	5.70	...

form II to form I, the ratio of the slopes being a measure of the ratio of solubilities for these two forms. This effect was not time reproducible and in most instances was not observed. It should be pointed out that this would be a function of nucleation and would not be expected to be reproducible. Also, experiments were terminated after 90 seconds for most runs, so that it would not be observed if it occurred beyond this time period. From this rapid and complete change in slope, it appeared highly probable that solid-state reversion occurred. Otherwise, an intermediate slope corresponding to an intermediate steady state concentration would have been expected over a longer time period.

Calculation of Solubilities.—The solubility of form I was determined at seven temperatures as follows. A large excess of form I powder was added to about 500 ml. of 95% alcohol in the beaker and was held at the desired temperature with stirring until equilibrium was obtained. Stirring was stopped, and samples were pipeted through glass wool to remove suspended particles. The samples were weighed and quantitatively diluted with 95% alcohol for spectrophotometric assay at 288 $m\mu$. Solubility data are given in Table I as grams dissolved per 1000 Gm. of solvent. Also included in Table I are the solubilities of the form II state calculated from the dissolution rate data. Figure 5 shows the van't Hoff plots for these data. Both plots deviate from linearity, showing an increasing negative slope with increase in temperature.

Test of Solubility Data.—Since the II→I system is enantiotropic, proper plotting of the solubility data should predict the transition temperature However, the van't Hoff plots were nonlinear and could not be extrapolated with accuracy. As was pointed out by Higuchi, *et al.* (3), if it is assumed that deviation from linearity is due mainly to solvent effects and Henry's law applies, then ratios of solubilities can be plotted in the same manner [log (solubility ratio) *versus* $1/T$] and the intersection at ratio = 1 would give the transition temperature. Figure 6 is such a plot for these data and predicts that the transition temperature is 94.5 ± 2.7°. That this predicted transition temperature is in the correct range was verified by equilibrating both forms in glycerin solution at 100° and at 90° on a Köfler hot stage. Figure 7 presents time photomicrographs showing the dissolution of I and growth of II at 100° and dissolution of II and growth of I at 90°.

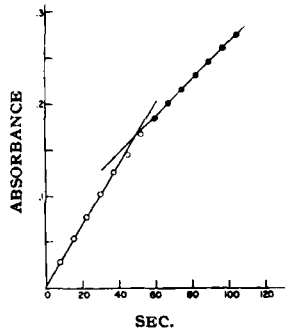

Fig. 4.—Dissolution of form II showing reversion to form I. Key: O, form II; ●, form I. 29.8°C.

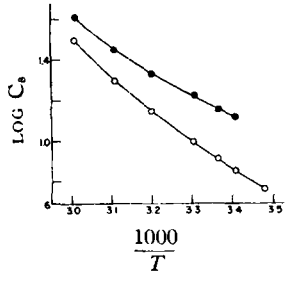

Fig. 5.—van't Hoff plots for sulfathiazole solid states. Key: O, form I; ●, form II.

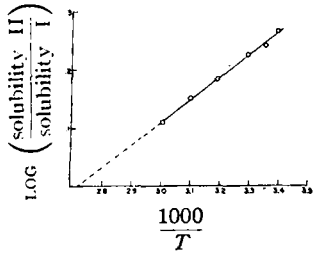

Fig. 6.—Plot of log solubility ratio against $1/T$. Transition temperature, 94.5±2.7°C.

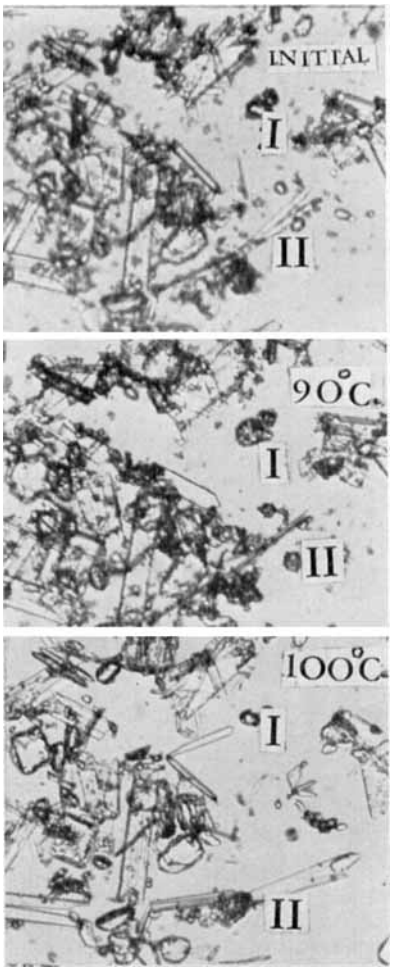

Fig. 7.—Photomicrographs showing reversion of II to I at 90°C. and I to II at 100°C. in glycerin suspension.

Thermodynamic Differences Between I and II.—The enthalpy and entropy differences between forms I and II can be calculated from the solubility data (3). The slope of the log (solubility ratio) *versus* $1/T$ plot was calculated to be 381.07. From this the enthalpy difference was calculated to be 1744 cal./

mole. This value along with the predicted transition temperature gave a value for the entropy difference equal to 4.75 e.u.

DISCUSSION

The method developed in this study to determine solubility of rapidly reverting polymorphic states was shown to work very well for sulfathiazole II. Even though the II→I reversion is rapid enough to preclude equilibrium measurement, it is sufficiently slow to allow use of this method. However, it is conceivable that reversions in other systems can be so rapid that this method will not be applicable. Thus, in systems where one form may be 10 times more soluble, the supersaturation obtained in the boundary layer may be such that instantaneous crystallization of less soluble forms will result.

The method has other applications. It can be used to measure rapidly the effect of nucleation and crystallization inhibitors in reverting systems. It can also be used for studying dissolution mechanism for systems that dissolve through acid-base reaction. It may also have value for studying the other factors influencing the dissolution process. More data will be forthcoming to test the general applicability of this method.

CONCLUSIONS

A method suitable for the rapid determination of solubility has been developed and used to obtain solubility and thermodynamic data for sulfathiazole II. The transition temperature predicted from these data was confirmed by an independent experiment.

REFERENCES

(1) Mullins, J. D., and Macek, T. J., THIS JOURNAL, **49**, 245(1960).
(2) Almirante, L., DeCarneri, I., and Coppi, G., *Farmaco Pavia Ed. Prat.*, **15**, 471(1960).
(3) Higuchi, W. I., Lau, P. K., Higuchi, T., and Shell, J. W., THIS JOURNAL, **52**, 150(1963).
(4) Higuchi, T., and Shefter, E., "Problems Related to Increasing Drug Solubility," Symposium, scientific Section, A.PH.A., Las Vegas meeting, 1962.
(5) Niebergall, P. J., and Goyan, J. E., THIS JOURNAL, **52**, 29(1963).
(6) Nernst, W., *Z. Physik. Chem. (Leipzig)*, **47**, 52(1904).
(7) Parrott, E. E., Wurster, D. E., and Higuchi, T., THIS JOURNAL, **44**, 269(1955).
(8) Nelson, E., *ibid.*, **46**, 607(1957).

Sustained-Release Aspirin Tablet Using an Insoluble Matrix

By MAHENDRA S. VORA, ARTHUR J. ZIMMER, and PAUL V. MANEY

The mode of administering drugs in a sustained-release form has recently assumed considerable importance in the pharmaceutical industry. Various resins, plastics, and polymers were investigated in this study. Polyvinyl chloride was selected as the base for the insoluble matrix. Evaluation of the sustained-release aspirin tablet was by *in vitro* and *in vivo* methods. Evidence is presented that the *in vivo* release rates provide a uniform blood level over a predictable period of time.

SUSTAINED-RELEASE tablets may provide the desired release rates by employing one of several techniques (1): (*a*) compressing coated pellets into a soft matrix, (*b*) mixing several granulations (each containing different retarding agents), (*c*) combining different layers of sustained-release granules, (*d*) forming an insoluble complex by ion-exchange methods, and (*e*) distributing medication in fatty bases. Oral sustained-action preparations are described in a Swedish patent (2) which outlines the use of synthetic resins and polymers for the purpose of imparting sustained-release properties to various drugs.

A comprehensive publication "Formulation and Experimental Evaluation of Oral Sustained Release Medication Based on the Principle of Delayed Diffusion," by Simoons (3), has recently been released. This paper advocates the use of several components to obtain the desired release rate.

A recent study by Levy (4) indicated that aspirin is rapidly absorbed from all parts of the gastrointestinal tract. Thus, aspirin can serve as an excellent tracer to assess the effect of certain formulation and dosage form characteristics upon absorption rate. It is understood that other drugs may give different results with these formulations.

Various *in vitro* methods for the evaluation of sustained-release products indicated that the use of radioisotopes could be of value (5). In this work an attempt was made to incorporate aspirin with the resin polyvinyl chloride, then to prepare a two-layer product—one layer to give immediate and the other time-delayed release.

The use of *in vitro* methods of testing by de-

Received May 16, 1963, from the St. Louis College of Pharmacy, St. Louis, Mo.
Accepted for publication August 29, 1963.
Abstracted from a thesis submitted by Mahendra S. Vora to the St. Louis College of Pharmacy, St. Louis, Mo., in partial fulfillment of Master of Science degree requirements.
The authors acknowledge the technical assistance of Z. Khatoon, M.D., City Hospital, St. Louis, Mo., and Mr. M. A. Ghafoor, St. Louis College of Pharmacy. The cooperation of volunteers, who served as test subjects in this study, is also acknowledged. The authors are grateful to Dr. B. A. Barnes of the St. Louis College of Pharmacy for the pharmacological and pathological examinations and interpretation.