mole) of the aromatic amide oxime and dimethyl acetylenedicarboxylate were dissolved in 100 ml. of anhydrous methanol. The mixing of the reactants was often mildly exothermic, but the solution was heated at reflux for 3 hr. to complete the reaction. The methanol was removed *in vacuo*, and the resulting oil was induced to crystallize by chilling and scratching (two exceptions as noted in Table I). These low melting solids were purified by repeated recrystallization from methanol to analytical purity.

General Procedure for Thermal Rearrangement to Imidazolinones (IIa–f)—A mixture of approximately 2.0 g. of the amide oxime–dimethyl acetylenedicarboxylate adduct and 25 ml. of diphenyl ether was heated at reflux for 2 hr. The solution was cooled to room temperature and diluted with *n*-hexane, and the precipitated solid was collected. The crude product was recrystallized from methanol with the aid of decolorizing carbon. Yields and melting points are reported in Table II.

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Differential Thermal Analysis and X-Ray Diffraction Studies of Griseofulvin–Succinic Acid Solid Dispersions

WIN LOUNG CHIOU▲ and SARFARAZ NIAZI

Abstract □ Differential thermal analysis and X-ray diffraction techniques were employed to study the phase diagrams of griseofulvin–succinic acid systems. The complications of the formation of a thermally decomposed product of succinic acid, succinic anhydride, on the thermograms were discussed. The appearance of typical eutectic peaks and X-ray diffraction peaks of griseofulvin in the resolidified preparations containing 10% or less of griseofulvin indicates that the binary system is a simple eutectic mixture with negligible mutual solid solubilities. This result is partly different from that obtained previously by the microthermal microscope technique, which showed the existence of an extensive solid solution of griseofulvin in succinic acid. The formation of a solid solution was previously concluded to be primarily responsible for the enhanced dissolution of griseofulvin.

Keyphrases □ Griseofulvin–succinic acid solid dispserions—phase diagrams, differential thermal analysis and X-ray diffraction, results compared to microthermal microscope technique □ Succinic acid–griseofulvin solid dispersions—phase diagrams, differential thermal analysis and X-ray diffraction, results compared to microthermal microscope technique □ Differential thermal analysis—phase diagrams of griseofulvin–succinic acid solid dispersions □ X-ray diffraction—phase diagrams of griseofulvin–succinic acid solid dispersions

The classification and pharmaceutical applications of solid dispersion systems were recently reviewed by Chiou and Riegelman (1). A knowledge of the physicochemical properties of a solid dispersion is very important toward an understanding of its applications. Chloramphenicol dispersed in urea was shown to result in faster dissolution and absorption rates (2, 3). The enhancement was thought primarily due to the formation of a solid solution of the drug in the carrier, urea (3). Recently, Chiou (4) used differential thermal analysis and X-ray diffraction methods to reexamine this system, and he concluded that the system is a simple eutectic mixture with negligible mutual solid solubility.

The observed enhancement in both dissolution and absorption rates must, therefore, be mainly due to the reduction of the chloramphenicol crystalline size fol-

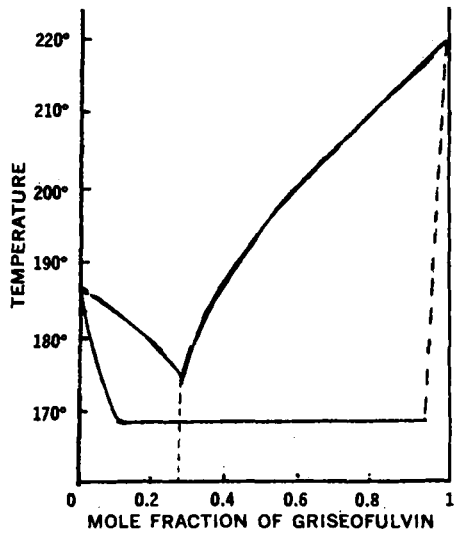

Figure 1—*Phase diagram for griseofulvin–succinic acid mixtures obtained by microthermal techniques. (From* Reference 5.)

lowing the solidification of the melt of the mixture. Griseofulvin dispersed in succinic acid was previously shown by Goldberg *et al.* (5) to produce a much faster dissolution rate and a supersaturation phenomenon. These observations were attributed to the formation of a solid solution of the drug in the carrier. This conclusion was based on their analysis of the phase diagram (reproduced in Fig. 1) determined by the microthermal microscope technique. The purpose of this paper is to report a different finding regarding the griseofulvin–succinic acid phase diagram study obtained through more sophisticated and objective techniques, namely differential thermal analysis and X-ray diffraction.

EXPERIMENTAL

Sample Preparations—Physical mixtures of griseofulvin[1] and succinic acid[2] were obtained by mixing in either a microball mill[3] or mortar. Griseofulvin–succinic acid solid dispersions were prepared by the fusion method (5). The concentration of griseofulvin in each preparation was confirmed spectrophotometrically using a spectrophotometer[4] (5).

Thermal and X-Ray Diffraction Studies—The procedure and instrumentation for differential thermal analysis, X-ray diffraction, and capillary tube melting-point studies were identical to those reported previously (6). Heating rates of 5 and 10°/min. used in this study were found to give almost identical thermograms.

RESULTS AND DISCUSSION

Phase Diagram Determination from Physical Mixtures—It has been generally found that the binary phase diagrams determined from physical mixtures through thermal analyses often correlate well with those determined from fused or evaporated mixtures (7, 8). The phase diagram of the griseofulvin–succinic acid system, determined from their physical mixtures, that has not been previously reported is shown in Fig. 2. The eutectic melting was observed in all samples containing 1–99% (w/w) of griseofulvin. This might be indicative of a lack of an extensive mutual solid solubility between the two components. Similar eutectic peaks were also observed in all physical mixtures of the sulfathiazole–urea binary system (6). However, certain mutual solid solubilities between the two components were found in their solidified fused preparations (6).

[1] Griseofulvin USP (micronized), supplied by McNeil Laboratories, Fort Washington, Pa.
[2] Succinic acid, supplied by Merck & Co., Inc., Rahway, N. J.
[3] Ball mill shaker, Crescent Dental Manufacturing Co., Chicago, Ill.
[4] Beckman DBG.

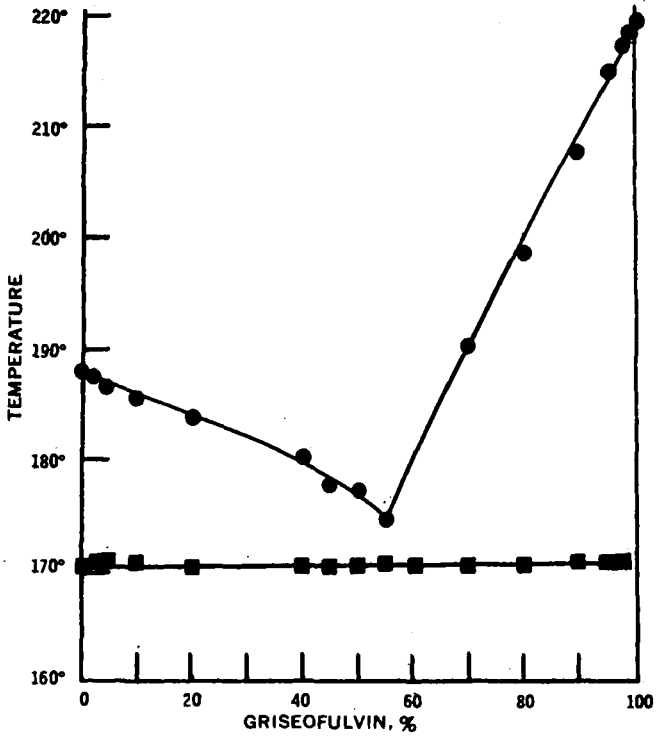

Figure 2—*Phase diagram of griseofulvin–succinic acid binary system determined from physical mixtures. Key:* ■, *thaw point; and* ●, *final melting point.*

The thaw points in this study were determined from the differential thermal analysis thermograms, because differential thermal analysis instruments are more sensitive than the conventional capillary tube method in detecting the beginning of melting of a small fraction of a sample (1, 6). They were all found to be around 170°, which is about 2.5° higher than the previously reported value (5). The final melting points of the samples were determined from both

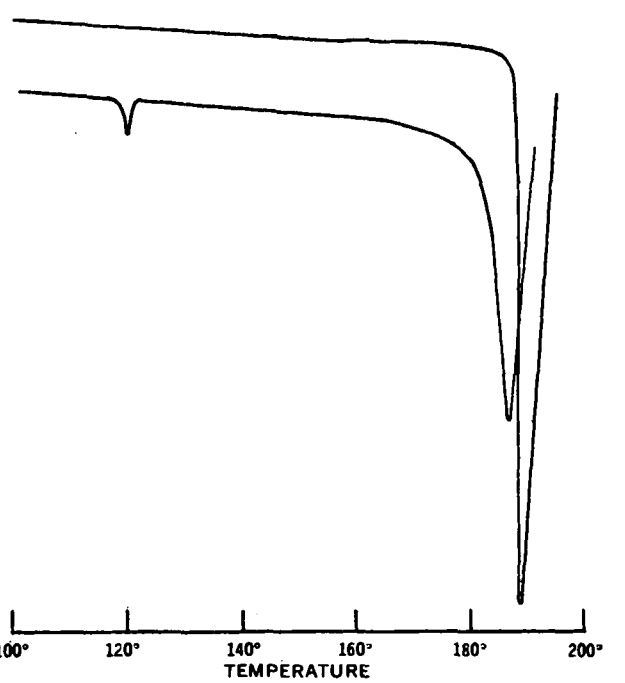

Figure 3—*Thermogram of succinic acid. Key: top, first run; and bottom, rerun of the sample after 5 min.*

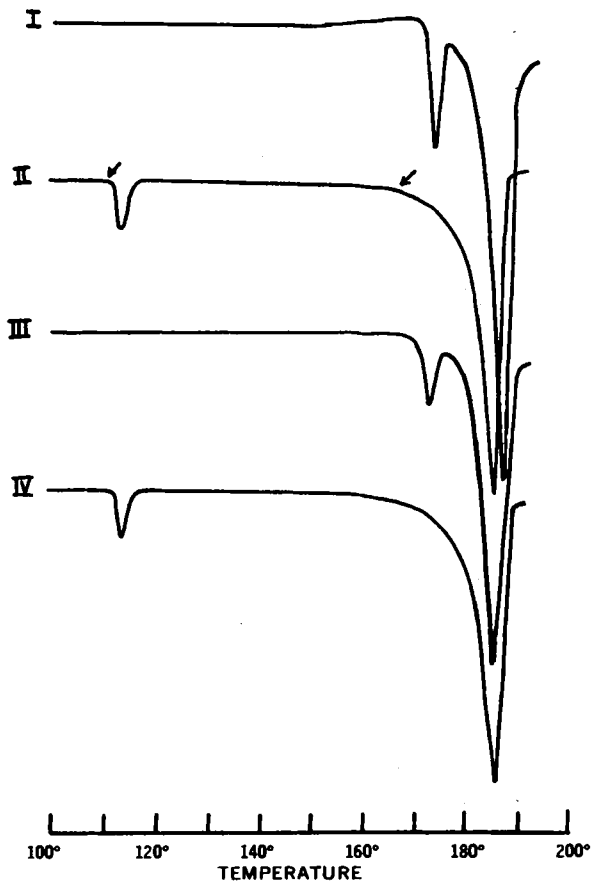

Figure 4—*Thermograms of different samples of 10% griseofulvin. Key: I, physical mixture; II, solid dispersion; III, solid dispersion incubated at 80° for 5 days; and IV, 10% griseofulvin–90% melted succinic acid physical mixture.*

the differential thermal analysis and capillary tube methods. However, for samples that showed ambiguities of the final melting on differential thermal analysis thermograms (6, 8), the values determined from the capillary tube method were used in the construction of the phase diagrams (1, 6).

Thermal Stability of Griseofulvin and Succinic Acid—To determine the phase diagram of a binary system from resolidified fused preparations, it is necessary to study first the thermal stability of both components. If any significant chemical decomposition takes place during the initial melting process, the phase diagram determined might be quite complicated or sometimes misleading because the system now contains three or more components. The thermal stability of griseofulvin was demonstrated by essentially the identical differential thermal analysis thermograms of its original and resolidified pulverized samples. This is in agreement with some previous studies (9, 10). Although succinic acid (m.p. 185–187°, b.p. 235°) has been reported (11) to undergo a partial conversion to succinic anhydride (m.p. 119.6°, b.p. 261°), it appears that no data are available in the literature regarding its thermal stability around its melting point.

The thermogram of the resolidified fused samples obtained from this study showed an extra endothermic peak beginning at 118°. The melting range of its major peak was also widened and considerably shifted to the lower temperature (Fig. 3). Furthermore, the intensity of the extra endothermic peaks and the widening and shifting of the major peaks were all further enhanced when the sample was fused and solidified repeatedly. From a theoretical consideration (1, 13), this observation agrees with a contention that succinic acid will partially decompose after melting and will form a eutectic mixture with its thermally decomposed product. The extent of decomposition also appears to increase with repeated fusion of the acid. It is reasonable to assume that succinic anhydride is also the decomposition product. The thermal decomposition was also confirmed by the sublimed deposition of a thin white layer of film on

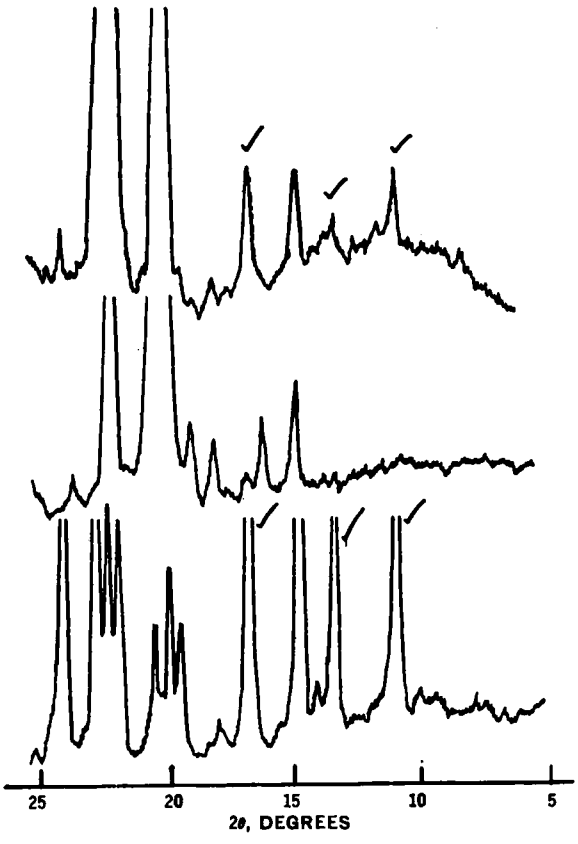

Figure 5—*X-ray diffraction spectra. Key: top, 10% griseofulvin solid dispersion; middle, resolidified succinic acid; and bottom, griseofulvin. Tick marks indicate the characteristic peaks of griseofulvin.*

the cover glass when the resolidified succinic acid powder was heated to about 120° on a hot stage attached to a microscope[5]. Such a sublimation, however, could not be detected when succinic acid was directly heated to 150° without prior fusion and solidification. The sublimation phenomenon of succinic anhydride was reported previously (11). The presence of succinic anhydride in the resolidified succinic acid sample was also confirmed by the preliminary X-ray diffraction study.

Thermal Analyses of Resolidified Fused Mixtures—Although thermal analyses were conducted for many resolidified preparations containing various amounts of griseofulvin and succinic acid, only the 10% (w/w) griseofulvin–90% succinic acid resolidified preparation (or solid dispersion) will be discussed in detail. Since succinic acid might undergo a partial thermal decomposition, its complicating effect on the differential thermal analysis thermogram of the 10% griseofulvin solid dispersion was reasonably anticipated.

Thermograms of both the solid dispersion and the physical mixture are shown in Fig. 4. Two endothermic peaks were present, beginning at 109 and 166°, respectively, in the solid dispersion thermogram (as shown by the arrows). In addition, its final melting peak appeared a few degrees lower than that of the physical mixture. The peak starting at 109° is attributed to the presence of succinic anhydride. This conclusion is also supported by the following evidence: (*a*) a similar sublimation phenomenon was also observed for the solid dispersion at about 120°; and (*b*) a similar thermogram pattern was also obtained from the physical mixture of 10% griseofulvin–90% resolidified succinic acid (Fig. 4) and from the physical mixture of 10% griseofulvin–87.5% succinic acid–2.5% succinic anhydride. It was estimated from the thermograms that about 7% of succinic anhydride was present in the 10% griseofulvin solid dispersion.

During the early stage of this investigation, it was thought that the observed peculiarities of the above solid dispersion thermogram might have been caused by the metastable state of the sample fol-

[5] Kofler.

lowing resolidification of the melt at room temperature. Therefore, the thermogram was again recorded for samples that had been incubated at 80° for 5 days in sealed capillary tubes. Surprisingly, the earlier peak disappeared and the griseofulvin–succinic acid eutectic peak, with an intensity similar to that found in the physical mixture, reappeared (Fig. 4). The disappearance of the earlier peak is thus likely to be due to the sublimation of succinic anhydride to the upper part of the capillary tube during the annealing process. The reappearance of the original eutectic peak also clearly indicates that the majority of griseofulvin is present as griseofulvin crystals and not as solid solution in the solid dispersion.

It must be emphasized that, based on the phase rules and differential thermal analysis principles (1, 4, 6), the thaw point or the beginning of the endothermic peak of the thermogram must be higher than the eutectic temperature if the sample is a solid solution as originally proposed by Goldberg *et al.* (5). The peculiar thermal characteristics of the 10% griseofulvin solid dispersion were also observed in the 1, 2, and 5% griseofulvin solid dispersions. In other words, based on this method of analysis, the solid solubility of griseofulvin in succinic acid at or above the eutectic temperature should be less than 1% or negligible. This is not in agreement with the previous study in which a solid solubility of 25% griseofulvin in succinic acid was reported. As reported (4) earlier for the chloramphenicol–urea system, such discrepancy is probably due to the more subjective visual method used in these previous studies. As beginners in microscopy, the present authors have experienced uncertainty in ascertaining the exact thaw points of the solid dispersion samples using an identical technique to that employed by previous workers (5). The thaw point varied between 110 and 170°. The reported limited solid solubility of succinic acid in griseofulvin was also confirmed by the present study. The resolidified samples containing 95 and 98% of griseofulvin all showed eutectic peaks at about 166°.

X-Ray Diffraction Studies—The X-ray diffraction technique was used recently to study the physical nature of drugs in solid dispersion systems (4, 6, 12). It was employed also in this investigation to support the differential thermal analyses results showing the limited solubility of griseofulvin in succinic acid. Theoretically, the characteristic diffraction peaks of the solid solute should be absent from the diffraction spectrum of a solid solution (1). However, this is not the case for the 10% griseofulvin solid dispersion. Three major peaks of griseofulvin at 10.8, 13.3, and 16.6° (13) were all present in the 10% griseofulvin solid dispersion (Fig. 5). The comparable areas under these peaks between the solid dispersion and physical mixture (10% griseofulvin) also indicate that most of the griseofulvin was present as crystals and not as a solid solution in the preparation. A slight line broadening effect was observed in the freshly prepared solid dispersion which might indicate the presence of ultrafine crystals of griseofulvin. For example, the ratio for the peak height over the peak width at 10.8° was increased about onefold after aging at 80° for 5 days. The effect of peak broadening on the dissolution rate of griseofulvin is currently under investigation in this laboratory.

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