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Dissolution Behavior of Griseofulvin Solid Dispersions Using Polyethylene Glycol, Talc, and Their Combination as Dispersion Carriers

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ABSTRACT

Griseofulvin solid dispersions were prepared using polyethylene glycol 6000 (PEG), talc, and their combination as carriers by the solvent method. The dissolution of griseofulvin from these dispersions was studied. It was found that in these carriers the drug dissolution rate was a function of drug loading. The dissolution rate from dispersions prepared using PEG was similar to that from PEG/talc dispersions, especially at a low percentage of drug loading. Dispersions of PEG and PEG/talc provided dissolution rates faster than those from dispersions of talc. The incorporation of talc in PEG yielded dispersions with properties of less tackiness and ease for handling. Dissolution kinetics, based on the Hixson-Crowell equation, was used to determine the characteristics of griseofulvin particles in dispersions. Linear relationships were obtained for PEG and PEG/talc dispersions that indicated the presence of a uniformly sized monoparticulate system, whereas deviation from linearity was observed for talc dispersions. This appeared to be a multiparticulate system in which particles were present as free form and adsorbed form on the surface of talc.

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INTRODUCTION

The use of solid dispersions containing water-soluble carriers to enhance the dissolution rate and bioavailability of poorly water-soluble drugs has been demonstrated by a number of investigators (1–6). The methods utilized in the preparation of solid dispersions include melting, use of common solvent, and a combination of melting and solvent approach (7,8). Solid dispersions prepared from soluble carriers, such as polyethylene glycols, usually have the disadvantage of being tacky and therefore difficult to subdivide and handle. Polyethylene glycol solid dispersions were formulated using an in situ fusion technique in which the melted drug and carrier mixture were granulated with excipients (9,10). This procedure resulted in a less tacky granulation.

Surface adsorption technique was also introduced to enhance drug dissolution rate (11,12). In this method, the drug is deposited in minuscule form on the surface of the adsorbent after removal of the solvent. The drug undergoes micronization as it is deposited on the extensive surface of the microparticular adsorbent. One of the disadvantages of the solvent deposition method is that the adsorption of drug onto the adsorbent causes an incomplete drug recovery (13).

In this study, polyethylene glycol 6000 (PEG), talc, and a combination of talc and PEG were used as dispersion carriers for griseofulvin to investigate drug dissolution behavior. The effect of drug loading and talc/PEG ratios on dissolution performance was studied. An attempt was also made to use the Hixson-Crowell dissolution equation (14) to describe the particulate properties of griseofulvin in the solid dispersions.

Talc, a widely used excipient, was used in this study due to its small particle size and similar chemical structure to magnesium aluminum silicate, which has been found (15) to enhance the dissolution rate of griseofulvin, prednisone, and indomethacin.

MATERIALS AND METHODS

Materials

Griseofulvin (micronized, USP grade) was obtained from Glaxo Inc. (U.K.). Polyethylene glycol 6000 was purchased from Union Carbide Corp. (U.S.). Talc (USP grade) was obtained from Ruger Chemical Co. (U.S.). General chemicals were of analytical grade.

Preparation of Solid Dispersion

Griseofulvin and dispersion carrier were accurately weighed and transferred to a beaker. A sufficient quantity of chloroform was added to dissolve and/or disperse the ingredients. The mixture was then stirred and evaporated to dryness. The samples were dried at 40°C for 1 hour, passed through a 60 mesh screen, and placed in an oven at 40°C overnight to complete the drying process.

Griseofulvin Content in Dispersions

An aliquot of dispersion equivalent to 10–20 mg of drug was weighed and transferred to a 50 ml volumetric flask. Isopropanol was added to the flask and sonicated for an hour to assure complete extraction of the drug from the dispersion. The mixture was filtered, diluted with water, and assayed spectrophotometrically at 295 nm to determine the amount of griseofulvin present in the dispersion.

Dissolution Study

Dissolution media of pH 1.2 and 7.5 were prepared according to the method described in the USP (16) but without the addition of sodium chloride and pepsin, and pancreatin respectively. A total of 5.5 mg sodium lauryl sulfate was added to each liter of dissolution medium to increase the wettability of griseofulvin.

Dissolution study was performed using USP Apparatus two method (paddle method) at an agitation speed of 100 rpm and 900 ml of dissolution medium at 37°C. Solid dispersions equivalent to 10 and 8 mg of griseofulvin for pH of 1.2 and 7.5, respectively, were introduced into the dissolution medium. Any lumps floating on the surface of the medium were separated gently with a glass rod immediately after the dispersion was introduced. At suitable time intervals, 6 ml of the sample was removed from a point midway between the surface of the dissolution medium and the bottom of the paddle. This volume was replaced with an equal volume of fresh dissolution medium to maintain a constant volume for drug dissolution. The sample was filtered and assayed for griseofulvin concentration at 295 nm. Calibration plots of griseofulvin in dissolution media of pH 1.2 and 7.5 were prepared in the concentration range from 0.384 to 12.8 mg/ml.

The dissolution of griseofulvin from the dispersion at each time interval was expressed as the ratio of cumu-

lative mass of drug dissolved to the initial mass of griseofulvin present in the dispersion.

Drug Loading

The influence of drug loading on the dissolution of griseofulvin from the dispersions was studied using dispersions containing 83.3%, 50.0%, 16.7%, and 9.1% griseofulvin in talc, PEG, and PEG/talc (1/1). The quantities of drug and carriers used are reported in Table 1.

PEG/Talc Ratio

The effect of PEG to talc ratio on the dissolution of griseofulvin was studied using dispersions containing 9.1% drug loading. The ratios of PEG to talc were 1/9, 1/3, 1/1, 3/1, and 9/1, as shown in Table 2.

RESULTS AND DISCUSSION

Appearance of Solid Dispersions

Physically, the talc dispersions were fine powder and easy to mix and screen following the evaporation of chloroform. On the other hand, the PEG dispersions were tacky and difficult to mix and screen during preparation. The partial replacement of PEG with talc yielded dispersions that were less tacky and easy to handle.

Effect of Drug Loading

The weight percentage of griseofulvin recovered from the dispersions was determined. The results indicated that, for all drug dispersions, the recovery was in the range from 95% to 100% of the theoretical amount.

Table 1

Amount of Griseofulvin and Carriers Used in the Preparation of Dispersions

Amount of Griseofulvin (g)	Amount of Carriers [talc, PEG, PEG/talc (1/1)] (g)	Drug Loading (%)
1.0	0.2	83.3
1.0	1.0	50.0
0.2	1.0	16.7
0.2	2.0	9.1

Figures 1 and 2 show the percentage of griseofulvin dissolved versus time from dispersions prepared using talc, PEG, and PEG/talc (1/1) at pH 1.2 and 7.5 respectively. The griseofulvin in the dispersions demonstrated a dissolution rate increased with decreasing drug loading. This may be attributed to the finer subdivision of drug particles in dispersions containing higher carrier loading. Griseofulvin pure drug showed the slowest dissolution rate. Similar results of dissolution were obtained as dispersions were tested in dissolution media of pH 1.2 and 7.5.

Effect of Carriers

Generally, for dispersions containing the same percentage of drug, talc provided the slowest drug dissolution rate in the time interval studied, as shown in Figures 1 and 2. This became more significant as drug loading increased. However, similar results of griseofulvin dissolution were obtained from PEG, talc, and PEG/talc solid dispersions at 83.3% drug loading.

Table 2

Ratio of PEG to Talc Used in the Preparation of Dispersions

Amount of Griseofulvin (g)	Amount of PEG (g)	Amount of Talc (g)	PEG/Talc Ratio	Drug Loading (%)
0.2	0.2	1.8	1/9	9.1
0.2	0.5	1.5	1/3	9.1
0.2	1.0	1.0	1/1	9.1
0.2	1.5	0.5	3/1	9.1
0.2	1.8	0.2	9/1	9.1

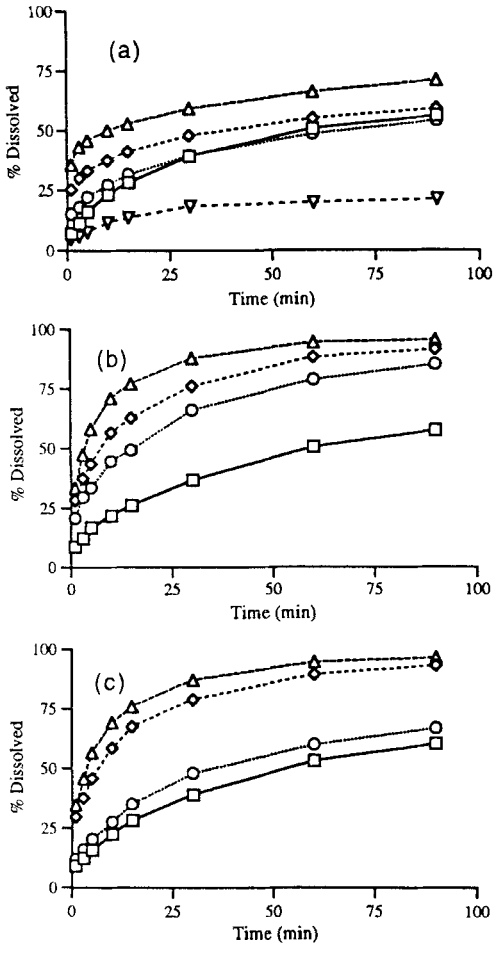

Figure 1. Dissolution of griseofulvin from (a) talc, (b) PEG, and (c) PEG/talc dispersions with (▽) 100%, (□) 83.3%, (○) 50%, (◇) 16.7%, and (△) 9.1% drug loading at pH 1.2.

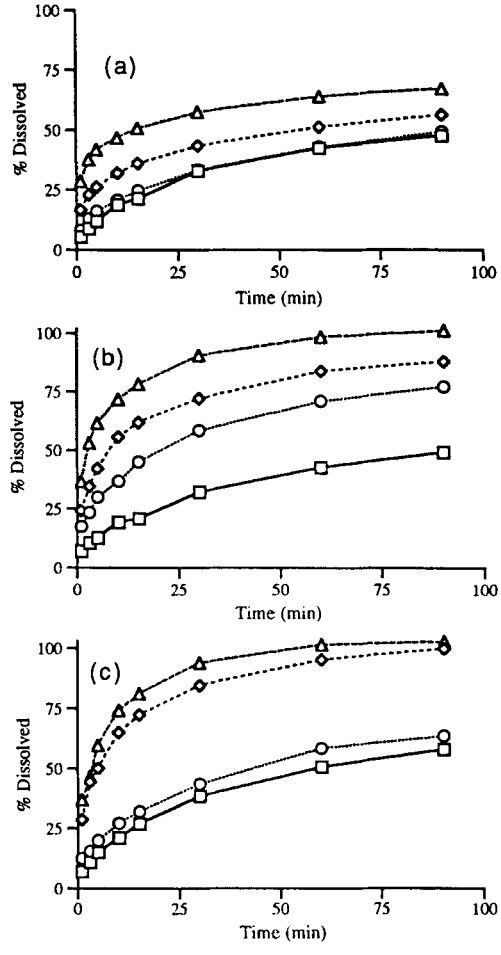

Figure 2. Dissolution of griseofulvin from (a) talc, (b) PEG, and (c) PEG/talc dispersions with (□) 83.3%, (○) 50%, (◇) 16.7%, and (△) 9.1% drug loading at pH 7.5.

PEG was found to be better than talc in enhancing the drug dissolution. This superior performance of PEG in enhancing drug dissolution may be explained in that PEG, being water-soluble, increases the wettability of griseofulvin, whereas talc, being insoluble, provides no effect on the wettability of griseofulvin. Also, the subdivision of drug particles in PEG dispersion is finer than that in talc dispersion. Furthermore, PEG may increase the solubility of griseofulvin as a result of overlapping the diffusion layers between PEG and drug.

Results of griseofulvin dissolution obtained from PEG/talc dispersions were greater than those of talc dispersions or comparable to those of PEG dispersions containing the same percentage of drug loading, except for dispersions containing 50% drug loading where the PEG/talc dispersions demonstrated values of percentage of drug dissolved less than those obtained from PEG dispersions. This suggests that replacing half the amount of PEG with talc in the PEG dispersions will not alter the drug dissolution, especially at a low percentage of drug loading.

Effect of PEG/Talc Ratio on Drug Dissolution

Figure 3 illustrates the percentage of drug dissolved versus time for dispersions containing 9.1% drug loading in a carrier composed of PEG/talc in the ratios of 1/9, 1/3, 1/1, 3/1, and 9/1. The drug dissolution rate increased with the increasing PEG/talc ratio until it was equal to or greater than one; then the difference of the dissolution rates became insignificant, indicating that increasing the PEG content does play a role in the en-

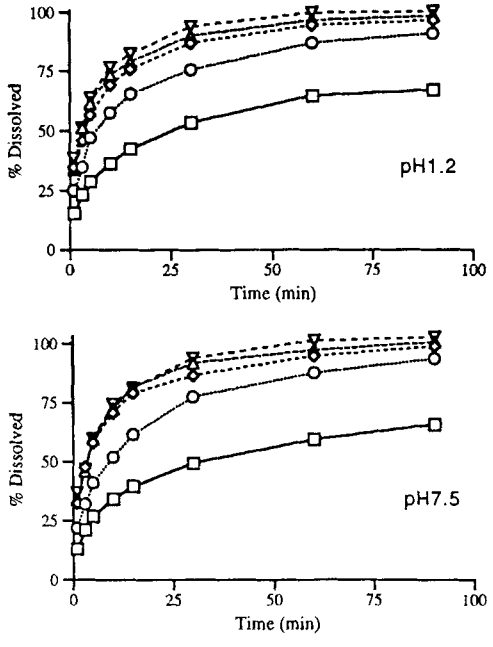

Figure 3. Dissolution of griseofulvin from dispersions with PEG/talc ratio of (□) 1/9, (○) 1/3, (◇) 1/1, (Δ) 3/1, and (▽) 9/1 at 9.1% drug loading.

hancement of drug dissolution from PEG/talc dispersions. It appears that the effect of pH of the medium demonstrated no effect on the drug dissolution from dispersions.

Dissolution Kinetics

Powder dissolution, when the surface area changes with time, can be described by the Hixson-Crowell cube root equations:

$$W_o^{1/3} - W^{1/3} = kt \quad (1)$$

$$W^{-2/3} - W_o^{-2/3} = kt \quad (2)$$

where W_o is the initial weight of the uniformly sized particles, W is the weight of the particles at time t, and k is the Hixson-Crowell cube root constant. Accordingly, a linear relationship will be obtained when $W_o^{1/3} - W^{1/3}$ or $W^{-2/3} - W_o^{-2/3}$ is plotted versus time. Eq. 1 is used for sink condition, whereas Eq. 2 is used for nonsink condition.

In solid dispersion, the drug may be present as solid solution, crystal, or amorphism in the form of uniformly sized particles. It will therefore follow the Hixson-Crowell pattern after dissolution of the solid dispersion. This may allow the application of the Hixson-Crowell equation to determine the physical form of drug particles in dispersion. If the drug particles exist as a multiparticulate system with varied size, the Hixson-Crowell equation may not be applicable.

For dissolution of a poorly water-soluble drug such as griseofulvin, sink condition is not practical. Therefore, Eq. 2 can be used. Figures 4 and 5 show plots of griseofulvin dissolution at pH 1.2 and 7.5, respectively, obtained according to Eq. 2. Linear relationships were obtained for drug in PEG and PEG/talc dispersions. This indicates the presence of a uniformly sized monoparticulate system, whereas deviation from linearity was shown for drug dispersed in talc. A fast drug dissolution rate was observed in the initial 5–10 minutes fol-

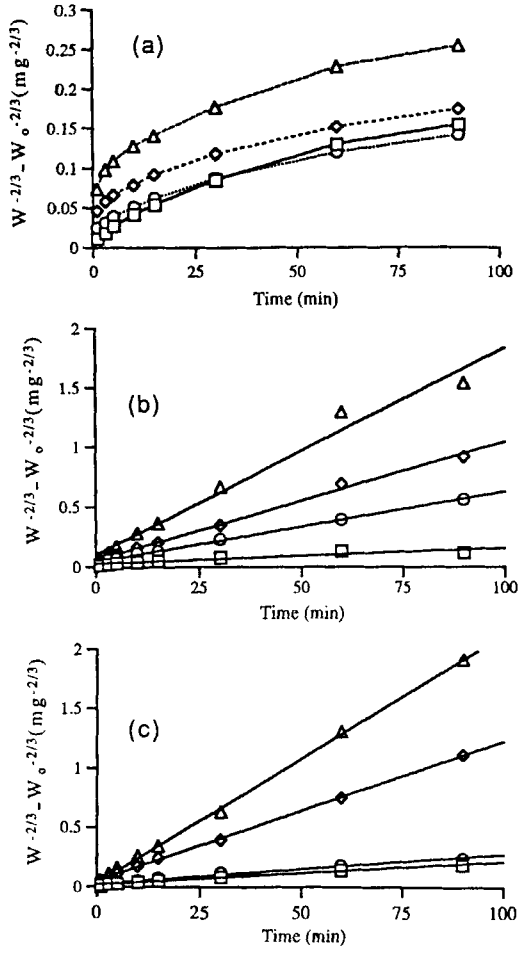

Figure 4. Hixson-Crowell cube root plots for the dissolution of griseofulvin from (a) talc, (b) PEG, and (c) PEG/talc dispersions with (□) 83.3%, (○) 50%, (◇) 16.7%, and (Δ) 9.1% drug loading at pH 1.2.

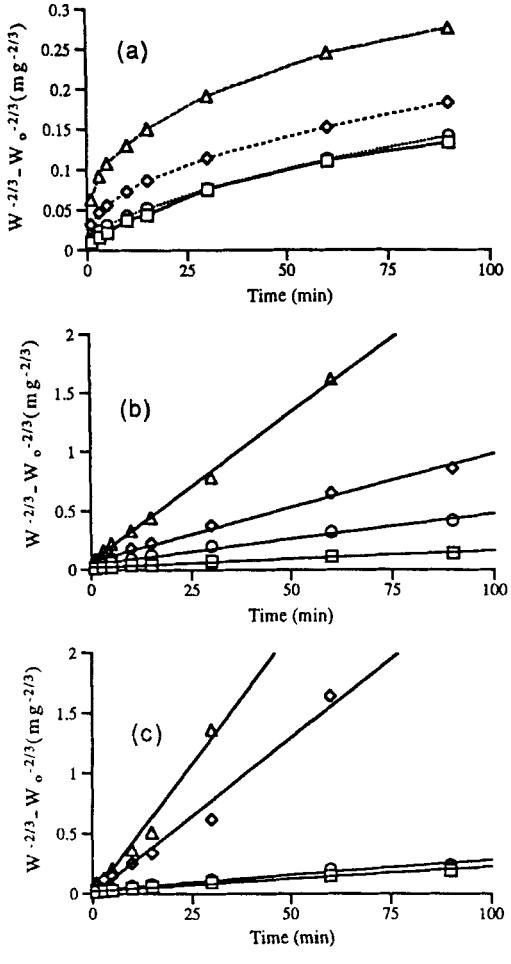

Figure 5. Hixson-Crowell cube root plots for the dissolution of griseofulvin from (a) talc, (b) PEG, and (c) PEG/talc dispersions with (□) 83.3%, (○) 50%, (◇) 16.7%, and (Δ) 9.1% drug loading at pH 7.5.

lowed by a slow dissolution rate. This dissolution pattern may be due to the presence of a multiparticulate system in the dispersion. That is to say, one type of the particles may be of those adsorbed on the surface of talc and others may be present in the form of free particles. The former type of particles is micronized on the surface of adsorbent, resulting in a faster dissolution rate.

Table 3 shows the Hixson-Crowell cube root dissolution rate constants for PEG and PEG/talc solid dispersions. The similarity of the rate constants from PEG and PEG/talc dispersions reveals that addition of talc to PEG dispersions will not affect the particle characteristics of griseofulvin in the dispersion, especially at a low concentration of drug loading.

Table 3

Cube Root Dissolution Rate Constants for PEG and PEG/Talc (1/1) Solid Dispersions

Griseofulvin Loading (%)	Cube Root Rate Constant[a] ($mg^{-2/3}min^{-1} \times 10^{-3}$)		
	pH	PEG	PEG/Talc (1/1)
83.3	1.2	0.18 ± 0.06	0.20 ± 0.05
50.0	1.2	0.59 ± 0.08	0.20 ± 0.05
16.7	1.2	1.03 ± 0.20	0.43 ± 0.70
9.1	1.2	2.20 ± 0.70	2.30 ± 0.76
83.3	7.5	0.15 ± 0.06	0.21 ± 0.03
50.0	7.5	0.46 ± 0.14	0.26 ± 0.06
16.7	7.5	0.92 ± 0.20	1.89 ± 0.03
9.1	7.5	2.75 ± 1.10	3.16 ± 0.70

[a]Mean ± SD of three determinations.

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