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Pharmaceutical Applications of Solid Dispersion Systems: X-Ray Diffraction and Aqueous Solubility Studies on Griseofulvin–Polyethylene Glycol 6000 Systems

WIN L. CHIOU

Abstract □ The X-ray diffraction method was used to characterize physicochemical properties of griseofulvin dispersed in polyethylene glycol 4000 and 6000. Results indicate a negligible or very limited solid solubility of griseofulvin in the pulverized solid dispersions. Pulverization and aging had pronounced effects on the X-ray diffraction spectrum. Results from aqueous solubility studies of griseofulvin in various concentrations of polyethylene glycol 6000 further indicate weak or insignificant interactions between the drug and the carrier. Mechanisms are postulated to account for the reported marked enhancement of dissolution rates and oral absorption of griseofulvin dispersed in these carriers.

Keyphrases □ Griseofulvin—dispersed in polyethylene glycol 6000, X-ray diffraction study, aqueous solubility, effects of pulverization and aging □ Polyethylene glycol 6000—dispersions with griseofulvin, X-ray diffraction study, aqueous solubility, effects of pulverization and aging □ Solid dispersions—griseofulvin–polyethylene glycol 6000, X-ray diffraction study, aqueous solubility, effects of pulverization and aging □ Dispersions, solid—griseofulvin–polyethylene glycol 6000, X-ray diffraction study, aqueous solubility, effects of pulverization and aging □ Solubility, aqueous—griseofulvin–polyethylene glycol 6000 dispersions, X-ray diffraction study □ X-ray diffraction—study, griseofulvin–polyethylene glycol 6000 dispersion, effects of pulverization and aging □ Antifungal agents—griseofulvin dispersed in polyethylene glycol 6000, X-ray diffraction study, aqueous solubility

The *in vitro* dissolution and oral absorption of griseofulvin in dogs and humans were markedly enhanced by the formation of solid dispersions in polyethylene glycol 6000 (1–3). Recently, these results were confirmed with a newly introduced commercial product[1] in single- (4) and multiple- (5) dose studies using larger numbers of test subjects. The new product requires only half of the dose recommended for conventional micronized products. Furthermore, the incidence of side effects decreased with this new formulation (5).

Although it was proposed that the enhancement of dissolution and absorption of griseofulvin dispersed in the polymer was primarily due to the molecular and colloidal dispersion of the drug in the highly water-soluble carrier (1–3), no extensive experimental data regarding physicochemical properties of such a dispersed system have been reported.

This paper reports the detailed results of X-ray diffraction and aqueous solubility studies on such a system. The X-ray diffraction data do not support the previous postulate regarding the extensive formation of a solid solution of griseofulvin in polyethylene glycol polymers. The aqueous solubility study was performed to investigate the possible interaction between the drug and the polymer in an aqueous medium. Findings from the present study should be valuable to the development of solid dispersion dosage forms of other poorly water-soluble drugs utilizing the same type of carriers. Some preliminary results were discussed in a review article (6).

Although different average molecular weights of polyethylene glycol polymers can be used as dispersion carriers (1–3), only polymer 6000 was studied in detail in the present investigation. This polymer has much less absorption in the UV and visible region than polymer 20,000 and thus interferes less with the direct spectrophotometric analysis of drugs (1). Furthermore, based on the author's experience, the solid dispersions prepared with this polymer were generally much easier to pulverize than those prepared with other molecular weights of the polymer.

[1] Gris-PEG, Dorsey Laboratories, Lincoln, Neb.

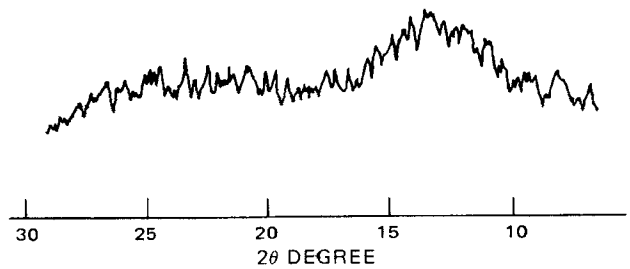

Figure 1—*X-ray diffraction spectrum of the unpulverized resolidified melt of griseofulvin.*

EXPERIMENTAL

Solid Dispersions—Griseofulvin[2]–polyethylene glycol 6000[3] solid dispersions containing 5, 10, 25, and 50% (w/w) griseofulvin were prepared by the melting method (1). After hardening, the melt was pulverized to a fine powder with a mortar and pestle. To study the effect of powdering on the X-ray diffraction pattern of the sample, some melts were poured directly into the sample holder used for the X-ray diffraction studies.

X-Ray Diffraction Studies—The procedure used was described previously (7, 8). The samples studied included the pure and resolidified griseofulvin and the polymers, solid dispersions and their physical mixtures.

Solubility Studies—Micronized griseofulvin, 10 mg, was evenly suspended in 15 ml of 0–10% (w/v) aqueous solutions of polyethylene glycol 6000 in screw-topped extraction tubes and equilibrated by shaking for 48 hr (a preliminary study indicated essentially a constant solubility value after 48 hr) in a constant-temperature water bath maintained at 22 ± 0.5°. The suspensions were then filtered through a 0.22-μm filter[4]. The first 10 ml of the filtrate was discarded to saturate the adsorption sites for griseofulvin on the filter (9); the last 5 ml of the filtrate was analyzed for the concentration of griseofulvin at 295 nm[5]. All experiments were performed at least in duplicate. The UV absorption, due to the presence of the polymer, was corrected in griseofulvin concentration determinations.

RESULTS AND DISCUSSION

X-ray diffraction spectra of the untreated griseofulvin and polyethylene glycol 6000 were previously reported (6). In the present study, essentially identical spectra were also obtained after they were melted, solidified, and pulverized. This, however, was not the case for the unpulverized resolidified griseofulvin melt (Fig. 1). The absence of major griseofulvin diffraction peaks indicates that an amorphous form existed in the unpulverized melt; this amorphous form is thought to convert to the crystalline form after pulverization. The observed glassy and brittle property of the melt and the appearance of an exothermic transition peak below the melting point when the melt was rerun in a differential thermal analyzer[6] are also in accordance with the postulate of the amorphous state of the melt sample. This effect of pulverization on the crystallinity was not observed for polyethylene glycol 4000 and 6000.

Major X-ray diffraction peaks of griseofulvin, particularly at 10.8, 13.3, and 16.6° (8), were all present in the pulverized dispersion samples containing 5–50% griseofulvin. A typical spectrum is shown in Fig. 2. The diffraction spectra of the 5% griseofulvin system were previously reported (6). The similarity of heights of the major diffraction peaks of griseofulvin in the physical mixture and dispersion samples with the same composition indicates the limited or negligible solid solubility of griseofulvin in the polymer. This result is obviously different from the previous postulation of the extensive solid solution formulation (1). Similar findings were also obtained for the griseofulvin–polyethylene 4000 system. Based on these findings and analyses, the (pulverized) dispersed systems of griseofulvin in polyethylene glycol 4000 or 6000 should be classified as simple eutectic mixtures with negligible or limited solid solubility. This result is similar to the findings with chloramphenicol–urea (10) and griseofulvin–succinic acid (8) binary systems and different from the finding on sulfathiazole–urea binary system (7).

[2] Griseofulvin USP, McNeil Laboratories, Fort Washington, Pa.
[3] Carbowax, Union Carbide Corp., New York, N.Y.
[4] Millipore.
[5] Beckman DBG spectrophotometer, Beckman Instruments, Inc., Fullerton, Calif.
[6] DuPont 900 thermal analyzer, DuPont Instruments Co., Wilmington, Del.

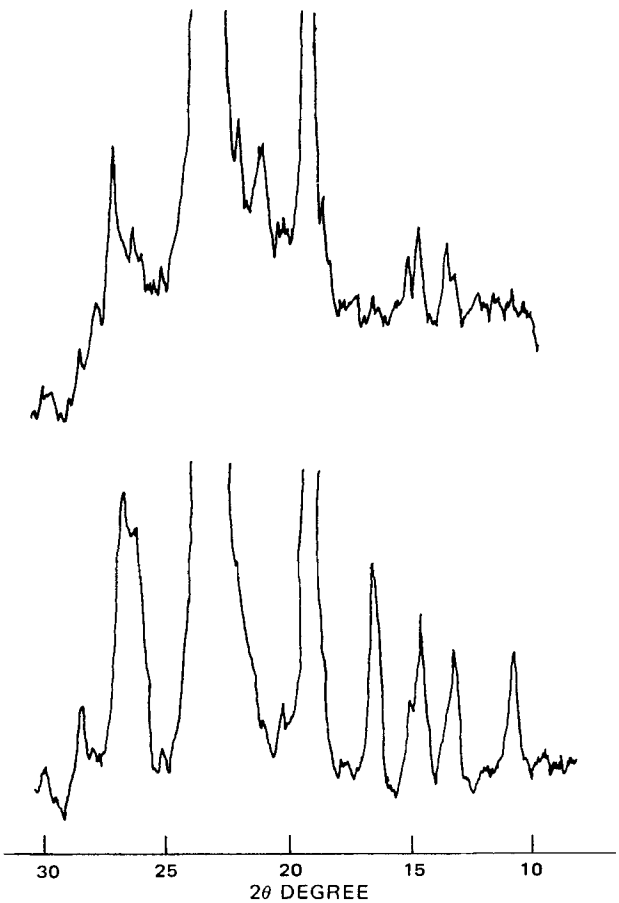

Figure 2—*X-ray diffraction spectra of 20% griseofulvin solid dispersion in polyethylene glycol 6000. Key: top spectrum, unpulverized sample; and bottom spectrum, pulverized sample.*

X-ray diffraction spectra of the freshly prepared (within 2 hr) unpulverized solid dispersions were quite different from those of freshly prepared or aged pulverized samples (Figs. 2 and 3). All major diffraction peaks of griseofulvin were absent. The most logical explanation is that the amorphous form of griseofulvin was precipitated from the melt after cooling, which is consistent with the observed formation of the amorphous form after resolidification of the pure griseofulvin melt, as discussed. The viscous property of the melt of the polymer also might retard the orderly crystallization of griseofulvin during the resolidification process.

The absence of those diffraction peaks, particularly in samples con-

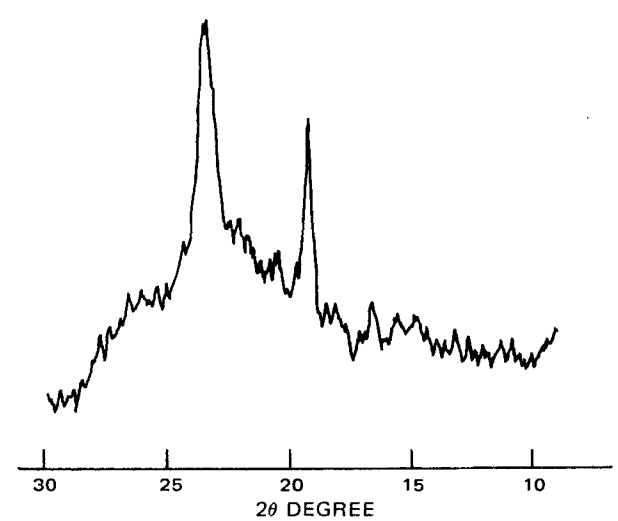

Figure 3—*X-ray diffraction spectrum of the freshly prepared unpulverized sample of 50% griseofulvin solid dispersion in polyethylene glycol 6000.*

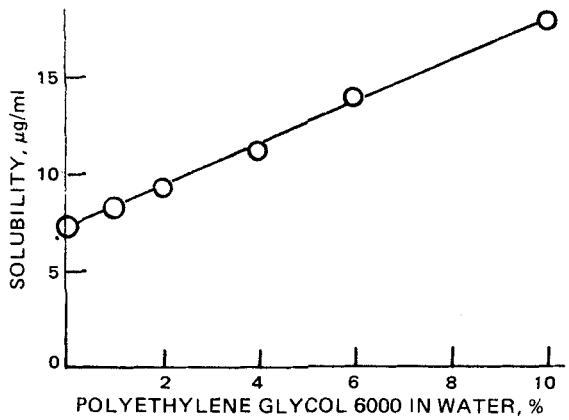

Figure 4—*Solubilities of griseofulvin in the presence of polyethylene glycol 6000.*

taining smaller fractions of griseofulvin, may also be attributed to the supersaturation of griseofulvin in the polymer caused by the retardation of the viscous polymer on the precipitation of griseofulvin (1, 6) and/or the colloidal or ultrafine crystallization. When X-ray diffraction studies were repeated several days later, major diffraction peaks of griseofulvin appeared in all samples except for the 5% griseofulvin system. Identical results for the latter system were obtained even after 3 months of storage at room temperature.

Intensive diffraction peaks of polyethylene glycol 6000 were present in all unpulverized, freshly prepared solid dispersions except for the 50% griseofulvin sample. It was soft and somewhat sticky 1 hr after preparation, and the hardness increased with time. The hardness of freshly solidified melts increased with the increase in griseofulvin concentration. This phenomenon is somewhat similar to that observed in the eutectic mixture of the sulfathiazole–urea system (7).

The effects of pulverization and aging on the X-ray diffraction pattern and hardness of the solid dispersions reported in this paper may also have some pronounced effect on their dissolution and absorption characteristics. The dissolution rate of sulfathiazole dispersed in urea with the eutectic composition decreased after storage (7). However, it is possible that no further changes in physical properties may occur after initial pulverization or a short period of storage. Identical dissolution profiles of griseofulvin were obtained for the pulverized samples of the 10% griseofulvin–90% succinic acid system and from its 10–20% dispersion in polyethylene glycol 4000 and 6000 even after 1 year of storage at ambient temperature. These original dissolution studies (not on samples aged for 1 year) were reported previously (1).

The absence of any X-ray diffraction peaks, other than those attributed to pure griseofulvin and the polymers in all solid dispersion samples, also indicates a lack of definite chemical complexation between the drug and the carrier polymer in their solid state. However, some interaction could be detected in their aqueous solutions, as shown by a moderate increase in the aqueous glycol 6000 (Fig. 4). Based on these data, the ratio for the number of molecules of the polymer required to solubilize one molecule of griseofulvin is 555. Since the ratio is so high, it is difficult to visualize the existence of any strong complexation between the two components. The high ratio can, however, be rationalized by the formation of a very weak complex with a high dissociation constant. The slight enhancement in the polymer solution can be equally well explained by the cosolvent effect of the polymer rather than by invoking complexation theory.

Based on the results of the X-ray diffraction and aqueous solubility studies, the previously reported marked enhancement of dissolution and absorption rates of griseofulvin dispersed in the polyethylene glycol polymers was primarily due to the reduction of the size of griseofulvin crystals rather than to the formation of solid solution, complexation, or metastable polymorphic forms. The generally observed decrease in the dissolution rate as the fraction of griseofulvin in solid dispersions increased (1) can be rationalized by the formation of larger crystals of griseofulvin due to the presence of relatively less carrier. This approach is in analogy to the griseofulvin–succinic acid solid dispersion system (11).

Other factors (6, 7, 11) such as increased wettability, reduction or absence of aggregation, and agglomeration and solubilization of the drug by the carrier at the diffusion layer of particles may also partially contribute to the enhancement of dissolution and absorption rates of griseofulvin dispersed in the polyethylene glycol polymers.

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