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HIGH ENERGY ORDERED MIXTURE FOR IMPROVING THE DISSOLUTION RATE OF SPARINGLY SOLUBLE COMPOUNDS

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ABSTRACT

Bioavailability of a sparingly soluble drug is often limited by the rate of dissolution of the drug substance. The drug in a micronized form is generally employed to maximize the bioavailability. However, the micronized drugs tend to agglomerates and do not always exhibit an improved dissolution rate. In this study, a simple processing using a high energy mill was demonstrated as an effective means to utilize the entire surface area available for drug release of the micronized drug. An experimental hydrophobic drug in a micronized form was milled with a carrier, hydrous lactose using Micropulverizer to achieve a uniform mixture so-called "high energy ordered mixture". The high energy ordered mixture provided a contact surface area taking part in dissolution 4-fold greater than the micronized drug agglomerates. Therefore, the dissolution was significantly improved, irrespective of test parameters such as agitation and the presence of surfactant. This high energy ordered mixture provided the advantages over a simple ordered mixture for: (i) complete

deaggregation of the micronized drug to fine primary particles, (ii) improving the efficiency of the carrier by increasing contact surface area, and (iii) enhancing the bonding effect between the drug and lactose particles due to free water molecules released from the crystal lattices of hydrous lactose during milling. This procedure could be applied to overcome dissolution problems of sparingly soluble drugs with cohesive nature.

INTRODUCTION

Bioavailability of a sparingly soluble drug from the absorption sites is often limited by rate of dissolution of the drug substance. The increase in surface area by reduction in particle size has been reported to result in a proportional increase in dissolution rate (1). However, with the micronized drugs that are strongly agglomerated do not always exhibit an improved dissolution rate (2). The contact surface area taking part in dissolution is substantially smaller than the external surface area of the primary particles (3). Surface active agents are generally employed to improve liquid penetration into the drug agglomerates and thus increase the contact surface area. The use of simple ordered mixture, where fine drug particles are evenly distributed on carrier particles, has been shown to increase the dissolution rate of micronized drugs (4).

In this study, a high energy milling was evaluated as an effective means to utilize the entire surface area available for drug release of the micronized drug. An experimental hydrophobic drug in a micronized form was milled with carrier, hydrous lactose using a Micropulverizer to achieve a uniform mixture so-called "high energy ordered mixture". In vitro performance of the high energy ordered mixture was compared to that of the simple ordered mixture of the same drug.

MATERIALS AND METHODS

Materials

Materials used in this study were: a sparingly soluble investigational drug (6-(2-chlorophenyl)-4-hydroxy-4H-imidazo 1,5-α 1,4 benzodiazepine-3-carboxamide; Hoffmann-La Roche Inc., Nutley, NJ), hydrous lactose (Matheson, Coleman and Bell Division, Norwood, OH), microcrystalline cellulose (Avicel PH 102; FMC Corp., Philadelphia, PA), corn starch (National Starch, Newark, NJ), polysorbate 80 (ICI Americas, Wilmington, DE) and magnesium stearate (Whittaker, Clark and Daniels, Plainfield, NJ). The drug was micronized using a fluid energy mill (Sturtevant, Boston, MA).

External Surface Area of the Micronized Drug as Agglomerates

The mean diameter of the drug agglomerates in the sieve fraction 300-450 μm was found to be 375 μm. If all agglomerates are considered to be spherical, the external surface area can be calculated as follows:

$$S_a = \pi.d^2.n$$

where S_a is the external surface area of the drug agglomerates, d and n are the diameter and number of the agglomerated particles, respectively.

External Surface Area of the Micronized Drug as Primary Particles

The external surface area of the primary particles was determined by optical microscopy (Kramer Scientific Corp., Yonkers, NY) as well as by Microtrac analysis (Leeds and Northrup Co., Largo, Florida).

Solubility Determination

Solubility of the drug was determined by adding an excess of the drug to water and shaking on a mechanical shaking bath for 24 hours at 25°C. The suspension was filtered and the solubility was determined by the method described by Nystrom at al (5).

Preparation of Simple Ordered Mixture

The micronized drug and carrier, hydrous lactose, were mixed in a weight ratio of 1:50. The mixture was transferred to a glass jar at a fill volume of approximately 50% and mixed using a Turbula Mixer (Impandex Inc., Maywood, NJ) at 10-15 revolutions per minute for 10 minutes. The powder mix was then passed through a #60 mesh screen and was used in the preparation of capsules.

Preparation of High Energy Ordered Mixture

The micronized drug and carrier, hydrous lactose, were mixed in a weight ratio of 1:50. The mixture was mixed in a glass jar and passed through a high energy mill (Micropulverizer; Hosokawa Micron International Inc., Summit, NJ) using a 0.02 inch plate opening with hammers at a medium speed. This mixture was used in the preparation of capsules.

Preparation of Capsules

The capsules were prepared from both the simple ordered mixture as well as from the high energy ordered mixture. An amount of ordered mixture equivalent to 5 mg of active drug was mixed with the other formulation ingredients, passed through a #60 mesh screen, and filled into #0 capsules. Each capsule was composed of micronized drug 5 mg, hydrous lactose 350 mg,

Avicel PH 102 50 mg, corn starch 50 mg and magnesium stearate 2 mg.

Dissolution Studies

Dissolution studies were performed according to the USP XXII Apparatus 2 (paddles) at various stirring speed. The dissolution medium was 900 mL of water or 0.1% polysorbate 80 solution at 37°C. The analysis was performed by UV spectrophotometry at 310 nm.

Wetting Characteristics

In order to evaluate wetting characteristics, the drug per se, as well as each ordered mixture equivalent to 5 mg of drug was placed into 100 mL of water and photomicrographs of the resulting surfaces were taken after 5 minutes.

Determination of Contact Surface Area

Mean contact surface area taking part in the dissolution can be calculated using the following equation as described by Nystrom et al (6):

$$S_c = W/t*G$$

where W is the amount of drug dissolved in time, t; S_c is the mean contact surface area taking part in dissolution in time, t; and G is the intrinsic dissolution rate, 2.8 μg/min.cm^2 which was determined by the Wood Apparatus (7) from our previous study.

TABLE I

Primary Characteristics of the Materials Used in the Study

Material	External Surface Area of Primary Particles (cm^2/g)	External Surface Area of Agglomerates (cm^2/g)	Solubility[a] C_s (per mL)
Drug	9400	375	80 μg
Hydrous Lactose	4500	---	200 mg

[a] in water at 25 °C.

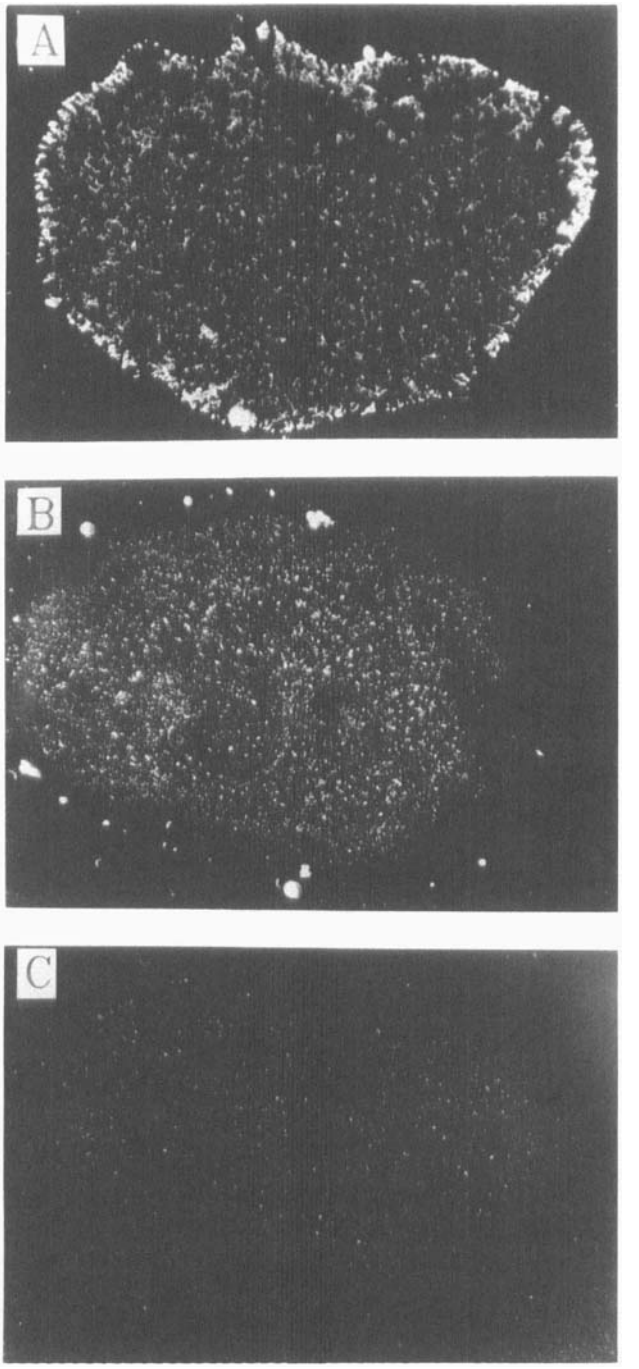
RESULTS AND DISCUSSION

External Surface Area

The results of the mean external surface area of the micronized drug as agglomerates and as primary particles were shown in Table I. The micronized drug as agglomerates was 25-fold lower in external surface area compared to the micronized drug as primary particles. The result indicates that a substantial agglomeration occurred in the micronized drug.

Wetting Characteristics

The photomicrographs showing the wetting characteristics of the micronized drug agglomerates, simple ordered mixture and



high energy ordered mixture are shown in Figure 1. The micronized drug agglomerates showing very poor wetting was clearly evident. The simple ordered mixture showed some improved wetting and deagglomeration of the drug : carrier particles. The high energy ordered mixture had the superior performance in terms of enhanced wetting properties and complete disintegration to primary particles.

Dissolution of the Micronized Drug as Agglomerates

Dissolution of the micronized drug was dependent of test parameters. Increases in the stirring speed could facilitate the disintegration of the agglomerates, thereby increasing the dissolution rate as shown in Figure 2A. The surface active agent, polysorbate 80, as well as increasing the stirring speed increased the dissolution rate of the micronized drug agglomerates (Figure 2B). The surface active agent enhanced penetration of the dissolution fluid into the agglomerates, thereby increasing the contact surface area. The results indicate that only a fraction of

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FIGURE 1

Photomicrographs showing wetting characteristics of the micronized drug agglomerates (A), simple ordered mixture (B) and high energy ordered mixture (C) after 5 minutes in water.

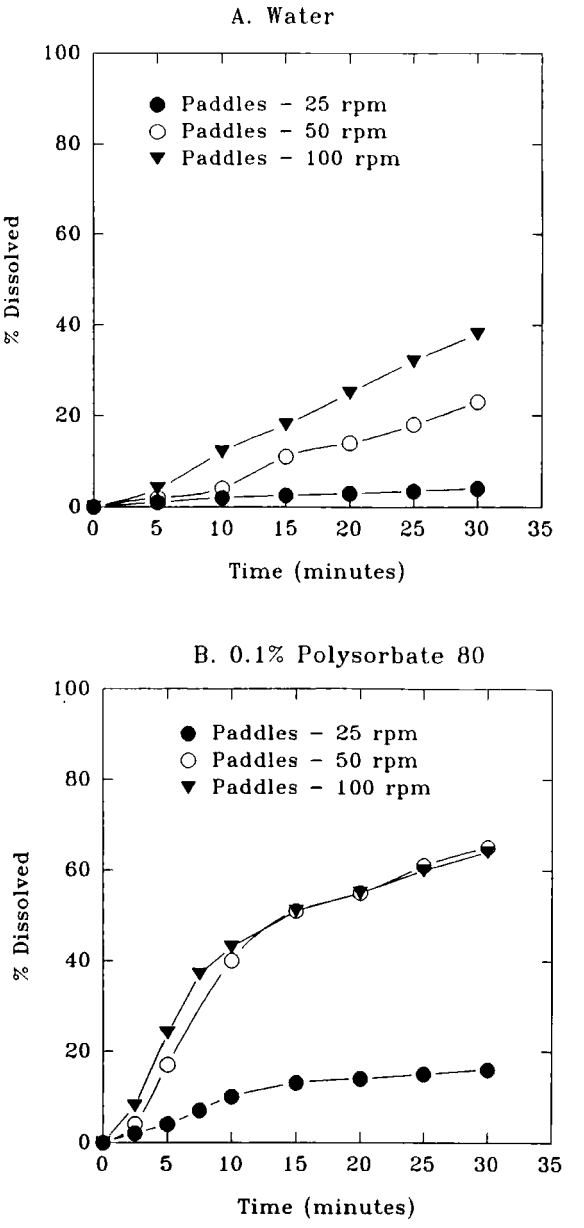

FIGURE 2

Effect of stirring speed and polysorbate 80 on dissolution of the micronized drug agglomerates.

external surface area took part in the dissolution process. Even though the experiments were performed under sink conditions, substantial amount of drug remained undissolved after 30 minutes.

Dissolution of the Ordered Mixtures

The dissolution profiles of the high energy ordered mixture, simple ordered mixture and micronized drug agglomerates in powders as well as in capsules are shown in Figures 3A and 3B, respectively. The dissolution rates increased in the order of the micronized drug agglomerates, simple ordered mixture and high energy ordered mixture.

In the preparation of simple ordered mixture, only a simple tumbling action is involved. This may not be sufficient for complete deaggregation of the micronized drug agglomerates into primary particles (Figure 1). Therefore, complete dissolution could not be achieved in 30 minutes.

In 30 minutes, almost all of the drug from high energy ordered mixture was dissolved. These results support the assumption that in the high energy ordered mixture, the drug is well distributed as primary particles on the carrier particles. Scanninig electron photomicrographs indicate that a significant

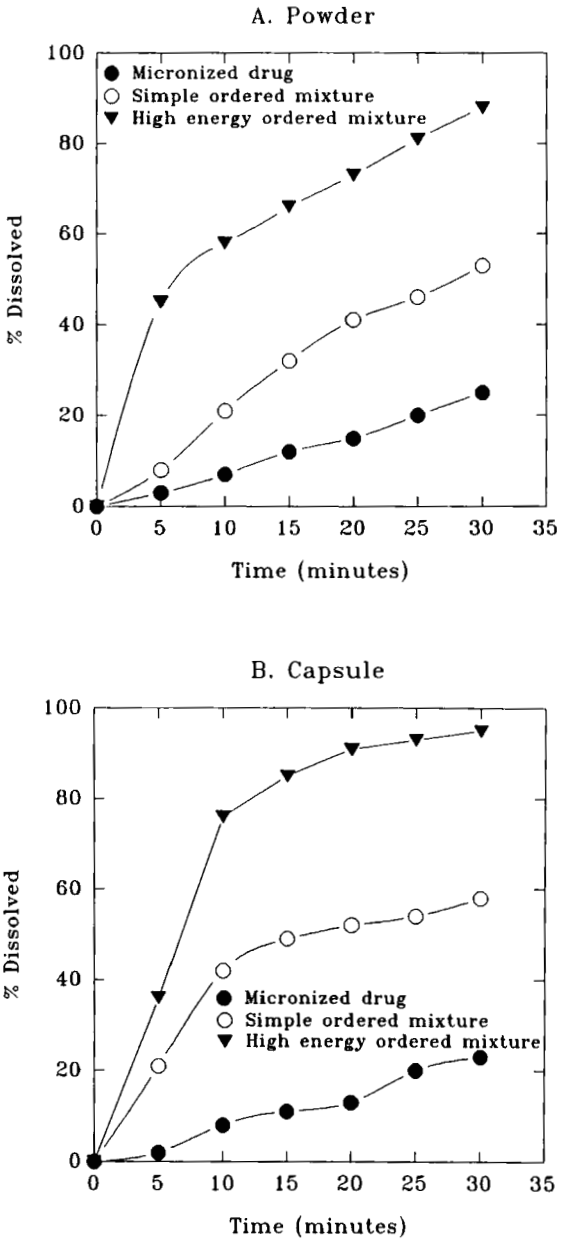

FIGURE 3

Dissolution profiles of different ordered mixtures in the forms of powder (A) and capsule formulation (B) in water using paddle method at 50 rpm compared to the micronized drug agglomerates.

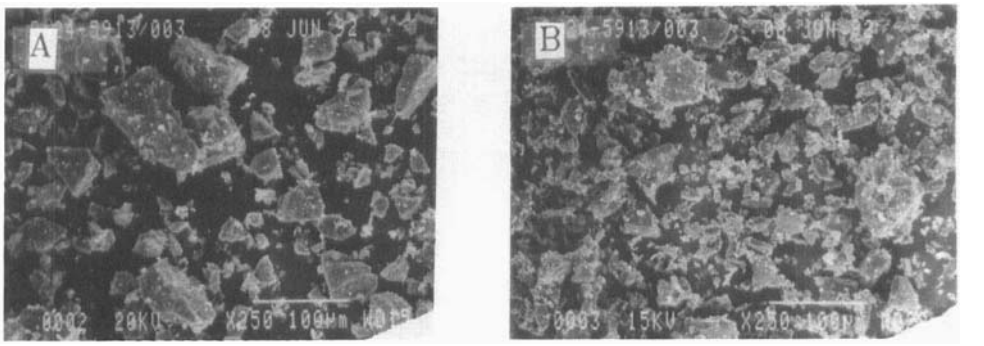

FIGURE 4

Scanning electron photomicrographs of the simple ordered mixture (A) and the high energy ordered mixture (B).

reduction in particle sizes of hydrous lactose occurred during the milling, resulting in improved contact between drug and carrier particles (Figure 4). When exposed to the dissolution medium, the drug : hydrous lactose particles immediately wetted allowing complete exposure of the primary drug particles to the dissolution medium even in the absence of surface active agent (Figure 1). The results obtained from DSC thermograms as reported by Lerk et al. (8) indicate that water molecules are released from the crystal lattices of hydrous lactose during the milling process. This free moisture could enhance the bonding effect between the micronized drug and lactose particles, thus contributing to improved wetting and improved dissolution rate.

TABLE II

Contact Surface Area[a] of 5 mg Experimental Drug Taking Part in 30 minutes of Dissolution

Test Products	Contact Surface Area (cm^2)
Micronized Drug Agglomerates	15
Simple Ordered Mixture	27
High Energy Ordered Mixture	59 (47)[b]

[a] Calculated according to Nystrom and Westerberg (6).
[b] Experimental value of mean external surface area of the primary particle.

Contact Surface Area Taking Part in Dissolution

The results of the mean contact surface area calculated from dissolution experiments without surface active agent are shown in Table II. The contact surface area increased in order of the micronized drug agglomerates, simple ordered mixture and high energy ordered mixture. The high energy ordered mixture provided a contact surface area taking part in dissolution 4-fold greater than that of the micronized drug agglomerates. The simple ordered mixture provided a 2-fold increase in contact surface area compared to the micronized drug agglomerates. The calculated contact surface area taking part in dissolution of the high energy ordered mixture was found to be close to the external surface area

of primary particles of the micronized drug. This result confirms the assumption that in the high ordered energy mixture the micronized drug was dispersed as primary particles on hydrous lactose particles.

CONCLUSION

The use of a high energy ordered mixture provides an effective means of utilizing the entire surface area available for drug release of a sparingly soluble micronized drug. This principle could provide a practical way to overcome dissolution problems, especially for a hydrophobic drug with a cohesive nature.

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