DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(4), 891-900 (1985)

DISSOLUTION AND UNIFORMITY PROPERTIES OF ORDERED MIXES OF MICRONIZED GRISEOFULVIN AND A DIRECTLY COMPRESSIBLE EXCIPIENT

J.W. MCGINITY, Chi-Tze KU, R. BODMEIER, and M.R. HARRIS

Drug Dynamics Institute, College of Pharmacy,

University of Texas at Austin, Austin, TX 78712

ABSTRACT

Ordered mixes of micronized griseofulvin were prepared with a commercially available directly compressible excipient. The excipient consisted of a combination of maltose and dextrose and a particle size fraction of approximately 250-850μ was employed in the mixing studies. Ordered mixes containing 0.25%, 0.5%, and 1% active ingredient were prepared and after thirty minutes of mixing, excellent content uniformity of the mixes was seen. Rapid dissolution of drug from the sugar granules was observed when the drug coated granules were tested using the U.S.P. Paddle Method. The ordered mixing process provided an even coat of the micronized drug onto the granules. As the granules dissolved, particle-particle interactions and aggregation problems with the hydrophobic drug were eliminated. The properties of griseofulvin tablets prepared from these ordered mixes were evaluated and the

0363-9045/85/1104-0891$3.50/0

tablets showed excellent content uniformity and rapid dissolution of griseofulvin from the dosage form.

INTRODUCTION

The slow rates of dissolution for poorly soluble and hydrophobic drugs can be increased by precipitating the drugs onto the surfaces of insoluble powders. Recent reports in the pharmaceutical literature have discussed the applications of magnesium aluminum silicate[1,2] and fumed silicon dioxide[3,4] for this purpose. Micronization has been employed to improve the dissolution rate of hydrophobic drugs. However, the resultant micronized drug particles are extremely cohesive and difficult to wet and this may result in slow dissolution rates. For potent drugs that occupy one percent or less of the solid dosage form, the added problem of content uniformity in the dosage form must be considered.

The purpose of the present study was to prepare and to investigate the properties of ordered mixes of a micronized hydrophobic drug and a commercially available directly compressible excipient (Emdex, Edward Mendell Co., Carmel, New York). The uniformity of drug content was examined in addition to the dissolution properties of drug-excipient mixes in both granules and tablets. Ordered mixes are expected to result from an adherence of fine particles of one constituent to considerably more coarse particles of a second constituent.[5] The adhesion results either from inherent surface forces of the smaller

particles or from surface tension effects of adsorbed moisture. Hersey[6] has reported that the cohesive properties of powders and other surface phenomena usually develop with increasing fineness resulting in an ordered rather than a random mixing operation. An indepth review of the advances in powder mixing and segregation in relation to pharmaceutical processing was recently published by Staniforth.[7]

RESULTS AND DISCUSSION

The degree of homogeneity of drug-excipient mixes was determined from the coefficient of variation in drug content of samples assayed. The direct compression excipient (Emdex) used in this study was a highly refined sugar product composed of free-flowing spray-crystallized porous spheres. Ordered mixes of griseofulvin with dried and non-dried granules were prepared at three levels of active ingredient. The degree of homogeneity of the mixes was determined from the coefficient of variation and the results of these homogeneity studies appear in Table 1. Coefficients of variation less than 4% were found with the dried granules. Dried granules gave slightly lower values than the non-dried granules. The excellent homogeneity of the drug-sugar granules as seen in Table 1 suggests a strong interaction between the two components. Such strong particle interactions may be the result of adsorption, surface tension, frictional or electrostatic forces or other possible forces of adhesion.[6]

The reported mixing times in the scientific literature for the preparation of ordered mixes, vary considerably. Thanomkiat

TABLE 1. Coefficient of variation (C.V.) of ordered mixes of griseofulvin with Emdex granules after mixing for 30 minutes in a twin-shell blender.

Concentration of Drug (%)	Dried Granules C.V. (%)	Non-Dried Granules[a] C.V. (%)
0.25	2.10	2.82
0.50	1.17	4.35
1.00	1.43	4.40

[a]As received from the manufacturer.

and co-workers[8] employed 100 minutes for the mixing of micronized prednisone (1%) with starch-lactose granules. These investigators reported that as the particle size distribution of the carrier granules increased, the tendency for granules to segregate increased which resulted in uneven drug distribution and poor homogeneity. Bryan and coworkers[9] found that after 15 minutes of mixing for micronized sodium salicylate (1%) and a starch-lactose granulation, ordered mixes with coefficients of variation less than 5% were obtained. This value increased as the concentration of drug in the mix was increased to 5% and 10%. A 30 minute period of mixing was selected in the present study although rapid homogeniety was achieved at much earlier mixing times, as shown in Figure 1 for griseofulvin. The rapid onset of formation of a homogeneous ordered mix may have been assisted by the excellent flow properties of the excipient granules due to their density and spherical shape. Mixing studies with drug and micronized

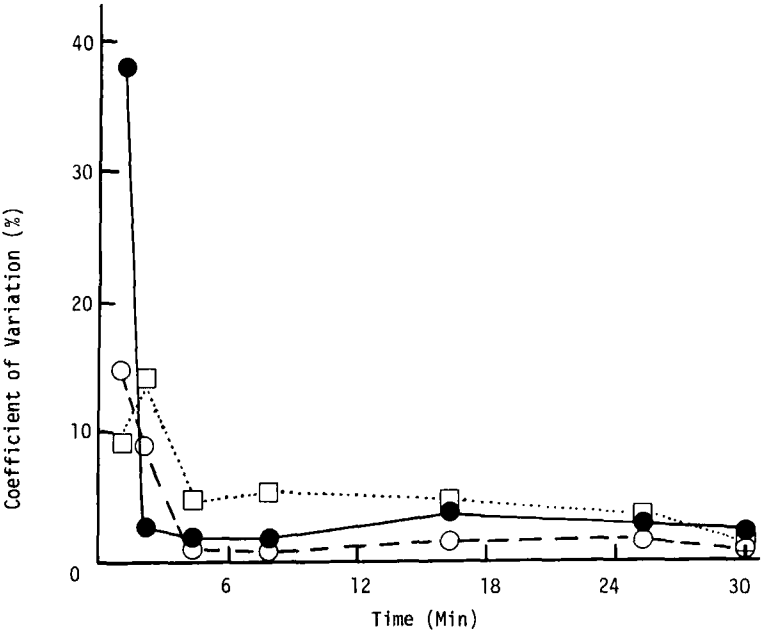

Fig. 1. Rate of mixing of various concentrations of micronized griseofulvin with granules of Emdex (250-850 μ). Key: ●—●, 0.25% griseofulvin; ○--○ 0.5% griseofulvin; □·····□, 1% griseofulvin.

excipient resulted in a coefficient of variation in excess of 30% after 30 minutes of mixing.

Scanning electron micrographs of the surface of a sugar granule with and without drug particles, appear in Figure 2. The surface morphology of the granule is clearly defined in photograph A. The coating of micronized griseofulvin onto the surface of the granule is evident in photograph B.

Rapid dissolution of griseofulvin from the sugar granules was observed when ordered mixes containing 5 mg of drug were tested with the U.S.P. paddle method (see Figure 3). As the granules dissolved, particle-particle interactions and aggregation problems

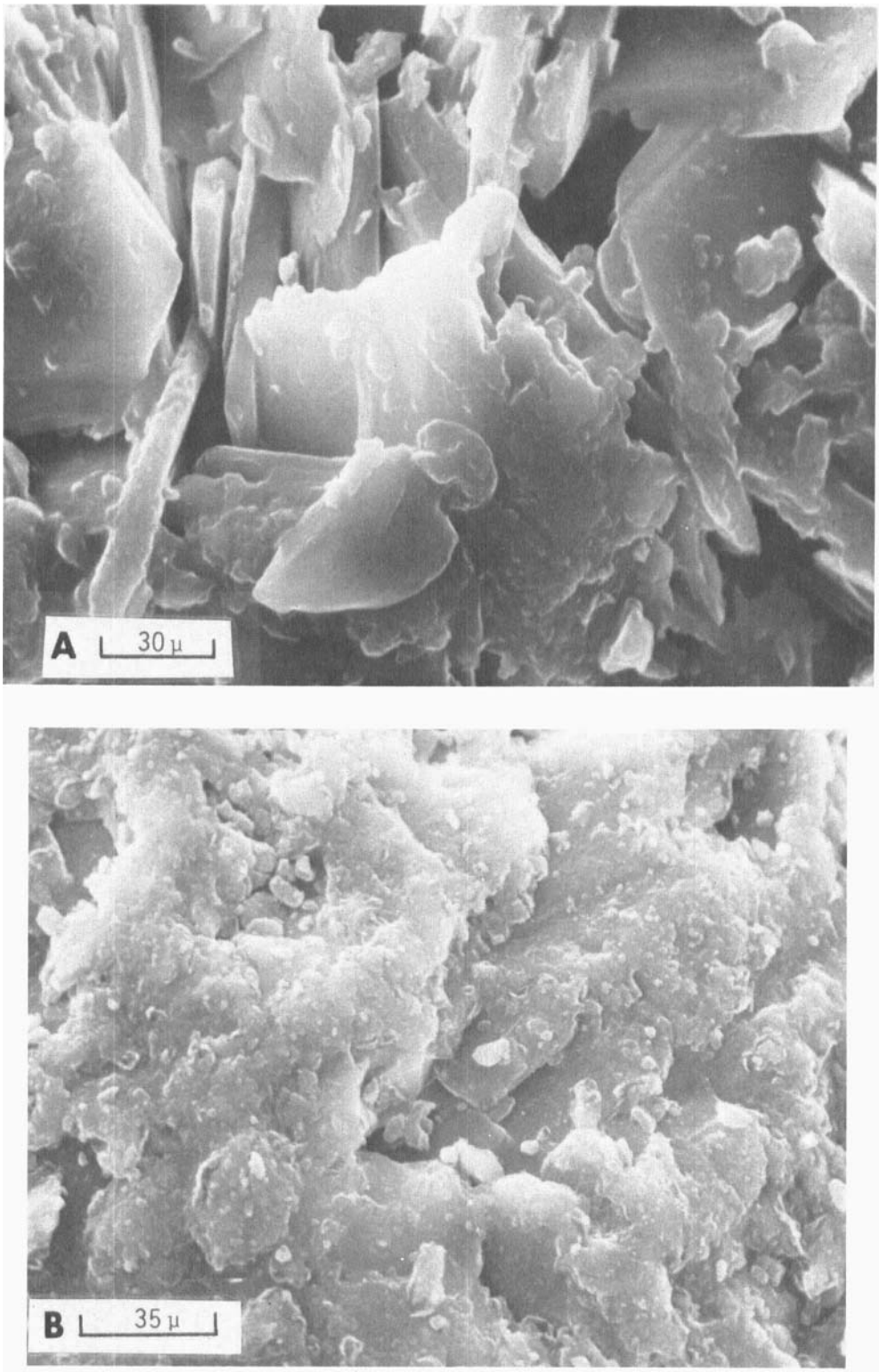

Fig. 2. Scanning electron micrographs of Emdex (A) and Emdex coated with 0.5% griseofulvin (B).

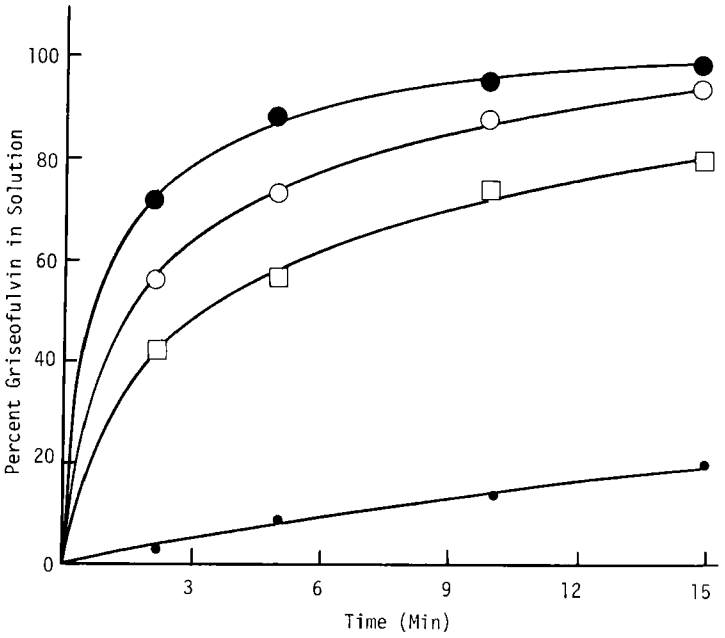

Fig. 3 Dissolution profiles of griseofulvin: Emdex ordered mixes containing 5 mg drug, in aqueous polysorbate 80 solutions 0.02%, at 37° C. Key: ●—●, 0.25% griseofulvin; ○—○, 0.5% griseofulvin; □—□, 1% griseofulvin; •—•, pure micronized drug.

with the hydrophobic drug were eliminated. These problems will occur with micronized drug alone and result in a significant reduction in the dissolution rate as shown in Figure 3. Rapid dissolution of griseofulvin from the ordered mix occurred during the first five minutes of the study. During the same period, less than ten percent of the griseofulvin passed into solution from samples of pure drug alone. Dissolution of drug from samples containing 0.25% active ingredient was faster than those containing 0.5% and 1% respectively. This could have been due to the possible formation of an uneven coating of drug onto the granule surface as the level of drug in the mix was increased

from 0.25% to the 1% level. The rapid dissolution of the sugar granule will also aid in the dissolution process for the drug.

Tablets containing ordered mixes of griseofulvin at the three concentration levels with dried granules and non-dried granules as received from the manufacturer, were prepared on a Stokes Model F single punch tablet press. The tablet formula is described in the experimental section. Tablets were compressed to a hardness of 8 to 10 kg and were found to disintegrate in water and dilute hydrochloric acid in the U.S.P. disintegration apparatus at 37°C, in less than two minutes. Tablet friabilities of less than 0.1% were obtained for all tablet formulations. Low values for the coefficients of variation for the tablet weight and content uniformity were obtained for griseofulvin tablets prepared from ordered mixes containing either dried or non-dried sugar granules, as shown in Table 2. The rapid dissolution of griseofulvin from these tablets is shown in Figure 4 and is compared with the dissolution profile of the pure micronized drug. Bolhius and Lerk[10] reported however that ordered mixing of lubricants with tablet ingredients should be limited. When an active ingredient has to be attached to carrier particles by ordered mixing, special attention should be paid to possible interactions of glidants and/or lubricants with the ordered mix.

In summary, the preliminary results of this investigation have shown that the preparation of ordered mixes containing a directly compressible vehicle and small amounts of a hydrophobic and poorly soluble model drug, may be a viable method to overcome

TABLE 2. Properties of griseofulvin tablets containing ordered mixes of griseofulvin with dried Emdex and non-dried Emdex.[a]

	Dried Emdex		Non-Dried Emdex	
Concentration of griseofulvin (%)	Content Uniformity C.V.(%)	Tablet Weight C.V.(%)	Content Uniformity C.V.(%)	Tablet Weight C.V.(%)
0.25	5.9	1.86	3.11	2.15
0.50	4.28	1.48	1.12	0.87
1.00	3.13	1.36	2.53	1.38

[a]As received from the manufacturer.

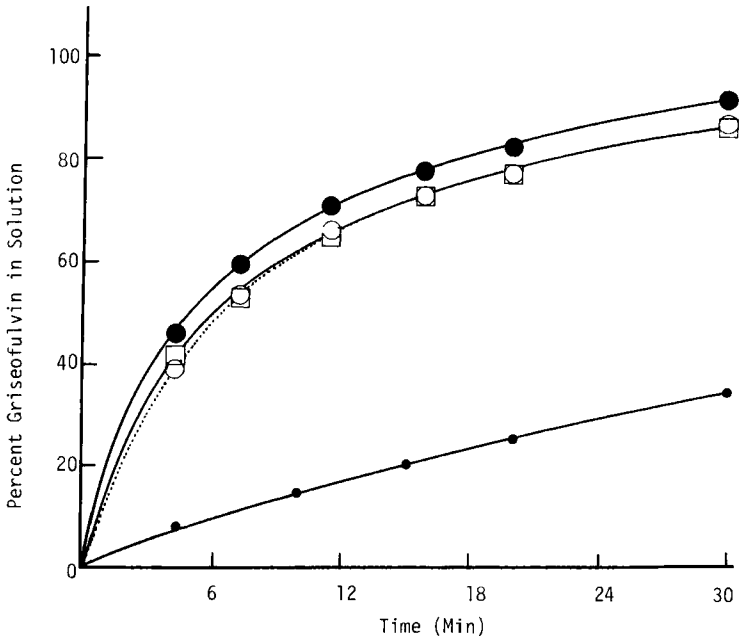

Fig. 4. Dissolution profiles of tablets containing griseofulvin: Emdex ordered mixes in aqueous polysorbate 80 solutions 0.02% at 37°C. Key: ●—●, 0.25% griseofulvin (3 tablets); ○···○, 0.5% griseofulvin (2 tablets); □—□, 1.0% griseofulvin (1 tablet); ●—●, pure micronized drug.

content uniformity and dissolution problems experienced with such pharmaceuticals. The directly compressible tablet excipient employed in these studies was a hygroscopic material and some of the small variability experienced may be due to the additional adsorption of moisture. Other directly compressible excipients are presently being evaluated.

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