Determination of the Degree of Crystallinity in Solid-Solid Equilibria

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Abstract □ A method based on dissolution rates was developed for estimating the ratio of crystalline drug to that dispersed at the molecular level within a carrier. In two diverse systems, it was shown that under appropriately chosen conditions, the dissolution rate of the drug was linearly related to its degree of crystallinity.

Keyphrases □ Crystallinity—solid-solid equilibria □ Polymorphic forms—indomethacin, sulfathiazole □ Indomethacin-PEG systems—dissolution rates □ Sulfathiazole-urea systems—dissolution rates □ Dissolution rates—surface area relationship

The use of solid solutions[1] and eutectic mixtures to effect an increase in the dissolution rate of sparingly soluble drugs has been described (1–5). Systems which form eutectic mixtures and true solid solutions may be characterized by their phase diagrams which, in the temperature regions of solid-liquid equilibria, can usually be determined by conventional techniques of thermal analysis (6). However, in the temperature regions below that of solid-liquid equilibria, the problem of analysis becomes more complex. It cannot be assumed that in the case of substances which form solid solutions, the composition of the solid solutions deposited from the fused mass remains unchanged in the solid state as the temperature is lowered (7). Since the region of solid-liquid equilibria is frequently well above normal temperatures, the nature of the solid phases which exist at room temperature may be quite different. Of course, the time required for the establishment of equilibrium may be, and for most systems probably is, quite substantial. However it is important to recognize that one may be dealing with an unstable, or at best, a metastable system. The question then arises as to how to determine phase changes within a solid matrix. Qualitatively, X-ray diffraction studies and microscopic examination may be fruitful. However, the latter cannot be used to quantitatively describe the system, and there appears to be some doubt as to the capabilities of X-ray analysis in this connection, particularly if the disperse phase is present at a low concentration.

Systems which supercool or those which exhibit a series of polymorphic changes do not lend themselves to accurate quantitative analysis, even in the temperature regions of solid-liquid equilibria, by conventional methods. A laborious "quenching method" has been described (8) for systems which exhibit excessive supercooling, but the nature of the solid phases at lower temperatures remains an enigma.

It is therefore sometimes difficult to decide whether a drug is distributed at the molecular level when the fused drug–carrier system is congealed and cooled to room temperature, or whether it is present in its normal solid state as a physical mixture with the carrier. This dilemma is more pronounced when the drug and carrier are mutually miscible in the fused state.

In this study, an attempt was made to develop methodology for determining the ratio of crystalline drug to that dispersed at the molecular level: (*a*) in a drug-polymer system which behaves as a supercooled liquid solution; and (*b*) in a drug-carrier system which apparently forms true solid solutions.

EXPERIMENTAL

The systems chosen for this study were indomethacin[2]–polyethylene glycol (PEG)[3] and sulfathiazole–urea.

Indomethacin–Polyethylene Glycol System—In this system, indomethacin was present at a 10% w/w concentration in PEG, both as a physical mixture (*A*) and as a supercooled liquid solution (*B*) which was a solid at room temperature. Mixture *A* was prepared by intimately blending finely powdered PEG 6000 with microatomized indomethacin, while Solution *B* was made by simply dissolving indomethacin in the fused polymer, congealing, and cooling to room temperature. Attempts to reduce *B* to a fine powder invariably resulted in some crystallization of indomethacin within the PEG matrix. Dissolution rates were measured from controlled surface areas of these preparations in distilled water at 25°. The dissolution apparatus used in this study is similar to that described by Milosovich (9) and is shown in Fig. 1. It consists of a tablet die holder machined so that it will fit securely to the base of a 2-l. stainless steel beaker. Four tablet dies may be mounted on the holder in fixed positions. The beaker is fitted with sleeves which serve as guides for positioning the die holder and which secure the positions of inlet and outlet for in-line spectrophotometric analysis. A pump[4] was used to circulate the 750 ml. of solvent through the spectrophotometer at a fixed rate of 400 ml. min.$^{-1}$ and the amount of drug dissolved was recorded[5] automatically as a function of time. The system was agitated by a 200-r.p.m., 3-blade impeller, centrally mounted so that the blades were opposite the surfaces being examined.

Smooth surfaces of Preparation *A* were made in a 0.95-cm. ($^3/_8$-in.) tablet die in accordance with the procedure developed by Milosovich (9). However, since the powder was self-lubricating, the die walls were not pretreated. A pressure of 50,000 p.s.i. was found satisfactory for the production of a uniform surface. Under higher pressures the die tended to "ride" up the punch.

Smooth surfaces of Preparation *B*, the "solid solution" of indomethacin in PEG, were prepared by congealing the fused material in a 0.95-cm. ($^3/_8$-in.) tablet die. Each die was stoppered on one end and sufficient molten material introduced so that an excess existed. Immediately prior to a determination, the excess was sliced away with a razor blade to give a smooth, uniform surface.

Initially, the dissolution rate of indomethacin from these preparations was measued as a function of their surface areas exposed to the solvent. This was accomplished by studying the dissolution of indomethacin from one, two, three, and four dies containing a particular preparation and using a corresponding number of blank dies to maintain the hydrodynamics of the system constant (for all intents and purposes).

[1] The term "solid solution" is used loosely in this paper to describe any solid system in which one component is dispersed at the molecular level within another.

[2] Indocin, Merck & Co., Inc., Rahway, N. J.
[3] Carbowax, Union Carbide Corp., New York, N. Y.
[4] Ministaltic, Manostat Corp., New York, N. Y.
[5] Atomic Accessories Inc., Valley Stream, N. Y.

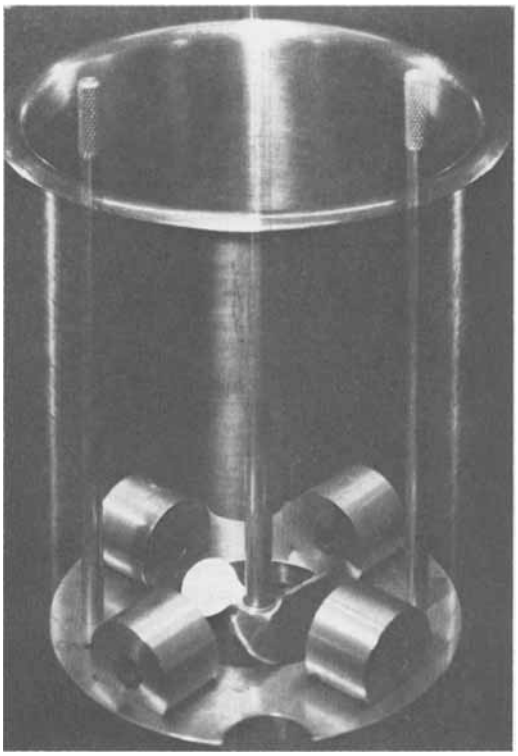

Figure 1—*Dissolution apparatus.*

Information on the dissolution behavior of surfaces corresponding to 75% *A*, 25% *B*; 50% *A*, 50% *B*; and 25% *A*, 75% *B* was obtained by subjecting all remaining combinations of these preparations to the test. For example, for 75 %*A*, 25% *B*, three dies containing Preparation *A* and one containing Preparation *B* were placed in the die holder and tested.

Sulfathiazole–Urea System—In this system, previously described by Sekiguchi and Obi (1) and by Goldberg *et al.* (3), sulfathiazole was present in urea both as a 5% w/w physical mixture (*C*) and as a 5% w/w solid solution (*D*). Preparation *C* was made by reducing urea to a fine powder and intimately mixing it with sulfathiazole. *D* was prepared by dissolving sulfathiazole in fused urea on a sand bath, congealing the solution, and pulverizing.

The experiments described for the indomethacin–PEG system were then performed; however, die walls were lubricated with a 1% solution of stearic acid in methylene chloride and smooth surfaces of *C* and *D* were made under a pressure of 80,000 p.s.i. An additional impeller, identical to the first and spaced 2.54 cm. (1 in.) above it on a common shaft, was used.

Since in this system, the solid solution *D* could be pulverized, apparently without inducing crystallization of sulfathiazole, it was possible to physically mix Preparations *C* and *D* so that additional data could be obtained when they were in intimate contact with each other, as opposed to being in separate dies. Thus physical mixtures of *C* and *D* were prepared to correspond to the degrees of crystallinity of sulfathiazole obtained by using combinations of these preparations in separate dies.

RESULTS

General—As has been previously observed with this type of apparatus (10), plots of amount of drug dissolved *versus* time were linear in the region where the concentration of drug in the bulk solution was much lower than its equilibrium solubility. Dissolution rates could therefore be obtained directly from the recorder chart paper as absorbance units $min.^{-1}$ and transformed to concentration $min.^{-1}$ using the appropriate predetermined *a*.

Indomethacin–PEG System—The data shown in Fig. 2 represent the dissolution rate of Preparation *A* as a function of its surface area. Some difficulty was experienced in reproducing these data. Since the rate was rather slow, it was felt that most of the error was due to recorder drift. Also shown in Fig. 2 is a similar plot for

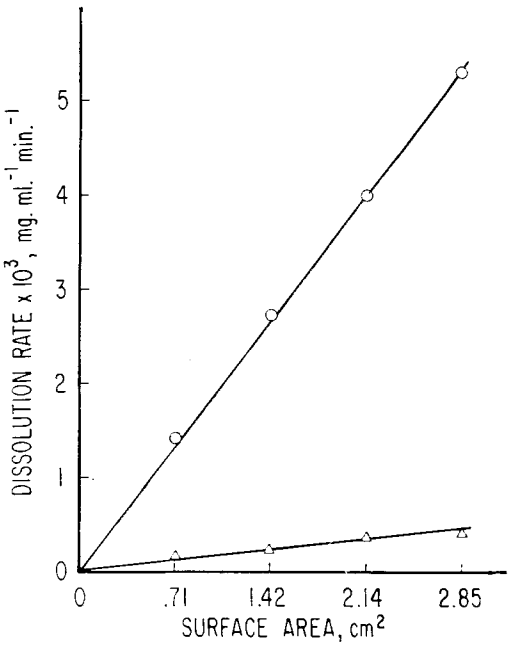

Figure 2—*Dissolution rate of indomethacin* versus *surface area of system. Key:* △, *Preparation* A; ○, *Preparation* B.

Preparation *B*, and it confirms that under the test conditions, *B* obeys the well known relationship:

$$\text{Rate} = kS, \qquad \text{(Eq. 1)}$$

where *S* is the surface area exposed to solvent action and *k* is a proportionality constant involving the hydrodynamics of the system and the equilibrium solubility of the compound being measured. From Fig. 3 it is evident that the nature of the total surface area exposed to the solvent is linearly related to the observed dissolution rate. From these data it is a simple matter to write the equation expressing the dissolution rate of "unknowns" as a function of the degree of crystallinity of the drug within the carrier.

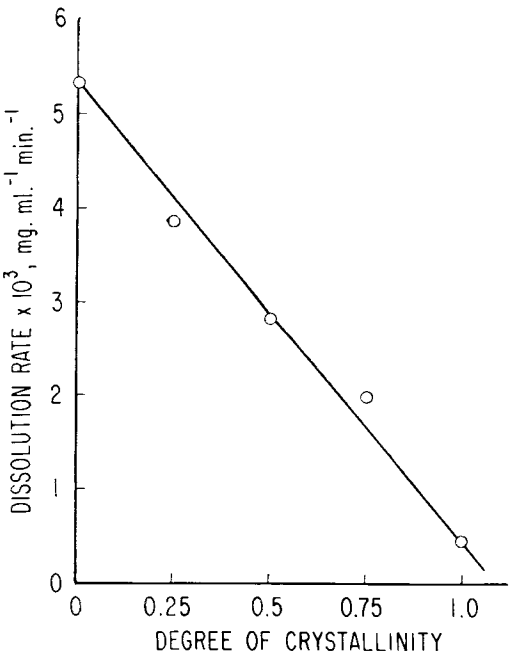

Figure 3—*Dissolution rate* versus *degree of crystallinity of indomethacin in indomethacin–PEG system.*

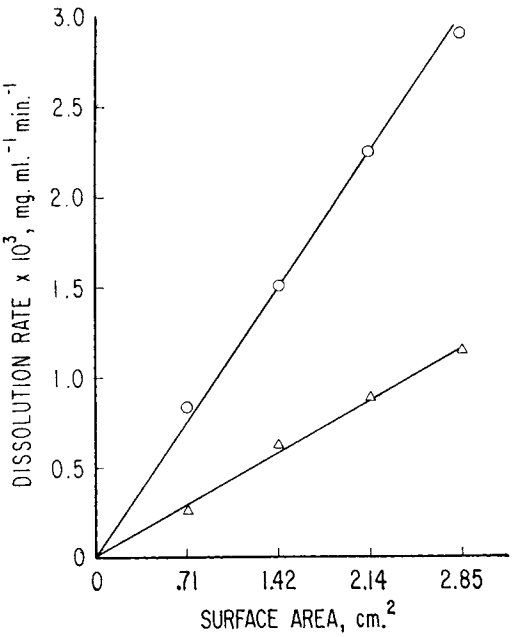

Figure 4—*Dissolution rate of sulfathiazole* versus *surface area of system. Key:* △, *Preparation* C; ○, *Preparation D.*

Sulfathiazole–Urea System—Preparations *C* and *D* were also shown to obey Eq. 1 under the test conditions (Fig. 4). Figure 5 shows the linear relationship of the nature of the surface being tested to the observed dissolution rate, determined by using combinations of the prepared surfaces in separate dies. Also shown in Fig. 5 are the data obtained when *C* and *D* were intimately mixed in corresponding ratios, compressed, and subjected to the test.

DISCUSSION

Indomethacin occurs as two crystalline polymorphs, arbitrarily designated as Form I and Form II, which melt at 160 and 154°, respectively. The fused drug will supercool in the absence of nuclei to a brittle amorphous mass which melts at about 67°.

Preparation *B*, a potential candidate for a dosage form, could be qualitatively characterized by polarized light microscopy and X-ray analysis. Slow crystallization of indomethacin in this system

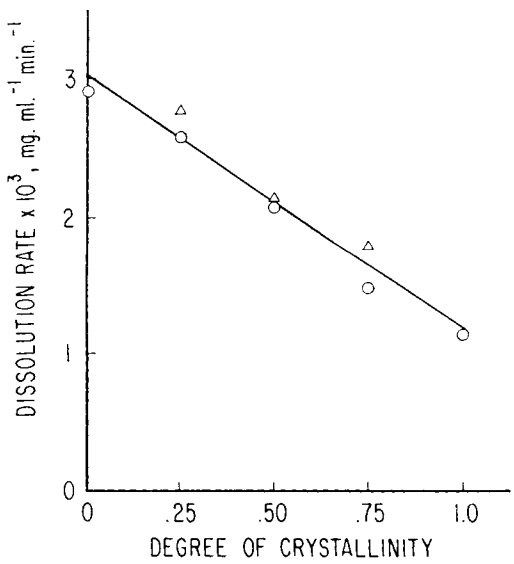

Figure 5—*Dissolution rate* versus *degree of crystallinity of sulfathiazole in sulfathiazole–urea system. Key:* ○, *separate dies;* △, *premixed.*

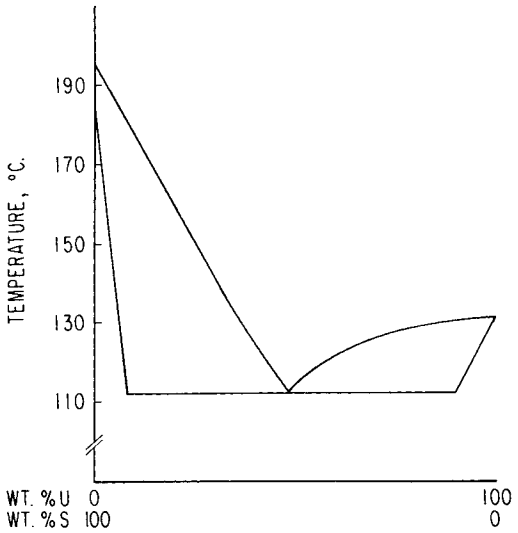

Figure 6—*Phase diagram for sulfathiazole–urea system. Key: U, urea; S, sulfathiazole (from* References *1 and 3).*

manifested itself as an opacity or "bloom" which adversely affected the aesthetic quality of the product and might possibly have had more far-reaching ramifications in its biological activity. Because of excessive supercooling, it was not possible to determine the temperature-composition relationship for this system, even in the region of solid-liquid equilibria, by conventional thermal analysis. The procedures described in this study made it possible to quantitatively determine the extent to which crystallization had taken place in the system.

X-ray studies indicate that indomethacin crystallizes from PEG solution as the lower melting polymorph, Form II. It was shown that Form II did not revert to Form I during preparation and compression of the physical mixture with PEG, and the two polymorphs were indistinguishable in the dissolution test. In order to ensure that all of the indomethacin was dispersed at the molecular level in *B*, the preparation was subjected to the test at various time intervals after congealing. The striking reproducibility of the data up to approximately 1 hr. after solidification, provided sufficient evidence to support this fact.

As already mentioned, it was not possible to test intimately mixed *A* and *B* in known ratios, in order to provide a more realistic model to correspond to "unknowns." In such a model it is probable that indomethacin from the rapidly dissolving system *B* could be redeposited on the crystalline drug in *A*. In order to investigate this possibility and to determine the general applicability of the method, the sulfathiazole-urea system was chosen for further study. The phase diagram for this system as illustrated first by Sekiguchi (1) and as reproduced by Goldberg *et al.* (3), is shown in Fig. 6. It is evident that apart from the eutectic composition, little can be said about the nature of the solid phases present below about 112°. Since it is not valid to assume, *a priori*, that the solid solutions which are deposited from the fused mass remain unchanged as the temperature is decreased (7), how can one be reasonably sure that all or at least part of the sulfathiazole is present as a molecular dispersion in urea at room temperature? Upon initial cooling to lower temperatures it seems reasonable that the sulfathiazole would remain in solution, even if the phase diagram dictated the contrary, since one can hardly conceive of diffusional processes in solid systems as being anything but slow. However, it is important to recognize that the equilibrium situation may be quite different and to appreciate the approach to equilibrium.

In the sulfathiazole–urea system, a 5% w/w level was chosen so that, at least initially, all of the sulfathiazole would be in solid solution in Preparation *D*. This was substantiated by repeated dissolution tests at various intervals after solidification. The reproducibility of the data suggests the absence of crystallization of sulfathiazole. Since it was possible to pulverize *D* and blend it with *C*, a more realistic model was used in constructing the dissolution rate *versus* degree of crystallinity curve. It can be seen from Fig. 5 that little or no interaction results from this blending and these data may be used to estimate the degree of crystallinity in "unknowns"

of the same chemical composition as the model system. Of course, if the drug being investigated exists as different polymorphs, and these are sufficiently different energetically, it is important to identify the crystal form which may separate from solid solution and to use this polymorph in constructing the standard curve.

CONCLUSIONS

Although the method developed in this study has its obvious drawbacks and limitations, it has been shown to be useful for estimating the degree of crystallinity in two diverse systems of known chemical composition. In the design of these experiments, it was necessary to choose conditions under which (*a*) the observed dissolution rate was directly proportional to the surface area and (*b*) a reasonably large difference existed between the dissolution rate of the physical mixtures and their corresponding solid solutions. In the case of the indomethacin–PEG system, for example, 0.01 *M*, pH 7.2 phosphate buffer could not be used since this difference was small and could easily lead to erroneous results. Data published by Goldberg *et al.* (4) appears to substantiate the usefulness of the method. Studying the dissolution characteristics of a griseofulvin–succinic acid system they reported, "Although it may be fortuitous, the eutectic mixture which consists of 60% solid solution shows a rate at 3 min. which is just 60% that of the solid solution." This result is not surprising in view of the fact that the dissolution rate of the physical mixture is much slower than that of the solid solution.

Various other applications of the method come to mind. It may be interesting to determine the dissolution rate of drug-carrier systems which form solid solutions as a function of drug concentration. In this way it may be possible to use this technique to construct phase diagrams in regions of solid-solid equilibria. It is expected that more data will be forthcoming when this and other applications have been investigated.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 22, 1968, from *Merck Sharp and Dohme Research Laboratories, West Point, PA 19486*

Accepted for publication April 22, 1969.

The technical assistance of Mr. Thomas Burton is gratefully acknowledged.

5(or 4)-[3,3-Bis(2-chloroethyl)-1-triazeno]imidazole-4(or 5)-carboxamide: A Titrimetric Determination of Its *v*-Triazolinium Transformation Product and Studies of Its Stability

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Abstract □ The transformation product, a *v*-triazolinium salt, of 5(or 4)-[3,3-bis(2-chloroethyl)-1-triazeno]imidazole-4(or 5)-carboxamide (I, NSC-82196) is sufficiently acidic to be titrated with standard base. Titrations of typical specimens of the triazene (I) indicate that they contain 2.5–4.2% of the transformation product. The titration method was used to estimate the rate of change of I to its transformation product in methanol and aqueous methanol solutions; for example, in 60% methanol at 25° the half-life of I is estimated to be about 25 min.

Keyphrases □ Triazenoimidazoles □ *v*-Triazolinium salts—analysis □ 5(or 4)-[3,3-Bis(2-chloroethyl)-1-triazeno]imidazole-4(or 5)-carboxamide—stability □ Titrimetry—analysis □ IR spectrophotometry—identity

5(or 4)-[3,3-Bis(2-chloroethyl)-1-triazeno]imidazole-4-(or 5)-carboxamide (I, NSC-82196) has demonstrated interesting antineoplastic activity in animal tumor systems (1–4). The triazene undergoes a change in solution and, very slowly, in the solid state at room temperature to a transformation product (II) containing ionic chloride (1, 5). A *v*-triazolinium salt structure (6) was considered (1, 5) to be one of the likely candidates for the structure of II, and this structure has recently been assigned to II on the basis of an X-ray crystal structure analysis[1] (7). Once a pure specimen of II had been obtained, the quality of specimens of the triazene (I) could be estimated qualitatively from distinctive differences in the IR spectra of I and II (5). A titrimetric method for the determination of II—and, indirectly, of I—is now reported together with additional information on the stability of the triazene (I). A colorimetric (10) and a microbiological (11) method of assaying I were recently reported. The possible formation of II from I was not mentioned in those reports, and it is not clear whether the material being assayed was I, II, or a mixture.

[1] Good chemical evidence for the formation of *v*-triazolinium salts in the benzenoid series has been reported by Mohr and Hertel (6). This type of structure has also been assigned (8, 9) to other phenyl derivatives, but evidence that would distinguish the *v*-triazolinium structure from alternative structures was not presented.