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IMPROVING DISSOLUTION RATES OF GRISEOFULVIN BY DEPOSITION ON DISINTEGRANTS

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ABSTRACT

The dissolution rate of griseofulvin was markedly enhanced by the solvent deposited on the disintegrants of Primojel, Mobile Starch and Nymcel.

The enhancement of the dissolution rate of the solvent deposition systems was due to the effects of wetting and deaggregation of the disintegrants. The dissolution of the griseofulvin from the Primojel system was at a higher rate than the other systems. This was attributed to the smaller particle size of the griseofulvin in the Primojel system. The tablets of the Primojel system demonstrated the

highest dissolution rate. This was resulted from the fast disintegration time of the tablets and the small particle size of the griseofulvin.

INTRODUCTION

The application of solvent deposition technique has successfully increased the dissolution rate of the poorly water-soluble drugs (1). The principle of this technique is by deposition of the drug from a solvent onto the surface of an inert excipient to obtain a high surface area by reduction of particle size, since the dissolution rate is directly proportional to the surface area.

Several excipients have been used for drugs deposition such as fumed silicon dioxide, silicic acid (1), potato starch, lactose (2) and montmorillonite (3).

Disintegrants are commonly used in tablets to assist disintegration. The disintegraton action of swelling, wicking and deformation during hydration resulting in deaggregation and wetting of the drug particles may provide a high surface area for dissolution.

In this study, an attempt was made to employ tablet disintegrants for drug deposition to

investigate their influence on drug dissolution. It is suggested that the dissolution rate of the drug can be improved by combination of the disintegration effect with the solvent deposition effect. Three types of disintegrants i.e. Primojel (modified starch), Mobile Starch (unmodified wheat starch) and Nymcel (modified cellulose) were used for griseofulvin deposition.

MATERIALS AND METHODS

The disintegrants used were Primojel (Generichem Corp., N.J., U.S.A.), Mobile Starch (Cheun Chi Pharmaceutical Co., R.O.C.) and Nymcel (Nyma corp., Nijmegen, Holland). Griseofulvin (Kingdom Pharmaceutical Co., R.O.C.) was obtained in a micronized form. All reagents used were of analytical grade.

Preparation of Solvent Deposition Systems

The required amount of the griseofulvin powder was dissolved in acetone. A known weight of the disintegrants was dispersed in the drug solution. The solvent was then evaporated at room temperature with constant stirring. The products were dried under vacuum for 24 hours and passed through a 70 mesh sieve.

Preparation of Physical Mixtures

Accurately weighed amounts of griseofulvin powder and disintegrants were mixed through a 70 mesh sieve 20 times. The mixtures were transfered to a vacuum desiccator and dried for 24 hours.

Preparation of Tablets

A Riken (Japan) tableting mechine was used. Sample powders equivalent to 125 mg griseofulvin were placed in the die and a pressure of 200 kgf/cm^2 was applied to the punch to form tablets.

Dissolution Study

This was conducted using the USP Apparatus 2 method; 500 ml of distilled water was used as the dissolution medium. The temperature was maintained at 37 °C and the stirring rate was 100 rpm. Samples equivalent to 125 mg of griseofulvin were used. 5 ml of sample solution was withdrawn as a function of time and analysed for drug concentration at 292 nm by spectrophotometry. After each sampling 5 ml of water was infused back to the beaker to maintain a constant volume for the dissolution medium. At least tripicate runs were made for each determination.

Disintegration of Tablets

This was determined according to the USP disintegration method for uncoated tablets using the Toyama Disintegration Tester (Japan).

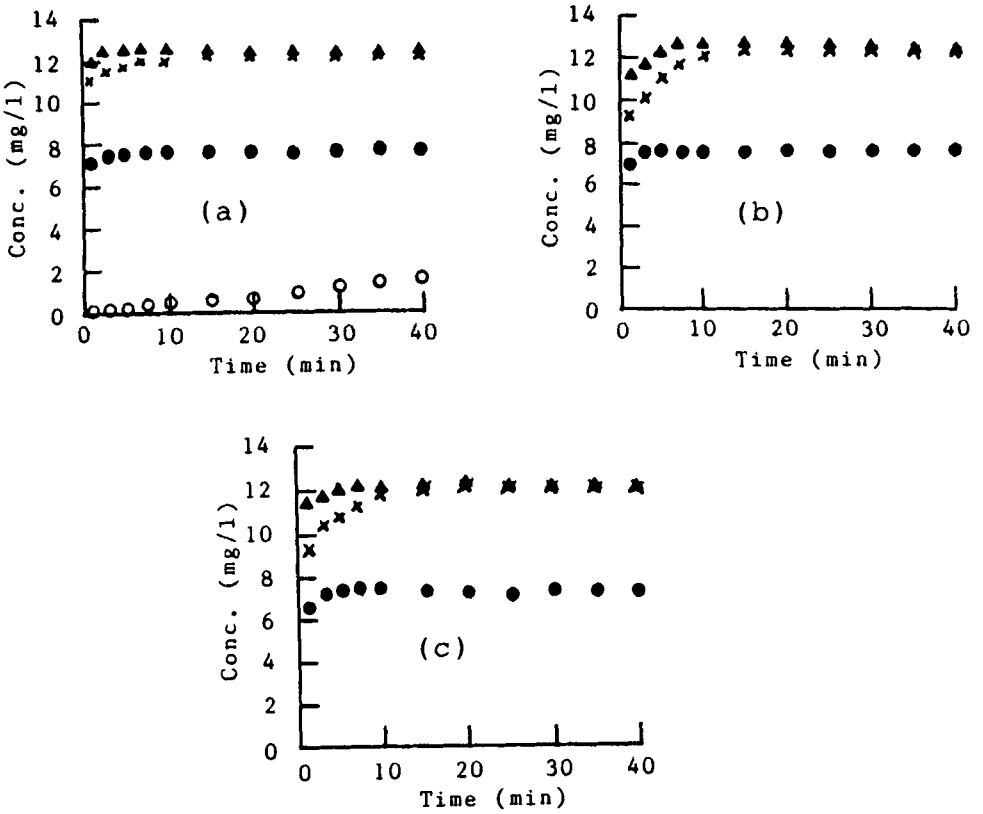

FIGURE 1

Dissolution profiles of griseofulvin (gri) from solvent deposition systems (sds) and physical mixtures (pm). (a) ▲ , gri-95% Primojel (sds); × , gri-60% Primojel (sds); ● , gri-60% Primojel (pm); ○ , micronized gri. (b) ▲ , gri-95% Mobile Starch (sds); × , gri-60% Mobile Starch (sds); ● , gri-60% Mobile Starch (pm). (c) ▲ , gri-95% Nymcel (sds); × , gri-60% Nymcel (sds); ● , gri-60% Nymcel (pm).

RESULTS AND DISCUSSION

The dissolution profiles for the solvent deposition systems, physical mixtures and pure griseofulvin are shown in Figure 1. It is clear that both the solvent deposition systems and the physical mixtures demonstrate a significant increase in the dissolution rate for griseofulvin from the disintegrants. The solvent deposition systems also show a higher dissolution rate than that of the physical mixtures.

Figure 2 shows the scanning electron micrographs of the griseofulvin powders and the solvent deposition systems. It is evident that the particles of the griseofulvin in the solvent systems are a larger size than the micronized ones.

According to the dissolution theories (4), The smaller particle size leads to a faster dissolution rate. The dissolution rate of griseofulvin, shown in Figure 1, follows the order of solvent deposition systems > physical mixtures > pure griseofulvin. However, the particle size of the drug is solvent deposition systems > physical mixtures = griseofulvin. Pure griseofulvin, because of its hydrophobic nature, tended to form large particle aggregates in the dissolution medium. This can diminish the surface area

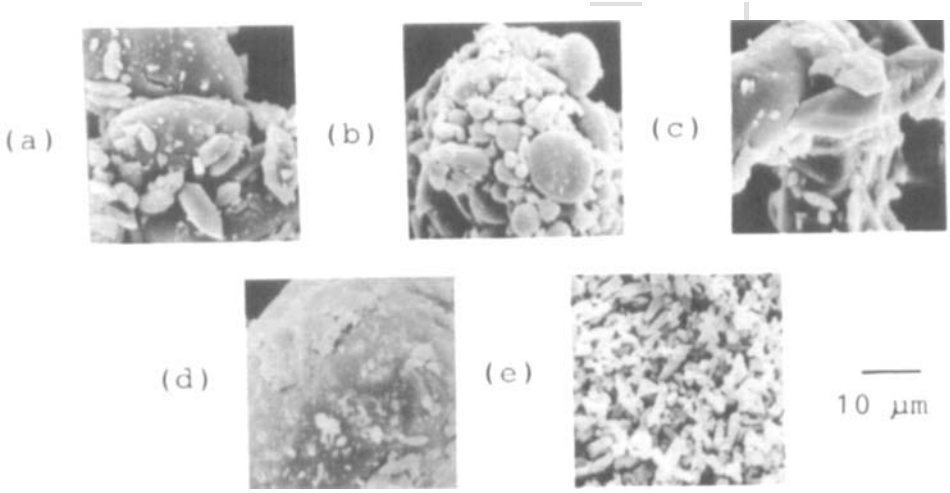

FIGURE 2

Scanning electron micrographs of griseofulvin deposited on (a) 60% Primojel, (b) 60% Mobile Starch (c) 60% Nymcel, (d) 95% Primojel and (e) micronized griseofulvin.

available for dissolution. Since Primojel, Mobile Starch and Nymcel are hydrophilic, the physical mixture of these disintegrants with the hydrophobic drug may render the mixture hydrophilic, easily wetted in the medium for dissolution (4). Also, the disintegrants may provide a deaggregation effect which prevents the particles from forming aggregates during dissolution. For the solvent deposition systems, the drugs are adsorbed on the surface of the disintegrants. During dissolution, the disintegrants absorb water and swell. The deformation of the

disintegrants results in the dislodgement of the drug particles from the surface of the disintegrant into the medium. This action provides both the wetting and deaggregation effects which faciliate the rapid dissolution of the particles. Discrete drug particles were released from the solvent deposition systems but a few clumpings of particles were observed in the physical mixtures. As a result, a higher dissolution rate for the solvent deposition systems was obtained.

The initial dissolution rates of the griseofulvin from the solvent deposition systems of 60% Primojel, 60% Mobile Starch and 60% Nymcel were 11.5 ± 0.6, 9.6 ± 0.5 and 9.7 ± 0.2 mg/l/min respectively (Figure 1). Scanning electron micrographs of these systems (Figure 2) show that the griseofulvin in the Nymcel system has a particle size larger than those in the Primojel and Mobile Starch systems. This may therefore lead to a slow dissolution rate. Although the particle size of griseofulvin for the Mobile Starch system is similar to that of the Primojel system, most of the drug particles and the Mobile Starch particles formed aggregates as seen in Figure 2. This may result in a slow dissolution rate for the Mobile Starch system.

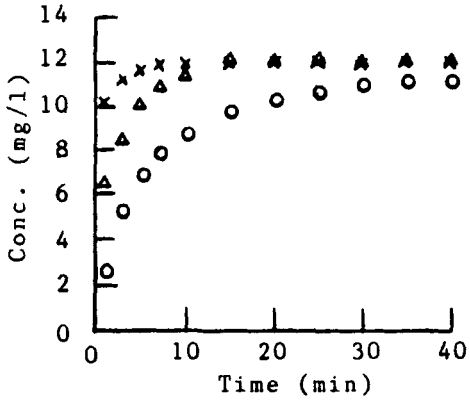

FIGURE 3

Dissolution profiles of griseofulvin from the tablets of solvent deposition systems. × , gri-60% Primojel; △ , gri-60% Mobile Starch; ○ , gri-60% Nymcel.

Figure 3 illustrates the dissolution profiles for the tablets of solvent deposition systems (60% disintegrants). The disintegration times of these tablets were 2.7 ± 0.4, 2.4 ± 0.3 and 24.0 ± 1.0 minutes for the Primojel, Mobile Starch and Nymcel systems respectively. The griseofulvin in the tablets of Nymcel, Mobile Starch and Primojel systems demonstrated an order of increased dissolution rates. There are two possible machanisms responsible for the increase of the dissolution rate of griseofulvin from these tablets i.e. the disintegration rate of the tablets and the particle size of the drug after disintegration. The fast disintegration rate of the

tablets enable the drug particles to deaggregate and wet rapidly in the dissolution medium. Since the particle size is smallest in the griseofulvin in the Primojel system and the particle size in the Mobile Starch (aggregates) and the Nmycel system is considerably larger (Figure 2), the Primojel system has, as expected, the highest dissolution rate. In the case of the Mobile Starch system, some of the aggregates may have been crushed by the pressure during tableting; thus, after disintegration, it showed a dissolution rate greater than that of the Nymcel system.

The effect of the drug to the disintegrant ratio on the dissolution rate is shown in Figure 1. The initial dissolution rate of griseofulvin from the 95% disintegrant systems was greater than that of the 60% disintegrant systems. This is probably due to the greater surface area for griseofulvin deposition resulting in a smaller particle size (as shown in Figure 2) for rapid dissolution (2,3,5).

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