Phase Diagram and Dissolution-Rate Studies on Sulfathiazole–Urea Solid Dispersions

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Abstract □ The phase diagram of the sulfathiazole–urea binary system was determined from the physical mixtures of sulfathiazole Form I–urea and sulfathiazole Form II–urea through differential thermal analysis (DTA) and conventional capillary tube methods. The eutectic temperature and the final melting points were found to be different for the two polymorphic systems. The mutual solid solubilities in solid dispersion forms were confirmed by DTA and X-ray diffraction methods. The characteristics of DTA thermogram, X-ray diffraction spectrum, and *in vitro* dissolution rates of the eutectic mixture containing 52% (w/w) of sulfathiazole were found to change with aging. This may have a significant effect on the clinical application of sulfathiazole. The dissolution rates of sulfathiazole in solid solutions of urea were found to be extremely fast, over 700 times higher than the pure compound.

Keyphrases □ Sulfathiazole–urea solid dispersions—phase diagrams, *in vitro* dissolution rates, aging effect □ Urea–sulfathiazole solid dispersions—phase diagrams, *in vitro* dissolution rates, aging effect □ X-ray diffraction—monitoring, aging sulfathiazole–urea solid dispersions □ Differential thermal analysis—monitoring, aging sulfathiazole–urea solid dispersions

The historical background, classifications, and pharmaceutical applications of solid dispersion systems were thoroughly reviewed by Chiou and Riegelman (1). The application to increase rates of dissolution and GI absorption of poorly water-soluble drugs was first introduced in 1961 by Sekiguchi and Obi (2). They showed a faster and more complete absorption of sulfathiazole in man when it was administered as a eutectic mixture with a water-soluble and physiologically inert carrier, urea. The eutectic mixture contained 52% (w/w) of sulfathiazole and 48% (w/w) of urea. The enhancement of the absorption was attributed primarily to the achievement of crystal size reduction of sulfathiazole in the eutectic mixture. After reexamining the phase diagram reported by Sekiguchi and Obi (2), Goldberg *et al.* (3) found that there existed a limited solid solution formation in both extremes of the phase diagram. Since, in a solid solution, the particle size of the solute will be reduced to its minimum state (*i.e.*, at the molecular level), they proposed that the existence of the solid solutions, rather than the reduced crystal size in the eutectic mixture, was the primary factor in producing enhanced dissolution and GI absorption of sulfathiazole.

In an excellent review article on the pharmaceutical applications of polymorphism, Haleblian and McCrone (4) pointed out that different polymorphs in a given system may result in isomorphous solid solutions, eutectics, or molecular addition compounds. Since sulfathiazole has been known to exist at least in two polymorphic forms, such as Forms I and II (5–10), it is logical to expect that the phase diagram of sulfathiazole–urea binary system may not be as simple as reported previously. This article conveys the results of such investigations. Attention was also directed to the effect of aging on the dissolution rate of sulfathiazole from the eutectic mixture. This aspect may be of extreme importance in the evaluation of potential solid dispersion dosage forms. The possible effects of aging on physicochemical properties of solid dispersion dosage forms were extensively reviewed (1). The *in vitro* dissolution rates of sulfathiazole in solid solutions and other possible mechanisms of dissolution enhancement from solid dispersion systems are also discussed.

EXPERIMENTAL

Materials—Form I[1] of sulfathiazole was confirmed by the X-ray diffraction spectrum (8, 9) and differential thermal analysis (DTA) (7, 10). Form II of sulfathiazole was obtained by heating sulfathiazole Form I to 180° (7), and the complete conversion to Form II was confirmed by the same methods (7–10). Both forms of sulfathiazole showed a melting range from 201 to 203°. The resolidified fused urea was prepared by carefully melting the pure urea[2] (m.p. 133–136°) in an oil bath and pouring the melt onto a stainless steel plate to induce rapid solidification. The resolidified fused urea has a melting range from 129 to 136°. The major portion of the X-ray diffraction spectrum was found to be essentially the same as that of the untreated urea.

Solid dispersions of the sulfathiazole–urea system were prepared by employing the fusion method (11). The concentration of sulfathiazole in the physical mixtures and the solid dispersions was confirmed by assaying the preparations spectrophotometrically at 227 nm., using a Beckman DBG spectrophotometer. The presence of urea does not show any interference in this range.

Thermal Analyses—The DuPont 900 thermal analyzer[3], attached with a standard DTA cell (500° model), was used for DTA studies. The samples were placed in microcapillary tubes and heated at a constant rate of either 5 or 10°/min., using glass beads as the reference material. The two different rates gave almost identical thermograms. The instrument was calibrated against two standard compounds, acetanilide (m.p. 115°) and sulfapyridine (m.p. 192°), supplied by the manufacturer of the instrument. In addition to the DTA analysis, the conventional capillary tube method, using a Thomas-Hoover capillary melting-point apparatus[4], was employed to study the thaw-melt points of certain samples.

X-Ray Diffraction Studies—Samples for X-ray diffraction studies were prepared as follows. A thin rectangular metal plate (28 × 70 × 2 mm.), with a cavity of 20 × 10-mm. dimension, was placed over a glass slide; the fine powder of the sample was packed fully and firmly into the cavity. The sample was then covered firmly with another glass slide, which was fastened to the metal plate with adhesive tape. The plate was reversed, the glass slide base was removed, and the flat surface of the sample was exposed for the diffraction study using a Norelco X-ray diffractometer[5]. All diffraction spectra were run at 2°/min. in terms of a 2θ angle.

Dissolution-Rate Studies—Unless otherwise specified, the dissolution studies were carried out on powdered samples, equivalent to 15 mg. of sulfathiazole, in 500 ml. of water in a 600-ml. water-

[1] Sulfathiazole, Eli Lilly & Co., Indianapolis, Ind.
[2] Urea NF, purified from methanol, J. T. Baker Chemical Co., Phillipsburg, N. J.
[3] E. I. duPont de Nemours & Co., Wilmington, DE 19898
[4] Arthur H. Thomas Co., Philadelphia, Pa.
[5] Philip Electronic Instrument Co.

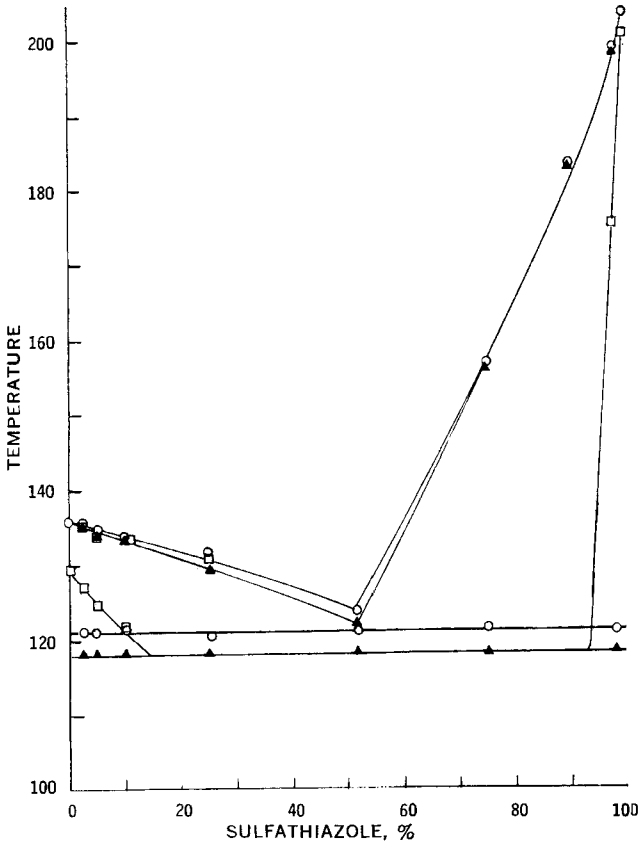

Figure 1—*Phase diagrams of the sulfathiazole–urea binary system determined from different mixtures. Key: ▲, sulfathiazole Form I–urea physical mixture; ○, sulfathiazole Form II–urea physical mixture; and □, solid dispersion.*

jacketed beaker being kept at 37°. A stirring rate of 60 r.p.m. and a recirculating flow rate of 70 ml./min. were employed (12). The dissolution rates of sulfathiazole were calculated from direct measurements of absorbance of the solution at 227 nm. All samples were run at least in duplicate. Highly reproducible results were obtained throughout the studies.

RESULTS AND DISCUSSION

Phase Diagram Determination from Physical Mixtures—It is regrettable that the methods of sample preparation and thaw-melt point determination were not clearly stated in the original article of Sekiguchi and Obi (2) for the construction of their phase diagrams. Phase diagrams erected from data on physical mixtures obtained through thermal analysis were often found to correlate well with those determined from the fused or evaporated mixtures (13, 14). The phase diagrams for the two polymorphic forms of sulfathiazole determined from homogeneous physical mixtures with nonfused urea are shown in Fig. 1. The thaw points were determined from DTA thermograms, since the DTA instruments are generally thought to be more sensitive and objective than the visual capillary tube method in detecting the beginning of melting (*i.e.*, thawing point) of a small fraction of a sample (15–17). The final melting points were, however, determined from both the DTA and capillary tube methods.

DTA thermograms may show some ambiguity as to the final melting range of certain samples. In such instances, the melting points determined from the capillary tube method were used to construct the phase diagrams.

As shown in Fig. 1, there are indeed some differences between the phase diagrams of two polymorphic forms. The eutectic temperature for sulfathiazole Form I–urea system is 118°, which is in good agreement with the previously reported data (2). The eutectic temperature for sulfathiazole Form II–urea system is, however, 3° higher than that of the Form I system. The final melting points of the eutectic mixture (52% sulfathiazole) determined from DTA thermograms are also higher by 2° for the sulfathiazole Form II–urea system. The differences of the melting points become smaller as the concentration of sulfathiazole decreases. The differences become almost negligible when the samples contain more than 75% of sulfathiazole. This may be due primarily to the transition of sulfathiazole from Form I to Form II at higher temperatures (around 150°), thus eliminating the original polymorphic difference of sulfathiazole.

Although there actually exists some degree of mutual solid solubilities in this binary system, samples of physical mixtures containing from 1 to 98% sulfathiazole showed their thaw points starting at the eutectic temperature. On the basis of the studies on the physical mixtures alone, this binary system may be mistakenly considered as a simple eutectic mixture with negligible solid solubilities. The DTA thermograms of 5% sulfathiazole–95% urea physical mixtures are shown in Fig. 2.

Phase Diagram Determination from Solid Dispersions—The DTA thermograms of 2.5 and 5% sulfathiazole solid dispersions (Fig. 2) show that the samples started to thaw at temperatures higher than the eutectic temperatures. This is indicative of solid solution formation (16). The solid solution formation in these samples is further

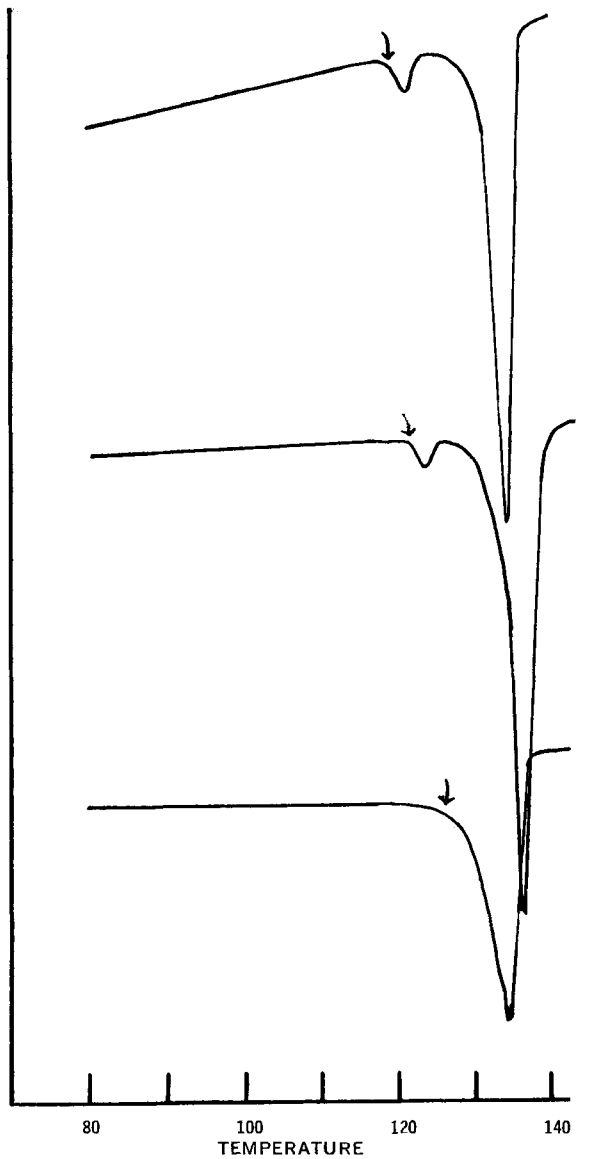

Figure 2—*DTA thermograms of various 5% sulfathiazole–95% urea systems. Different thaw points are indicated by the arrows. Key: top thermogram, sulfathiazole Form I–urea physical mixture; middle thermogram, sulfathiazole Form II–urea physical mixture; and bottom thermogram, solid dispersion.*

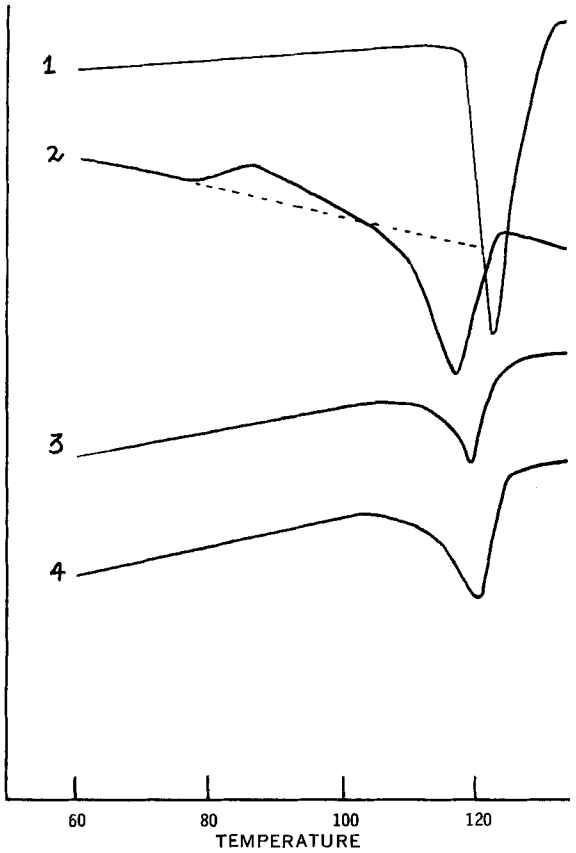

Figure 3—*DTA thermograms of the sulfathiazole–urea system with eutectic composition (52% sulfathiazole–48% urea). Key: 1, physical mixture of sulfathiazole Form I–urea; 2, freshly prepared solid dispersion (melting method); 3, solid dispersion kept at ambient temperature for 1 week; and 4, solid dispersion kept at ambient temperature for 2 months.*

substantiated by the absence of sulfathiazole X-ray diffraction peaks in their diffraction spectra.

As shown in Fig. 1, the extent of the maximum solid solution formation of sulfathiazole in urea depends on the type of polymorphic form of sulfathiazole precipitated from the solid solution. By intersecting the solidus line with the two eutectic isothermal lines, one can calculate that the solubility of sulfathiazole in the binary system will be 10% (w/w) at 121°, when the sulfathiazole Form II precipitates, and 15% (w/w) at 118°, when the sulfathiazole Form I precipitates. The solid solubility of sulfathiazole in urea at the eutectic temperature was previously reported to be 10% (w/w); that of urea in sulfathiazole was reported to be around 8% (w/w) (3).

Solid dispersions containing more than 80% (w/w) of sulfathiazole, prepared by the melting method, were intensively discolored (light to dark brown) and somewhat soft and sticky. This may be due to the thermal decomposition of sulfathiazole at higher temperatures. Obviously, these samples could not be used to obtain the pertinent data. Such a problem has not been reported previously in the literature. An alternative solvent method was then used to prepare intimately mixed mixtures. Generally speaking, a common solvent is preferred to dissolve the two solid components initially, followed by the evaporation of the solvent (18). It is, however, difficult to find a truly common solvent because of the extreme difference in solubility properties between the polar urea and nonpolar sulfathiazole. Nevertheless, absolute ethanol was chosen as a solvent, although solubilities of the two components were about 20 times different in this solvent (19). The sample of 98% sulfathiazole–2% urea solid dispersion prepared by the solvent method did show, indeed, on the DTA thermogram the thaw point higher than the eutectic temperature. The extrapolated solubilities of urea in both polymorphic forms of sulfathiazole at the eutectic temperatures were found to be around 7% (Fig. 1). This value is in good agreement with the previously reported figures. Ironically, 96% sulfathiazole–4% urea solid dispersion prepared by the same solvent method showed a eutectic peak on the DTA thermogram. This is due to the independent crystallization of both components from the nonideal solvent. Theoretically, the two components should crystallize simultaneously as mixed crystals if they form a solid solution (1, 18).

The DTA thermograms of 25, 52, and 75% sulfathiazole solid dispersions prepared by the fusion method (in the case of 75% sulfathiazole solid dispersion, the DTA rerun of its physical mixture was used) show irregular and lower thaw points ranging from 90 to 110°. Furthermore, the thermal properties of these samples were found to change after aging. Typical DTA thermograms of the 52% sulfathiazole (eutectic composition) solid dispersion are shown in Fig. 3. The X-ray diffractometry was employed subsequently to reveal this peculiarity. As shown in Fig. 4, the diffraction spectrum of the freshly prepared 52% sulfathiazole solid dispersion contains none of the diffraction peaks of sulfathiazole but only those of the resolidified fused urea. The complete absence of any sulfathiazole diffraction peaks may be due to the presence of sulfathiazole in an amorphous form (more correctly, the glass solution of urea in sulfathiazole) or in extremely fine crystallites (9) (more correctly the solid solution of urea in sulfathiazole). In the light of the ability of sulfathiazole to supercool to a glassy, amorphous form and the transparent nature of the freshly prepared mass containing more than 75% sulfathiazole, one can conclude more likely that the sulfathiazole was present as an amorphous form in the solid dispersion. Such contention is also substantiated by the presence of an exothermic peak in its DTA thermogram (Fig. 3), which probably is due to the transition of the higher energy amorphous form to the lower energy crystalline form of sulfathiazole. Furthermore, the presence of crystalline forms of both urea and sulfathiazole in the solid dispersion should not theoretically result in a considerable decrease in the thaw point and a wider range of melting. This phenomenon, therefore, may be attributed to the presence of the metastable amorphous form.

As found in the DTA studies, the diffraction spectrum of 52% sulfathiazole solid dispersion also changed with time. After storage at 27° for 2 weeks, weak diffraction peaks of the sulfathiazole Form II appeared (Fig. 5). Storage at 5° for the same period of time caused no change in the spectrum, indicating a slower rate of conversion of the amorphous form to Form II at lower temperatures. Interestingly, an incubation at 105° for only 1 hr. resulted in the appearance of strong sulfathiazole Form II peaks (Fig. 6). The sulfathiazole Form II diffraction peaks were present in the freshly prepared 25% sulfathiazole solid dispersion, even though it showed an earlier thawing and melting in the DTA thermogram.

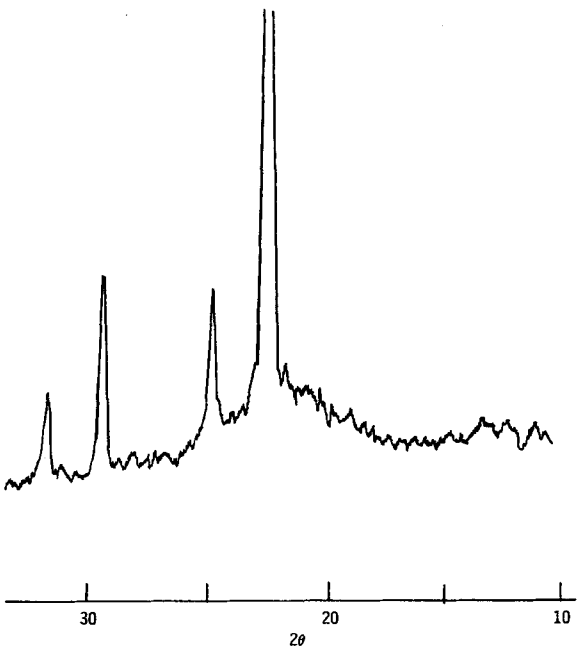

Figure 4—*X-ray diffraction spectrum of the freshly prepared sulfathiazole–urea eutectic mixture (52% sulfathiazole).*

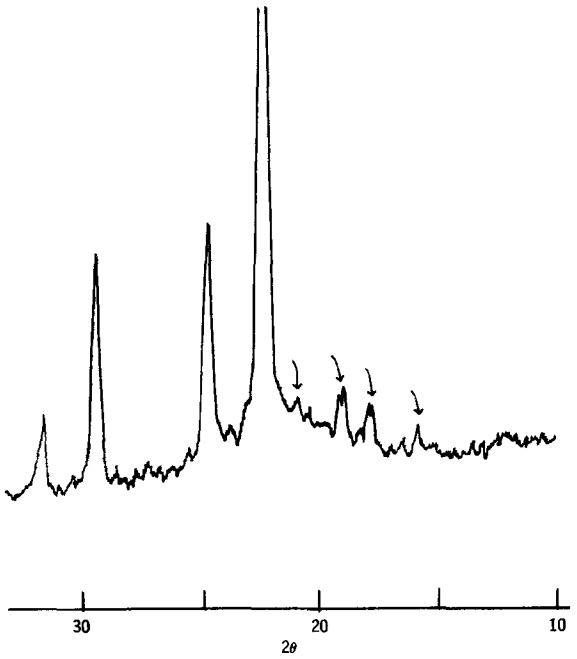

Figure 5—*X-ray diffraction spectrum of the sulfathiazole–urea eutectic mixture kept at 27° for 2 weeks. Peaks indicated by arrows correspond to sulfathiazole Form II diffraction spectrum.*

The positions of the diffraction peaks of either sulfathiazole or urea in all of the solid dispersions studied were not altered as compared with that of pure compounds, albeit there existed certain degrees of solid–solid solubilities which might affect the crystalline lattice parameters of the pure compounds (20, 21).

Effect of Aging on Dissolution Rates of Sulfathiazole Solid Dispersions—Sekiguchi *et al.* showed that the GI absorption of sulfathiazole could be enhanced when it was administered as a 52% solid dispersion. Since the history of the solid dispersion used for oral studies was not specified in their article and the possible conversion of the amorphous sulfathiazole to crystalline sulfathiazole is not a rapid process at ambient temperature, it will be of interest to know how the aging of the sample can affect the *in vitro* dissolution rate of sulfathiazole. The data on the freshly prepared sample and the sample kept at 105° for 1 hr. are shown in Fig. 7. The aged sample shows a slower dissolution rate, especially during the first few minutes of the study. Its effect on the *in vivo* absorption of the drug, however, remains to be studied. Furthermore, since the Form I of sulfathiazole is the stable form, the ultimate conversion of the metastable Form II to Form I also may have a significant effect on the dissolution rate and bioavailability of the preparation.

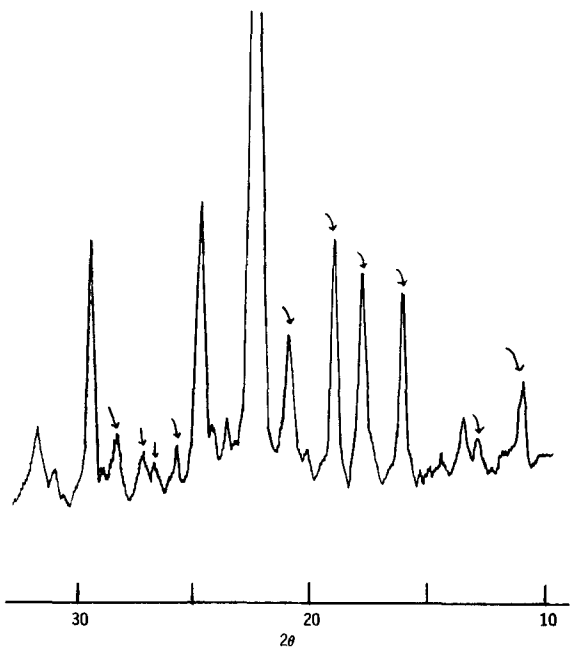

Figure 6—*X-ray diffraction spectrum of the sulfathiazole–urea eutectic mixture kept at 105° for 1 hr. Peaks indicated by arrows correspond to sulfathiazole Form II diffraction spectrum.*

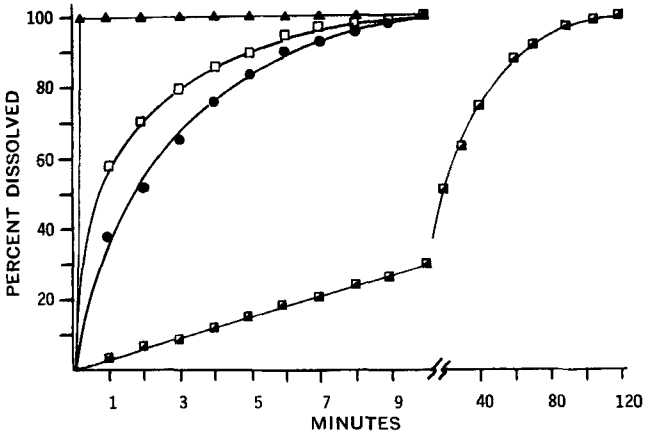

Figure 7—*Dissolution rates of sulfathiazole in various forms in 500 ml. water at 37°. Key: ▲, 5 or 10% sulfathiazole solid solution (60–100 or 10–20 mesh); □, freshly prepared eutectic mixture (52% sulfathiazole, 60–100 mesh); ●, eutectic mixture kept at 105° for 1 hr. (60–100 mesh); and ◪, pure sulfathiazole Form I (60–100 mesh).*

Dissolution Rates of Pure Sulfathiazole—Although the administration of the 52% sulfathiazole solid dispersion was shown to increase the physiological availability of the drug, no rank correlation between its *in vivo* availability and *in vitro* dissolution rate was reported. The *in vitro* dissolution rates of sulfathiazole powder with the same particle size are shown in Fig. 7. Comparison of the time required for the complete dissolution of sulfathiazole reveals that the solid-dispersed form is about 12 times faster than the pure Form I. Since the coadministration of urea was not found to interfere with the GI absorption of sulfathiazole in a pure form (2), these data clearly indicate that the increased dissolution rate of sulfathiazole in a solid-dispersed form is the principal factor contributing toward its faster absorption in man.

Dissolution Rates of Sulfathiazole in Solid Solutions—Although the solid solution approach has been advocated to obtain faster dissolution rates of poorly soluble drugs since 1965 (3), no *in vitro* dissolution-rate studies of the powder of a drug in a complete solid solution form have been reported so far. The DTA and X-ray diffraction methods were recently employed to disprove (22, 23) the previous studies on the existence of extensive solid solution formation in the chloramphenicol–urea (3, 24) and griseofulvin–succinic acid systems (25). Both of these systems appear to be simple eutectic mixtures with negligible solid solubilities.

The dissolution rates of sulfathiazole in the 5 and 10% solid solutions were found to be extremely fast (Fig. 7). After about 15 sec. of dissolution in a recirculating flowcell system, the absorbance of the dissolution media reached a constant, indicating complete dissolution of sulfathiazole. More surprisingly, no noticeable differences in dissolution rates between the fine 60–100-mesh powders and the coarse 10–20-mesh granules were found. Visual observation revealed that all of the powder disappeared into dissolution media in about 10 sec. Furthermore, the big 10–20-mesh particles were found to disappear completely (probably dissolve completely) before they settled down to the bottom of the beaker in an unstirred condition (in the order of seconds). Such an almost instantaneous dissolution is not surprising if one considers that sulfathiazole has already dissolved *in situ* in the urea matrix and urea is extremely and readily water soluble (19). The solubility of urea in water at room temperature is about 1 g. in 1 ml. In these solid solutions, the rate-limiting step of the dissolution of sulfathiazole in water is mainly the dissolution of the matrix. The observed fast dissolution is also in analogy with the mixing of a sulfathiazole solution in a water-miscible organic solvent such as ethanol or polyethylene glycol 300 with water.

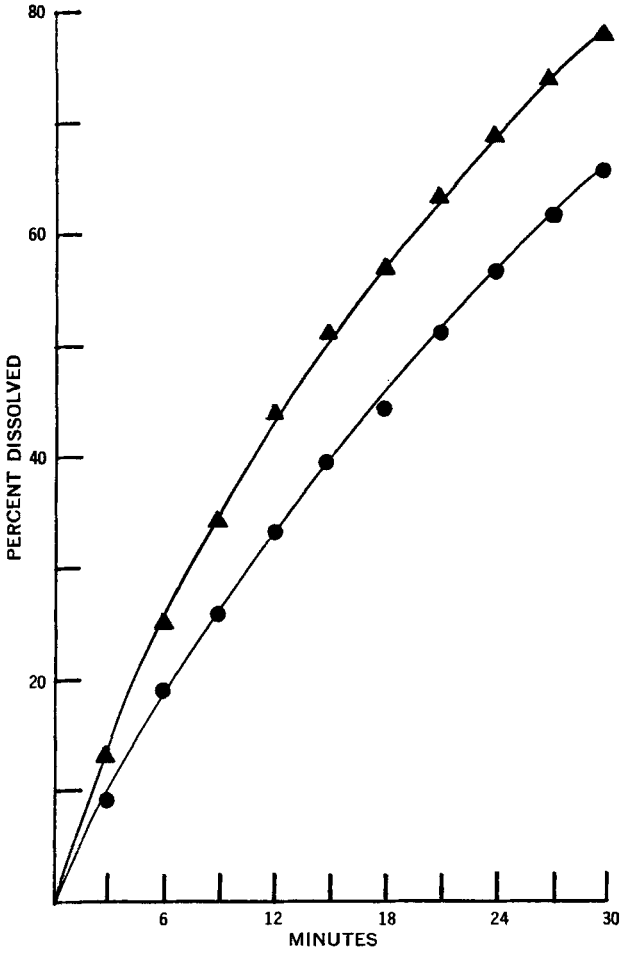

Figure 8—*Dissolution rates of sulfathiazole Form I in distilled water* (●) *and in 10% aqueous urea solution* (▲).

In comparing the time required to obtain 100% dissolution of sulfathiazole in solid solutions with that of the 60–100-mesh sulfathiazole Form I, the dissolution rates from the solid solutions are estimated to be about 700 times faster. If one compares dissolution rates of 10–20-mesh powders, the ratio would be in the order of thousands; the particle size has very slight effect on the dissolution rate of sulfathiazole in the solid solutions, but it has a great effect on the dissolution rate of the pure sulfathiazole. Such marked enhancement of *in vitro* dissolution rates was not found in dispersion systems of griseofulvin–succinic acid (25) and chloramphenicol–urea (24, 26). By using constant-surface tablets, Allen and Kwan (27) found that the dissolution rate of sulfathiazole in 5% sulfathiazole–95% urea solid solution was only about three times higher than that in the 5% sulfathiazole–95% urea physical mixture. Their finding seems to have no correlation in terms of the degree of enhancement with the present results using the powder method. Attempts to compare the dissolution rate of 10% sulfathiazole–90% urea systems using the constant surface method had to be given up since the hard tablets of the physical mixture compressed at even 62,500 p.s.i. or 94,750 p.s.i. started to disintegrate immediately when the assembly containing the tablet was moved down to the bottom of the aqueous dissolution medium at 37°.

Effect of Urea on Dissolution Rate of Sulfathiazole—Solubilization of drugs in carriers often was thought to be one factor to increase dissolution rates of the drugs in solid-dispersed forms (1, 9, 11, 12, 23–25). Since the solubility of sulfathiazole in water, on the contrary, was found to be decreased by the presence of urea (2), it will be interesting to know whether such desolubilization has any effect on the sulfathiazole dissolution. The result of the dissolution study on the powder of the pure Form I in a 10% (w/v) aqueous urea medium is shown in Fig. 8. Surprisingly, the dissolution rate also was increased by urea. It is postulated that such an enhancement must be due to better wetting of the powder in the urea solution, presumably with a lower surface tension. Such effect also may operate significantly in the microenvironment (diffusion layer) immediately surrounding the drug particles, especially in the early stage of dissolution from solid-dispersed forms since the carrier will completely dissolve in a short period of time. The lower surface-tension effect also has been thought to contribute to the increased dissolution rate of reserpine from reserpine–cholanic acid precipitates (29).

CONCLUSION

Different phase diagrams of the sulfathiazole–urea binary system were obtained for the two polymorphs of sulfathiazole. The mutual solid solubilities at the eutectic temperatures were found to be dependent upon the presence of a specific polymorphic form of sulfathiazole in the solid dispersion. The effect of aging on the eutectic mixture (52% sulfathiazole–48% urea) was studied by noting the changes in DTA thermograms, X-ray diffraction patterns, and *in vitro* dissolution rates. The dissolution rate of sulfathiazole in a solid solution was found to be almost instantaneous, more than 700 times the dissolution rate of the pure compound. Although urea decreases the solubility of sulfathiazole, its presence in the dissolution medium was shown to increase the dissolution rate, probably due to the lowering of interfacial tension.

REFERENCES

(1) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60,** 1281(1971).
(2) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9,** 866(1961).
(3) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **54,** 1145(1965).
(4) J. Haleblian and W. McCrone, *ibid.*, **58,** 911(1969).
(5) D. C. Grove and G. L. Keenan, *J. Amer. Chem. Soc.*, **63,** 97(1941).
(6) G. Milosovich, *J. Pharm. Sci.*, **53,** 484(1964).
(7) J. K. Guillory, *ibid.*, **56,** 72(1967).
(8) W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, *ibid.*, **56,** 200(1967).
(9) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *ibid.*, **58,** 538(1969).
(10) L. S. Shenouda, *ibid.*, **59,** 785(1970).
(11) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *ibid.*, **55,** 482 (1966).
(12) W. L. Chiou and S. Riegelman, *ibid.*, **58,** 1505(1969).
(13) K. Sekiguchi, Y. Ueda, and Y. Nakamori, *Chem. Pharm. Bull.*, **11,** 1108(1963).
(14) J. K. Guillory, S. L. Hwang, and J. L. Lach, *J. Pharm. Sci.*, **58,** 301(1969).
(15) K. Sekiguchi, K. Ito, and Y. Nakamori, *Chem. Pharm. Bull.*, **11,** 1123(1963).
(16) R. F. Schwenker and P. D. Garn, "Thermal Analysis," vol. 2, Academic, New York, N. Y., 1969, p. 829.
(17) DuPont Instruments, Publication 900 C, E. I. duPont de Nemours & Co., Instrument Product Division, Wilmington, DE 19898, p. 9.
(18) A. Findlay, "The Phase Rule," 9th ed., Dover, New York, N. Y., 1951.
(19) "The Merck Index," 8th ed., P. G. Stecher, Ed., Merck & Co., Inc., Rahway, N. J., 1968, p. 1094.
(20) R. Smoluchowski, "Phase Transformation in Solids," Wiley, New York, N. Y., 1951.
(21) G. R. Mallett, M. Fay, and W. M. Mullett, "Advances in X-ray Analysis," vol. 9, Plenum, New York, N. Y., 1965, p. 159.
(22) W. L. Chiou, *J. Pharm. Sci.*, **60,** 1406(1971).
(23) W. L. Chiou and S. Niazi, to be published.
(24) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55,** 581(1966).
(25) *Ibid.*, **55,** 487(1966).
(26) K. Sekiguchi, N. Obi, and Y. Ueda, *Chem. Pharm. Bull.*, **12,** 134(1964).
(27) D. J. Allen and K. C. Kwan, *J. Pharm. Sci.*, **58,** 1190(1969).
(28) L. Lachman, H. A. Lieberman, and J. L. Kanig, "The Theory and Practice of Industrial Pharmacy," Lea & Febiger, Philadelphia, Pa., 1970, p. 518.
(29) R. G. Stoll, T. R. Bates, K. A. Karl, and J. Swarbrick, *J. Pharm. Sci.*, **58,** 1457(1969).

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Influence of First-Pass Effect on Availability of Drugs on Oral Administration

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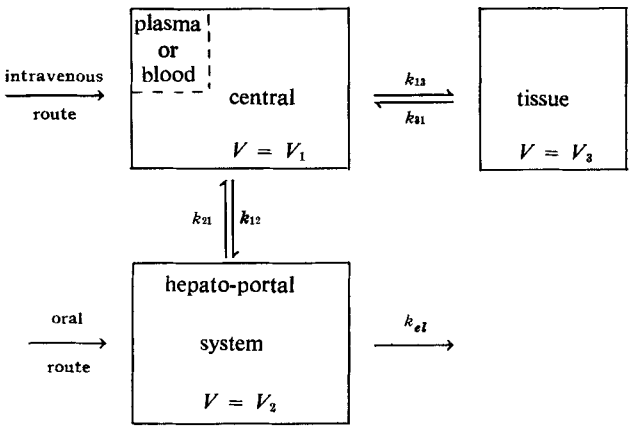
Abstract □ Currently used pharmacokinetic models assume that drug administered both intravenously and orally initially enters the same vascular pool. However, literature data suggest that although a drug is completely absorbed, the area under the plasma level–time curve after oral administration may be considerably less than the corresponding area following intravenous therapy. This has been explained on the basis of a "first-pass" effect in the liver. Simple equations have been derived, allowing prediction of the extent of this first-pass effect for a particular drug. Plasma level data for propranolol in man have been used to indicate the utility of these equations. The significance of these calculations to the design of clinical studies with new drugs intended for oral use is discussed.

Keyphrases □ Bioavailability, estimate calculations—from plasma levels, first-pass effect □ Absorption kinetics, oral—plasma level data, first-pass effect

Pharmacokinetic analysis of plasma level data for drugs generally assumes that the site of elimination is an integral part of the same compartment as the sampled plasma. For drugs eliminated by hepatic metabolism, this assumption may not be valid under all circumstances. Two recent papers (1, 2) indicated that the areas under the blood level–time curves for aspirin and lidocaine were considerably greater when a dose of the drug was infused into a peripheral vein as compared to results observed upon infusion of an equal dose into the portal vein of the dog. Administration of a drug directly into the portal vein is, in most instances, equivalent to the pathway followed after oral administration. The reduction in area under the blood level–time curves following portal vein infusion has been attributed to the fact that the drugs were exposed to the liver before reaching the vascular site being sampled. This phenomenon has been commonly termed the "first-pass" effect. Clearly, then, differences in areas under blood level–time curves as a function of route of administration may reflect not only differences in the amount of drug absorbed but the first-pass phenomenon as well. Based on these considerations, a somewhat different model or a correction factor may be required to compare plasma levels of certain drugs following oral and intravenous administration. The purpose of this communication is to present a simple method of calculation which can be used to predict, from plasma levels following intravenous or oral administration, the approximate reduction in area under the curve due to the first-pass phenomenon.

THEORETICAL

In a previous report (3), a linear three-compartment open model was proposed to explain the influence of route of administration (*i.e.*, intravenous *versus* oral) on the area under the plasma concentration–time curve. A modification of the model is shown in Scheme I. The essential feature of this model is that the hepatoportal system is treated as being, or being within, a compartment distinct from the compartment containing the vascular site sampled. Moreover, it was suggested that it often is exceedingly difficult to justify the existence of three distinct compartments solely on the basis of curve-fitting plasma concentration–time data after intravenous administration. Hence, although the plasma concentration data suggest simply a two-compartment model, an additional, rapidly accessible compartment might well exist and, in fact, must exist, from a mathematical point of view to explain certain pharmacokinetic anomalies (1, 2).



Scheme I—Three-compartment open model

If the vascular system being sampled is a component of the central compartment (inset of Compartment 1 of Scheme I), a difference will indeed occur with respect to the area under the drug concentration *versus* time curve as a function of route of administration (3). When the drug is given directly into Compartment 1, a situation comparable to intravenous administration, the total area under the plasma concentration–time curve is given by:

$$(\text{area})_1 = \text{dose}\ (k_{21} + k_{el})/(V_1 k_{12} k_{el}) \qquad \text{(Eq. 1)}$$