Pharmaceutical Applications of Solid Dispersion Systems: Dissolution of Griseofulvin–Succinic Acid Eutectic Mixture

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Abstract □ The dissolution profile of the griseofulvin–succinic acid eutectic mixture system was evaluated using the powder and constant-surface area tablet methods. Factors contributing to the enhancement of griseofulvin dissolution from the dispersion in succinic acid are discussed. Contrary to the original proposal of Sekiguchi and coworkers, dissolution rates of griseofulvin from solid dispersions were found to be markedly affected by the particle size of solid dispersions.

Keyphrases □ Dispersion systems, solid—evaluation of dissolution profile of griseofulvin–succinic acid eutectic mixture system, effect of particle size □ Dissolution—griseofulvin from dispersion in succinic acid, profile evaluated, effect of particle size □ Griseofulvin—dissolution from dispersion in succinic acid, profile evaluated, effect of particle size □ Antifungal agents—griseofulvin, dissolution from dispersion in succinic acid, profile evaluated

Pharmaceutical applications of solid dispersion systems were extensively reviewed by Chiou and Riegelman (1). In the past, these systems were primarily used to increase the dissolution and absorption rates of poorly water-soluble or insoluble solid drugs by dispersing them in a water-soluble carrier. More recently, they have also been employed to formulate liquid drugs in solid dosage forms (2) and to prepare sustained-release dosage forms by dispersing a drug in a water-insoluble carrier (3).

The dissolution rate of griseofulvin, a water-insoluble antifungal antibiotic, was enhanced significantly by solid dispersion in water-soluble succinic acid (4); the investigators attributed this result to the extensive formation of a solid solution of griseofulvin in succinic acid (4). Later, it was shown by X-ray diffraction and differential thermal analysis methods that the solid solubility of griseofulvin in succinic acid was negligible and such a binary system could more adequately be classified as a simple eutectic mixture (5).

In light of these findings, additional dissolution studies using constant surface area and powder methods were undertaken to explore the dissolution profile for certain compositions of the binary system. Results of these studies and their implications in using the solid dispersion method for dissolution and absorption enhancement are discussed in this paper.

EXPERIMENTAL

Sample Preparation—Solid dispersions containing 2.5, 5, 10, 25, and 55% (eutectic composition) of griseofulvin[1] in the griseofulvin–succinic acid[2] system were prepared by the fusion method (5). They were pulverized with a mortar and pestle, and the 60–100-mesh fraction was collected. For the 10% griseofulvin solid dispersion, the following mesh sizes of powder were also collected: 10–20, 20–40, 40–60, 60–80, and 80–100. The same mesh sizes of succinic acid were prepared after fusion and resolidification.

Tablets (1.3 cm in diameter) for use in constant surface area dissolution studies were prepared by compressing 300 mg of fine powder at 50,000 psi pressure in a press[3]. The tablets prepared included pure griseofulvin, 10% griseofulvin solid dispersion, 10% griseofulvin–90% succinic acid physical mixture, and 10% griseofulvin–90% succinic anhydride[4] physical mixture.

Dissolution Rate Studies—The powder dissolution method used was identical to that reported previously (6). The solid-dispersed samples containing 5 mg of griseofulvin were used in each study in 500 ml of distilled water at 37°. The amount of griseofulvin dissolved was monitored spectrophotometrically at 295 nm. The dissolution rate of succinic acid (45 mg) from various sizes of powder was measured spectrophotometrically at 195 nm based on the established Beer's law plot.

Dissolution rates of griseofulvin from constant surface area tablets were also studied in 500 ml of distilled water at 37°. The tablet was mounted into a tablet holder with only one surface area exposed to the dissolution medium. The tablet contained in the holder was placed vertically against the wall of the beaker in the middle of the dissolution medium.

The griseofulvin concentration was determined using a spectrophotofluorometer[5] with excitation at 298 nm (uncorrected) and fluorescence at 440 nm (uncorrected). Both succinic acid and succinic anhydride were found not to interfere with the griseofulvin measurement. The sample (1 ml) was returned immediately to the dissolution medium after measurement. This fluorometric assay was employed because of its high sensitivity, since griseofulvin concentrations obtained from the tablet study were too low to be measured by the UV spectrophotometric method.

All dissolution studies were conducted at least in duplicate, and highly reproducible results were always achieved. Only the average values are reported.

RESULTS AND DISCUSSION

Goldberg *et al.* (4) reported the dissolution properties of only two compositions of the solid-dispersed system and found that the dissolution rate from the 20% griseofulvin powder was much higher than that from the 55% griseofulvin powder due to the presence of the entire griseofulvin in the form of a solid solution in the former composition. In the present study, five different compositions with the same particle size were evaluated. Their dissolution profiles are shown in Fig. 1.

The dissolution rate of griseofulvin was inversely proportional to the concentration of griseofulvin in the dispersed system. Since such a binary system was shown to be a simple eutectic mixture, one can conclude that the faster dissolution rate observed with a lower concentration of griseofulvin dispersion was primarily due to the finer crystals formed in a low concentration dispersion system (1). Furthermore, Fig. 1 shows that the 55% solid dispersion dissolved somewhat more slowly than the micronized griseofulvin. This finding indicates that the average particle size of griseofulvin crystals formed in the solid dispersion was larger than that of the micronized griseofulvin.

The similar dissolution rate observed between the 25% solid dispersion and the 10% physical mixture made of 60–100-mesh succinic acid and micronized griseofulvin also indicated that the griseofulvin

[1] Griseofulvin USP (micronized), McNeil Laboratories, Fort Washington, Pa.

[2] Succinic acid, Merck & Co., Rahway, N.J.

[3] Carver Press, Fred S. Carver Co., Summit, N.J.

[4] Succinic anhydride, Merck & Co., Rahway, N.J.

[5] Aminco-Bowman spectrophotofluorometer, American Instrument Co., Silver Spring, Md.

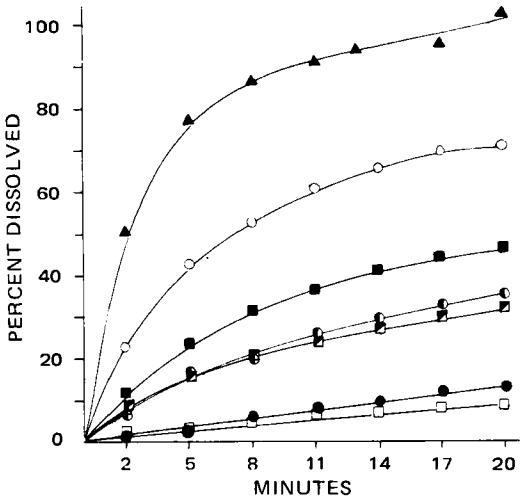

Figure 1—*Dissolution rates of griseofulvin from micronized griseofulvin, physical mixture, and 60–100-mesh fraction of various solid dispersions. Key: ▲, 2.5% solid dispersion; ○, 5% solid dispersion; ■, 10% solid dispersion; ◐, 25% solid dispersion; ◩, 10% physical mixture; ●, pure griseofulvin (micronized); and □, 55% solid dispersion.*

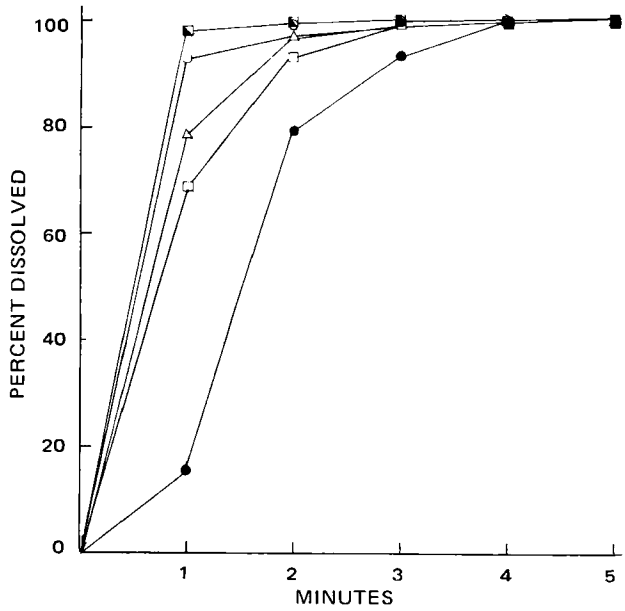

Figure 3—*Dissolution rates of various mesh sizes of succinic acid. Key: ◙, 80–100; ○, 60–80; △, 40–60; □, 20–40; and ●, 10–20.*

crystals in that dispersion were similar in size to the micronized powder. These findings are supportive of the previous study on the limited solid solubility of griseofulvin in succinic acid (5).

If the solid solubility of griseofulvin in succinic acid is as high (up to 25%) as reported by Goldberg *et al.* (4), one probably should not observe the marked difference in dissolution rate from dispersed systems containing 25% or less griseofulvin because the griseofulvin molecules should all be present in the same molecular form. The dissolution rates of sulfathiazole from the solid solutions of 5% sulfathiazole–95% urea and 10% sulfathiazole–90% urea systems were shown to be the same and to approach instantaneousness. The dissolution rate at 2 min from the 2.5% solid dispersion was about 30 times faster than from the micronized griseofulvin, indicating an extremely fine dispersion of griseofulvin in such a low concentration dispersed system. In the previous study (4), the dissolution of griseofulvin from the 25% "solid solution" was only about twice as fast as that of the micronized griseofulvin.

Although solid dispersion methods for increasing dissolution rates of drugs have been used for more than a decade, no comparison of the dissolution rates of various particle sizes of the same composition of solid dispersions apparently has been reported. According to the theory of Sekiguchi *et al.* (7), the eutectic mixture composed of intimately mixed fine crystals of each component will quickly disintegrate in water or GI fluids into finely divided particles of the drug because the water-soluble carrier will dissolve rapidly into the medium. Accordingly, one would expect that the particle size of solid dispersions should have little effect on the dissolution rate of the drug.

Surprisingly, opposite results were obtained even for the 10% griseofulvin solid dispersion where an excess amount of the soluble carrier was available (Fig. 2). The particles of the solid dispersion

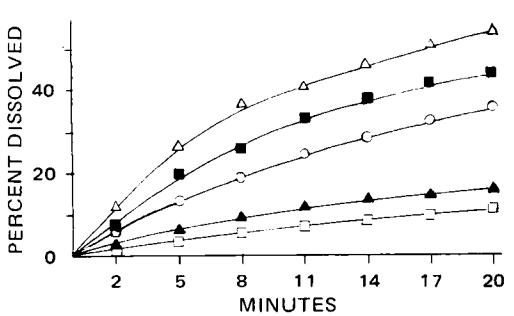

Figure 2—*Dissolution of various sizes of 10% griseofulvin solid dispersion particles. Key: △, 80–100 mesh; ■, 60–80 mesh; ○, 40–60 mesh; ▲, 20–40 mesh; and □, 10–20 mesh.*

powder, especially in the 10–20- and 20–40-mesh ranges, appeared not to decrease in size or disintegrate even after 20 min. Subsequently, the dissolution characteristics of succinic acid alone in various particle sizes were investigated (Fig. 3). Particles of all sizes were found to dissolve within 1–4 min. This finding indicates that the soluble carrier in the dispersed system might dissolve rapidly into the dissolution medium, leaving a strong, cohesive, and dissolution rate-limiting layer of griseofulvin at the outer surface of the particle. This assumption was substantiated by the following experiment.

One gram of the 10–20-mesh size of the 10% solid dispersion was stirred in 100 ml of water at 37° in the dissolution apparatus. After 10 min of stirring, the suspended particles were removed, dried, and analyzed. They were found to contain 79% of griseofulvin, indicating that most succinic acid had already dissolved. A 100% griseofulvin content was found after 20 min. No disintegration or reduction in particle size of the granules was observed.

These results clearly indicate that the unique feature of the ultrafine crystals of griseofulvin in the eutectic mixture might be lost if large particles are used. However, it remains to be investigated whether this will significantly affect the bioavailability of the drug in humans. The results of the present study did not contradict the previous findings that showed disintegration of solid dispersion particles under observation with a microscope.

The constant surface area tablet technique often has been used to study dissolution mechanisms of various systems. Only the 10% griseofulvin composition was selected for evaluation in the present study (Fig. 4).

As expected, a zero-order dissolution rate of griseofulvin from the pure griseofulvin tablet was found. The dissolution rate of griseofulvin from the 10% griseofulvin–90% succinic acid physical mixture at the early stage (less than 30 min) was faster than that from the pure compound. This result can be explained by the solubilizing effect of succinic acid (4). As succinic acid was depleted, the effect disappeared and the dissolution rate became identical to that from a pure griseofulvin tablet (8).

Such a dissolution enhancement was not observed in the previous study using the powder method, probably due to the lack of intimate contact between the two components in the physical mixture of powder. Therefore, one can postulate that the solubilizing effect of succinic acid can contribute partially to the observed dissolution enhancement in the solid dispersion system. The increased wettability of the hydrophobic griseofulvin by the intimate contact of the polar succinic acid also may play a role in the enhancement of the dissolution rate (1).

The dissolution profile from the 10% solid dispersion was interesting. A constant release of griseofulvin was observed for up to about 24 min. This rate was about 2.6 times higher than that of the physical mixture and about 4 times higher than that of pure griseofulvin. Such

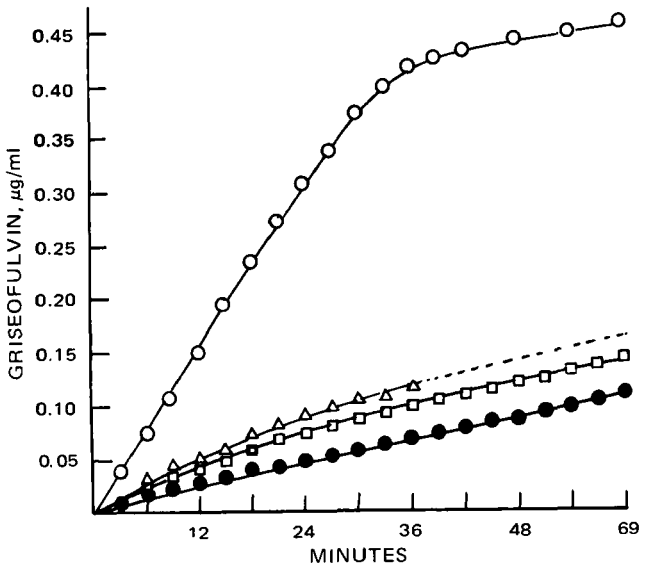

Figure 4—*Release of griseofulvin from constant surface tablets. Key: ○, 10% solid dispersion; △, 10% griseofulvin–90% succinic anhydride physical mixture; □, 10% griseofulvin–90% succinic acid physical mixture; and ●, pure griseofulvin.*

a marked increase in dissolution rate cannot be explained by the presence of a higher energy polymorphic form because the X-ray diffraction study showed that the identical crystalline form was present in the dispersed system as the pure griseofulvin used in the present study (5).

Since some succinic anhydride (about 7% w/w) was formed during the preparation of solid dispersions (5), it was thought that such an impurity might enhance the dissolution rate. The fact that the dissolution rate of griseofulvin was only moderately increased in the presence of 90% succinic anhydride (Fig. 4), however, rules out the important role of this decomposition product. Based on these results and analyses, it is postulated that the major factor in the increasing dissolution rate in the 10% griseofulvin dispersion was the presence of extremely fine crystals of griseofulvin. Crystalline size alone has been shown to affect the solubility of drugs (9).

After about 42 min, the cumulative plot curve of the 10% griseofulvin solid dispersion became parallel with that of pure griseofulvin. This result probably was due to the presence of negligible concentrations of the solubilizers, succinic acid and succinic anhydride, at the outer controlling layer of the tablet and to the presence of a coarser particle size of griseofulvin at the dissolution surface; this coarser particle size was formed as a result of the aggregation and/or crystal growth of ultrafine crystals. It must be noted that these tablet dissolution studies were carried out under essentially sink conditions (the solubility of griseofulvin at 37° is about 12.5 µg/ml).

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Application of Trichloroacetyl Isocyanate to NMR Analysis of Steroids of Pharmaceutical Interest I: Corticosteroids and Chemically Related Compounds

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Abstract □ The trichloroacetyl carbamates of 38 corticosteroids and chemically related compounds were prepared, and their NMR spectra in deuterochloroform were obtained. The effects of the introduction of a number of functional groups on the chemical shift of the carbamate proton signals were determined.

Keyphrases □ Trichloroacetyl isocyanate—reaction with corticosteroids to form carbamates, application to NMR analysis □ NMR—analysis, carbamates of corticosteroids formed by reaction with trichloroacetyl isocyanate □ Corticosteroids—NMR analysis of carbamates formed by reaction with trichloroacetyl isocyanate □ Carbamates—formed by reaction of trichloroacetyl isocyanate with corticosteroids, NMR analysis

Over the past several years, trichloroacetyl isocyanate has been used as a synthetic (1–6) and as a diagnostic (7–10) reagent. It reacts with hydroxyl groups to form carbamates of type I. Such derivatives are usually much more soluble in deuterochloroform than are the parent compounds; indeed, many underivatized corticosteroids