Drug Development and Industrial Pharmacy, 34:206–214, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701542291

informa
healthcare

Interactive Mixture as a Rapid Drug Delivery System

Chin Chiat Lee
ISP Asia Pacific Pte Ltd, Singapore Science Park, Republic of Singapore

Charlene Li Ching Ong, Paul Wan Sia Heng, and Lai Wah Chan
Department of Pharmacy, Faculty of Science, National University of Singapore, Republic of Singapore

Tin Wui Wong
Particle Design Research Group, Faculty of Pharmacy, and Non-Destructive Biomedical and Pharmaceutical Research Centre, Universiti Teknologi MARA, Shah Alam, Selangor, Malaysia

The effectiveness of an interactive mixture as a rapid drug delivery system is compared with that of a solid dispersion. The influences of drug load, particle size, and crystallinity of these test systems are investigated. The interactive mixtures and solid dispersions were prepared from polyethylene glycol (PEG) 3350 and hydrophobic nifedipine drug by means of physical mixing and melting methods, respectively. The formed products were subjected to drug particle size and crystallinity analyses, and dissolution tests. In comparison with the interactive mixtures, the solid dispersions with low drug load were more effective as a rapid drug delivery system, as the size of a given batch of drug particles was markedly reduced by the molten PEG 3350. The rate and extent of drug dissolution were mainly promoted by decreasing effective drug particle size. However, these were lower in the solid dispersions than in the interactive mixtures when a high load of fine drug particles was used as the starting material. This was attributed to drug coarsening during the preparation of the solid dispersion. Unlike solid dispersions, the interactive mixtures could accommodate a high load of fine drug particles without compromising its capacity to enhance the rate and extent of drug dissolution. The interactive mixture is appropriate for use to deliver a fine hydrophobic drug in a formulation requiring a high drug load.

Keywords drug dissolution; interactive mixture; nifedipine; rapid drug delivery system; solid dispersion

INTRODUCTION

The bioavailability of hydrophobic drugs such as griseofulvin, nifedipine, felodipine, oxazepam, and diazepam is limited by their poor dissolution in the gastrointestinal tract. This limitation leads to the concept of solid dispersion, whereby one or more active ingredients are embedded in an inert solid matrix by the melting, solvent, or melting-solvent method (Sekiguchi & Obi, 1961; Chiou & Riegelman, 1971). The dissolution of poorly water-soluble drugs is greatly enhanced by the reduction of drug particle size and/or crystallinity that results from the preparation of a solid dispersion (Sjökvist & Nyström, 1988; Rabasco, Ginés, Fernández-Arévalo, & Holgado, 1991; Save & Venkitachalam, 1992; Jachowicz, Nürnberg, & Hoppe, 1993; Lin & Cham, 1996; Doshi, Ravis, & Betageri, 1997; Kerć, Srćić, & Kofler, 1998; Chutimaworapan, Ritthidej, Yonemochi, Oguchi, & Yamamoto, 2000; Vippagunta, Maul, Tallavajhala, & Grant, 2002; Ren et al., 2006). The fine and/or amorphous drug particles released after dissolution of the matrix have been found to increase the bioavailability of the drug (Goldberg, Gibaldi, & Kanig, 1966a, 1966b; Sugimoto et al., 1980; Joshi et al., 2004).

Over the past 40 years, numerous difficulties have been encountered in the design of solid dispersion, thereby limiting its commercial application in the pharmaceutical industry. Preparation of solid dispersion by the melting method involves heat, which may lead to decomposition or evaporation of the drug and/or matrix. On the other hand, the solvent method demands a high operating cost for solvent, flame-proof facilities, and solvent removal and recovery systems. The drug particles in the solid dispersion prepared by either method tend to exhibit polymorphism and changes in state of crystallinity, and their dissolution properties are affected appreciably by the storage conditions, such as length of time, temperature, and humidity (Serajuddin, 1999).

Alternatively, the dissolution of poorly water-soluble drugs may be enhanced by combining the drug particles with a soluble carrier system to form an interactive mixture. In this mixture, fine drug particles are distributed on coarse carrier particles. The aggregation level of drug particles is reduced, thereby increasing their surface area for dissolution (Nyström & Westerberg, 1986;

Address correspondence to Tin Wui Wong, Particle Design Research Group, Faculty of Pharmacy, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia. E-mail: wongtinwui@salam.uitm.edu.my

Westerberg, Jonsson, & Nyström, 1986; Nilsson, Westerberg, & Nyström, 1988; Westerberg & Nyström, 1991, 1993). The preparation of an interactive mixture is an economical one-step process that avoids the use of heat and solvent. Hence, the physicochemical stability of the drug and carrier particles is affected to a smaller extent by the preparation process compared with the melting and/or solvent methods. Nonetheless, it is frequently reported that the dissolution rate and extent of poorly water-soluble drugs from the interactive mixtures are lower than that of the solid dispersions (Rabasco et al., 1991; Sheu, Yeh, & Sokoloski, 1994; Betageri & Dipali, 1995; Jachowicz & Nürnberg, 1997; Liu et al., 2006). In the solid dispersion, there is a marked reduction in the particle size and/or crystallinity of embedded drugs, thereby leading to a higher degree of drug dissolution than the interactive mixture.

Karavas and colleagues (2005, 2007) have recently established the fact that fine drug particles in solid dispersion are released into the dissolution medium at a faster rate than their larger particulate fractions. On the other hand, there is no known report that investigates the drug dissolution performances of an interactive mixture at comparable particle sizes of drugs in the final dosage form against that of solid dispersion. The present study aims to investigate the effectiveness of an interactive mixture as a rapid drug delivery system, in relation to a solid dispersion, through formulating the interactive mixture using fine drug particles. The dissolution properties of nifedipine from interactive mixtures and solid dispersions are examined with respect to the influences of nifedipine particle size and crystallinity. The limitation of solid dispersion as a rapid drug delivery system is discussed.

MATERIALS AND METHODS

Materials

Nifedipine USP (Shilpa Antibiotics Ltd., India) was selected as the model drug of poor aqueous solubility. Polyethylene glycol 3350 (PEG 3350, Clariant GmbH, Germany), previously passed through a 125-μm sieve, was employed as the inert and soluble polymeric carrier. The D_{99} value of the PEG 3350 was 170.07 ± 10.83 μm. Hydrochloric acid (HCl, Merck, USA) was used to prepare the acidic medium for the drug dissolution study. Ethylparaben (Tokyo Kasei Kogyo Co. Ltd., Japan), methanol, acetonitrile (EM Science, Germany), anhydrous sodium acetate (BDH Laboratory Supplies, UK), and glacial acetic acid (Merck, USA) were employed in the analysis of nifedipine using high performance liquid chromatography (HPLC). Sodium lauryl sulphate (BDH Laboratory Supplies, UK) was employed as a wetting agent for particle sizing.

Methods

Nifedipine is a light-sensitive drug. All experiments were carried out under subdued light to avoid the degradation of nifedipine.

Preparation of Different Size Fractions of Nifedipine

Four batches of nifedipine were prepared by means of sieving or milling. The milled nifedipine particles were obtained by subjecting the nifedipine to a size reduction process using a fluidized bed hammer mill (50 ZPS, Hosokawa Micro Corporation, Germany) or a fluidized bed opposed jet mill (100 AFG, Hosokawa Micro Corporation, Germany). The particle size of nifedipine at the 99th percentile of cumulative undersize distribution (D_{99}) was determined with the aid of a laser diffraction particle size analyzer (Coulter® LS 230, Coulter Corporation, USA), in accordance with the procedure described later in the section "Drug Particle Size." All the measurements were carried out in triplicates and the results averaged. Table 1 shows the modes of preparation and the D_{99} values obtained from the nifedipine particles.

Preparation of Interactive Mixture

The required amount of PEG 3350 with 10% or 30% w/w nifedipine, expressed as the percentage weight of the interactive mixture, was blended using a vertical shaker at 1800 rpm for 22 minutes (IKA®, Labotechnik, Germany). The intramixture variation of drug content was kept below 5% in all the interactive mixtures. A control sample was similarly prepared, except that no drug was incorporated. The control sample was coded as IM0.

Preparation of Solid Dispersion

PEG 3350 was melted using a thermostat-controlled water bath at 80 ± 5°C. Low processing temperature was employed in order

TABLE 1
Particle Size of Nifedipine Prepared by Sieving and Milling Methods

Batch of Nifedipine	Method of Preparation	D_{99} (μm)
N1	Passed through a 125-μm sieve	233.23 ± 18.82
N2	Milled using a fluidized bed hammer mill at A beater rotational speed of 12,000 rpm, classifier wheel rotational speed of 5,000 rpm, and airflow rate of 80 m^3/h	36.79 ± 1.32
N3	Milled using a fluidized bed opposed jet mill at a milling pressure of 0.5 MPa and classifier wheel rotational speed of 5,000 rpm	29.94 ± 4.70
N4	Milled using a fluidized bed opposed jet mill at a milling pressure of 0.5 MPa and classifier wheel rotational speed of 14,000 rpm	7.51 ± 0.05

to prevent the nifedipine from undergoing thermal degradation (Save & Venkitachalam, 1992). Ten percent w/w nifedipine, expressed as the percentage weight of the solid dispersion, was dissolved in the molten PEG 3350. After 20 minutes, the molten solution was poured into a glass petri dish and immediately placed in a desiccator for solidification by cooling to room temperature at 25 ± 1°C. The solid dispersion was further conditioned in the desiccator for 24 hours. The cooled solid mass was pulverized and passed through a sieve of aperture size 125 μm. Solid dispersion containing 30% w/w nifedipine was similarly prepared.A molten nifedipine-PEG 3350 suspension was formed at 30% w/w drug loading instead of a molten solution. A control sample without drug was similarly prepared and was coded as SD0.

Assay of Nifedipine

Nifedipine was assayed by HPLC-ultraviolet (UV) method (Thermo Separation Products, USA). The HPLC analysis was conducted using a Zorbax® Bonus RP analytical column-guard column system (4.6 mm ID × 150 mm L, Hewlett® Packard, USA and 4.6 mm ID × 12.5 mm L, Hewlett® Packard, USA, respectively). The average size of the Zorbax® Bonus RP adsorbent particles embedded in both columns was 5 μm. A composite mixture of methanol, acetonitrile, and acetate buffer of pH 4.85 at a volume ratio of 2:1:2 was employed as the mobile phase. The flow rate of the mobile phase was 1.0 ml/min. Ethylparaben was used as an internal standard. Both standard solutions of nifedipine and ethylparaben were freshly prepared by dissolving the required amount of materials in 2 ml of acetonitrile and made up to 20 ml in a volumetric flask in the mobile phase. The content of nifedipine was assayed spectrophotometrically at 238 nm (Spectra Monitor® 5000, Thermo Separation Products, USA).

Drug Dissolution

The pure nifedipine, interactive mixtures, and solid dispersions were subjected to drug dissolution study in accordance with the USP XXI procedure, using the paddle method (VanKel Ind. Inc., USA). The pure nifedipine, interactive mixtures, or solid dispersions containing an amount of drug equivalent to 10 mg of nifedipine was added to 900 ml of 0.1 M HCl solution, previously equilibrated to 37 ± 0.5°C, and stirred at a constant speed of 100 rpm. Aliquot was withdrawn at specific intervals up to 30 minutes of dissolution and the amount of dissolved drug was determined using the HPLC-UV method previously described. The weight of drug dissolved was expressed as a percentage with respect to the drug content of pure nifedipine, interactive mixtures, or solid dispersions. All experiments were carried out in triplicates and the results averaged. The percentage weight of nifedipine dissolved after 30 minutes of dissolution, $T_{30\ min}$, was computed.

Aqueous Solubility

Excess amount of pure nifedipine N1 and N4 were added to 0.1 M HCl solution without and with various predissolved amounts of PEG 3350. The latter represented the amounts of PEG 3350 possibly present in 0.1 N HCl solution upon dissolution of the interactive mixture or solid dispersion. The aqueous solubility of pure nifedipine was determined at 37 ± 0.5°C by subjecting the drug suspension to agitation at a speed of 40 cycles/minute in a shaker bath (M20S, Lauda, Germany). The content of drug dissolved after 24 hours was measured by the HPLC-UV method. All experiments were carried out in triplicate and the results averaged.

X-Ray Diffraction

The crystallinity of nifedipine in the drug powder, interactive mixtures, and solid dispersions was determined by X-ray diffraction (XRD-6000, Shimadzu, Japan) using nickel filtered Cu-K_α radiation, at 40 kV and 30 mA. The scanning interval was 0.02° (2θ), between 8 to 32°. The duration of X-ray irradiation was set at 5 s/0.02° (2θ). The degree of crystallinity of nifedipine was represented by the peak intensity of the X-ray diffractogram at 11.76° (2θ; I_N; Sjökvist, Nyström, & Aldén, 1991; Sjökvist, Nyström, Aldén, & Caram-Lelham, 1992; Sjökvist Saers, Nyström, & Aldén, 1993). All experiments were carried out in triplicate and the results averaged.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms were obtained using a differential scanning calorimeter (DSC-50, Shidmazu, Japan). Particles of 4 mg to 5 mg of the sample were crimped in a standard aluminum pan and heated from 25°C to 200°C at a heating rate of 1°C/minute under constant purging of nitrogen at 40 ml/min. The specific heat and melting peak temperature of the characteristic peaks were recorded. All experiments were carried out in triplicate and the results averaged.

Drug Particle Size

An excess amount of pure nifedipine was dissolved in an aqueous solution containing 0.02% w/v sodium lauryl sulphate. The dispersion was subjected to magnetic stirring and left to stand for 24 hours at 25 ± 0.5°C before passing through a membrane filter with a pore size of 0.45 μm (Sartorius, Germany). The filtrate was collected as a dispersion medium for sizing of nifedipine particles in drug powders, interactive mixtures, and solid dispersions. The dispersion medium was saturated with nifedipine prior to sizing to avoid further dissolution of nifedipine particles under study. Sodium lauryl sulphate was added to the dispersion medium, as this surfactant was capable of preventing aggregation of nifedipine particles.

An appropriately weighed amount of sample was suspended in the dispersion medium and subjected to ultrasonication for two consecutive periods of 15 minutes, with a resting interval of 10 minutes to disperse the nifedipine particles and to ensure complete dissolution of PEG 3350 where appropriate. The particle size of nifedipine was measured using a laser diffraction

particle size analyzer (Coulter® LS 230, Coulter Corporation, USA). All experiments were carried out in triplicate and the results averaged. It was acknowledged that the dissolution of PEG 3350 from the interactive mixtures and solid dispersions might modify the solubility of nifedipine and thus the drug particle size. The effect was, however, expected to be insignificant as the aqueous solubility of nifedipine in 0.1 M HCl was not affected by the addition of PEG 3350.

RESULTS AND DISCUSSION

Aqueous Solubility of Nifedipine

The aqueous solubility of pure nifedipine in 0.1 M HCl, with or without the addition of PEG 3350, was approximately 0.0011% w/v. This was equivalent to about 10 mg of nifedipine dissolvable in 900 ml of 0.1 M HCl solution. Incidentally, 10 mg of nifedipine is the therapeutic dose for orally administered dosage form. Thus, an amount equivalent to 10 mg of nifedipine was employed in the subsequent investigation of drug dissolution characteristics of pure nifedipine, interactive mixtures, and solid dispersions.

Dissolution Profiles of Nifedipine

Pure Nifedipine

The dissolution profiles of N1, N2, N3, and N4 in 0.1 M HCl solution are shown in Figure 1. The $T_{30\ min}$ values of pure nifedipine increased from 13.9 ± 2.9% (N1) to 23.1 ± 2.7% (N2; Table 2), with a corresponding reduction in the D_{99} values of pure nifedipine from 233.23 ± 18.82 μm to 36.79 ± 1.32 μm (Table 1). This could be attributed to an increase in specific particulate surface area participating in the dissolution process. Nonetheless, a further decrease in D_{99} value of nifedipine from 36.79 ± 1.32 μm (N2) to 29.94 ± 4.70 μm (N3) resulted in a decrease in the $T_{30\ min}$ value from 23.1 ± 2.7% to 18.8 ± 1.8%. The $T_{30\ min}$ value of N4 was unexpectedly low among all batches of nifedipine studied. The smaller nifedipine particles had a higher propensity to aggregate due to Van der Waals' forces (Parrott, 1974; Hickey & Ganderton, 2001). This increased the diffusion boundary layer thickness and decreased the effective particulate surface area for drug dissolution (Lin, Menig, & Lachman, 1968; Westerberg & Nyström, 1993). Hence, micronization of drug might not enhance but rather result in poorer drug dissolution.

The X-ray diffractograms showed that the peak characteristics of all batches of nifedipine were similar and exhibited the typical profile of a type I polymorph (Figure 2; Vippagunta et al., 2002). The type I nifedipine polymorph is known to be the most stable crystallite (Vippagunta et al., 2002). The DSC study indicated that the melting temperature and endothermic specific heat of nifedipine were not markedly different among batches N1 to N4 (Table 3). The above results show that the drug crystallite profiles were comparable among all batches of nifedipine. Thus, the varying dissolution profiles of N1 to N4 were due to factors other than drug crystallinity.

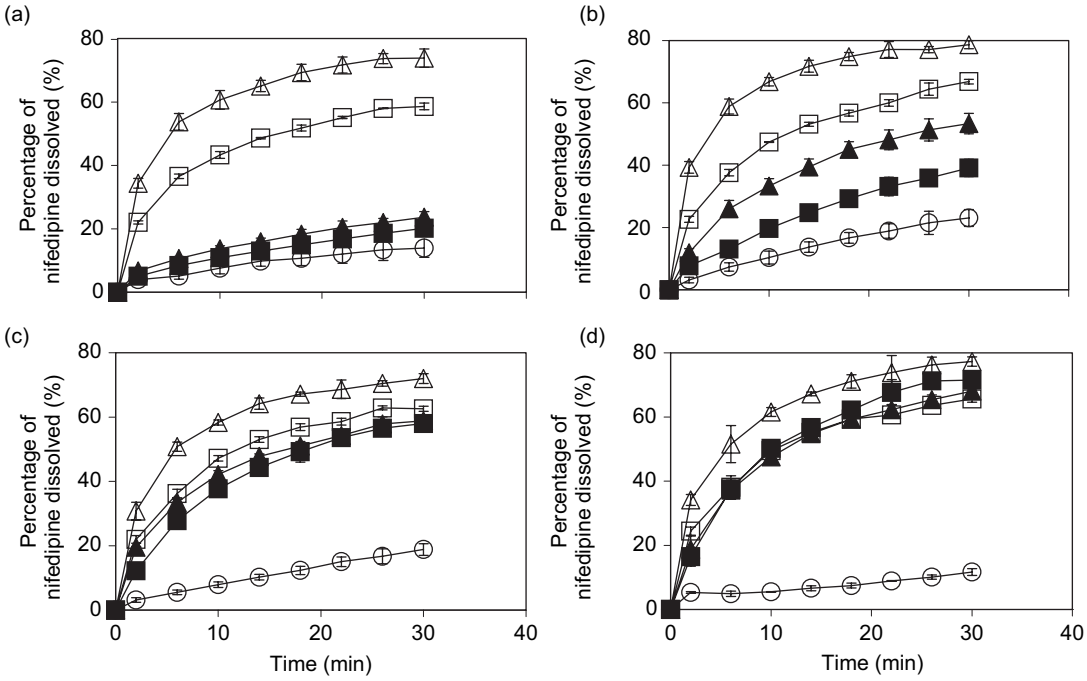

FIGURE 1. Dissolution profiles of (a) N1, (b) N2, (c) N3, and (d) N4 and their respective interactive mixtures and solid dispersions in 0.1 M HCl solution. (Pure nifedipine, ❍; interactive mixture 10% w/w drug (IM10), ▲; interactive mixture 30% w/w drug (IM30), ■; solid dispersion 10% w/w drug (SD10), Δ; solid dispersion 30% w/w drug (SD30), □).

TABLE 2
Dissolution $T_{30\ min}$ Values of Pure Nifedipine, Interactive Mixtures, and Solid Dispersions

	Dissolution $T_{30\ min}$ Value (%)				
		Interactive Mixture		Solid Dispersion	
Batch of Nifedipine	Pure Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine
N1	13.9 ± 2.9	23.6 ± 1.8	20.2 ± 1.6	73.8 ± 2.9	58.6 ± 1.1
N2	23.1 ± 2.7	53.4 ± 3.3	39.1 ± 2.8	78.7 ± 1.3	66.8 ± 0.7
N3	18.8 ± 1.8	58.8 ± 0.7	58.0 ± 1.9	72.0 ± 1.5	62.6 ± 0.8
N4	11.7 ± 1.1	68.0 ± 1.0	71.5 ± 2.8	77.3 ± 1.5	65.6 ± 1.0

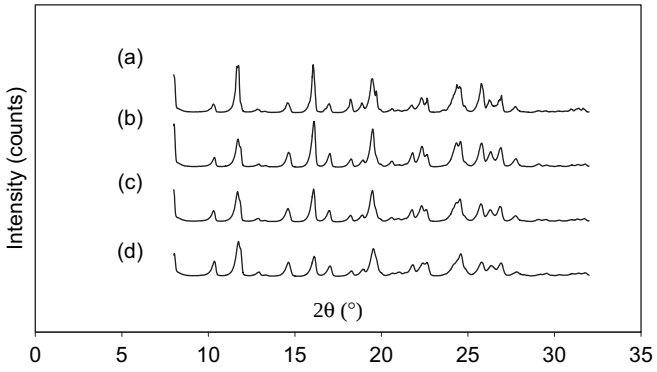

FIGURE 2. X-ray diffractograms of (a) N1, (b) N2, (c) N3, and (d) N4.

Interactive Mixtures

The interactive mixture is a solid blend of nifedipine-PEG 3350 prepared without the application of heat. The percentage of nifedipine dissolvable from the interactive mixture was significantly higher than that of the pure drug throughout the entire period of dissolution (Figure 1; One-Way ANOVA, $p < .05$). During the preparation process of the interactive mixture, the nifedipine particles were deposited onto the surfaces of the PEG 3350. The aggregation propensity of drug particles was thus reduced, thereby decreasing the thickness of the diffusion boundary layer and promoting drug dissolution (Nyström & Westerberg, 1986; Westerberg et al., 1986; Nilsson, Westerberg, & Nyström, 1988; Westerberg & Nyström, 1991, 1993). The $T_{30\ min}$ value of nifedipine was greater with the application of smaller drug particles to prepare the interactive mixture (Table 2; One-Way ANOVA, $p < .05$). The results showed that the mixing procedure employed in the preparation of the interactive mixture promoted distribution of drug particles on the surfaces of PEG 3350 particles, thereby aiding in the dispersion of drug aggregates. As smaller drug particles had a larger specific surface area able to make contact with the dissolution medium, the net effect promoted the dissolution of nifedipine. It should however be pointed out that the dispersion of drug aggregates would be less effective if the PEG 3350 particles (D_{99} = 170.07 ± 10.83 μm) were smaller than the drug particles (D_{99} = 233.23 ± 18.82 μm), as indicated by the smaller increase in $T_{30\ min}$ value between N1 and the corresponding interactive mixture (Table 2).

Theoretically, the addition of a larger amount of PEG 3350 would bring about a higher level of drug deposition onto the polymeric carrier. This in turn would result in a further reduction in the extent of drug aggregation and subsequent increase in the percentage of nifedipine dissolved. In the case of the present investigation, the dissolution profiles of N1, N3, and N4 were, nevertheless, not substantially affected by the proportion of PEG 3350 in the interactive mixtures (Figures 1a, 1c, and 1d). Due to its larger particle size, the extent of N1 deposited onto the surfaces of PEG 3350 in interactive mixtures containing 10% and 30% drug was likely to be low. The tumbling action of the mixing process employed in the preparation of interactive mixtures reduced the drug particle size, as indicated by the significantly lower D_{99} values of nifedipine in IM10 N1 (147.27 ± 5.92 μm) and IM30 N1 (142.43 ± 4.84 μm) compared with that of N1 (233.23 ± 18.82 μm; Table 4; Independent Student's *t*-Test, $p < .05$). As the resultant particle sizes were comparable with that of PEG 3350, the formation of interactive mixtures was not favored by the incorporation of a larger fraction of PEG 3350, and this accounted for the insignificant difference between the dissolution profiles of interactive mixtures containing 10% and 30% w/w of N1. Unlike the particles of N1, those of N3 and N4 were small and showed greater resistance to size reduction brought about by the turbulent mixing forces (Tables 1 and 4; Parrott, 1974; Hickey & Ganderton, 2001). The dissolution profiles of the interactive mixtures containing 10% and 30% w/w of N3 or N4 were comparable (Table 2). This strongly suggests that the amount of PEG 3350 in the interactive mixtures was sufficient to accommodate the drug particles present, with minimal drug aggregation. Consequently, the percentage of drug dissolved was not markedly affected by the concentration of polymeric carrier employed. The dissolution profiles of interactive mixtures of

TABLE 3
DSC Specific Heats and Melting Temperatures of Pure PEG 3350, Pure Nifedipine, Interactive Mixtures, and Solid Dispersions

	Specific Heat (J/g)		Melting Temperature (°C)	
Sample	PEG 3350	Nifedipine	PEG 3350	Nifedipine
PEG 3350	205.97 ± 2.11	–	55.18 ± 0.05	–
N1	–	118.86 ± 3.08	–	169.64 ± 0.07
N2	–	117.71 ± 2.15	–	169.78 ± 0.03
N3	–	117.41 ± 6.52	–	169.63 ± 0.02
N4	–	118.26 ± 9.91	–	169.65 ± 0.01
IM0	206.32 ± 3.53	–	55.29 ± 0.07	–
IM10 N1	194.96 ± 4.43	–	54.31 ± 0.08	–
IM30 N1	158.72 ± 1.38	–	53.70 ± 0.09	–
IM10 N2	201.86 ± 2.05	–	54.01 ± 0.04	–
IM30 N2	160.32 ± 3.06	–	53.66 ± 0.17	–
IM10 N3	199.66 ± 1.77	–	53.91 ± 0.10	–
IM30 N3	152.53 ± 7.25	–	53.39 ± 0.10	–
IM10 N4	195.41 ± 10.05	–	53.76 ± 0.13	–
IM30 N4	159.93 ± 1.46	–	53.44 ± 0.02	–
SD0	203.22 ± 3.80	–	55.37 ± 0.14	–
SD10 N1	180.51 ± 3.04	–	52.97 ± 0.52	–
SD30 N1	139.34 ± 1.72	–	53.44 ± 0.07	–
SD10 N2	179.20 ± 8.43	–	53.32 ± 0.05	–
SD30 N2	138.24 ± 2.21	–	53.43 ± 0.18	–
SD10 N3	177.24 ± 5.43	–	53.22 ± 0.02	–
SD30 N3	138.54 ± 1.91	–	53.32 ± 0.12	–
SD10 N4	181.33 ± 3.96	–	53.33 ± 0.06	–
SD30 N4	141.26 ± 1.16	–	53.28 ± 0.04	–

TABLE 4
Particle Size of Nifedipine in Drug Powders, Interactive Mixtures, and Solid Dispersions

	D_{99} (μm)				
		Interactive Mixture		Solid Dispersion	
Batch of Nifedipine	Pure Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine
N1	233.23 ± 18.82	147.27 ± 5.92	142.43 ± 4.84	8.25 ± 0.97	61.76 ± 4.06
N2	36.79 ± 1.32	35.48 ± 0.51	34.04 ± 0.61	5.00 ± 0.01	29.70 ± 1.12
N3	29.94 ± 4.70	25.70 ± 1.01	26.08 ± 1.09	8.83 ± 0.39	24.35 ± 0.27
N4	7.51 ± 0.05	7.33 ± 0.27	7.69 ± 0.36	6.76 ± 0.07	10.87 ± 1.26

D_{99} of PEG 3350 = 170.07 ± 10.83 μm.

10% and 30% w/w of N2, on the other hand, were markedly affected by the ratio of PEG 3350 to nifedipine (Table 2; Figure 1b). The N2 had a relatively small particle size when compared with PEG 3350, but a larger particle size in comparison with N3 and N4. It could be deposited onto the PEG 3350 and required a higher content of the latter to enhance its extent of dissolution. A Pearson's correlation study of $T_{30\ min}$ versus D_{99} values of nifedipine in the interactive mixtures consisting of a constant concentration of drug showed that the $T_{30\ min}$ value was well correlated to the final particle size of nifedipine ($r \geq -0.9$, $p < .05$). The drug dissolution can be promoted through the use of small drug particles to prepare the interactive mixtures.

Solid Dispersions

The solid dispersions consisted of a solidified molten mixture of nifedipine and PEG 3350. The percentage of nifedipine dissolvable from the solid dispersions was significantly higher than that of the pure drug throughout the entire period of dissolution (Figure 1; One-Way ANOVA, $p < .05$). Table 4 shows that the sizes of nifedipine particles embedded in the solid dispersions were generally smaller than those of pure drug and interactive mixtures. The reduction in nifedipine particle size could readily explain the enhancement in drug dissolution from solid dispersions over pure nifedipine. In the preparation of the solid dispersion, the nifedipine particles were either completely or partially dissolved in molten PEG 3350 depending on the amount of nifedipine incorporated. On cooling, the dissolved drug could recrystallize from the matrix. The net effect was a reduction in the particle size of nifedipine in solid dispersion, with N1 being affected to a greater extent than N2, N3, and N4 (Table 4). The extent of particle size reduction was greater at a lower nifedipine:PEG 3350 ratio. At 10% w/w nifedipine, the drug particles were completely dissolved in the molten polymeric carrier. Small drug nuclei were formed through recrystallization of dissolved drug upon cooling. The drug dissolution from solid dispersion was promoted by the formation of small nifedipine particles in association with an increase in specific surface area for drug dissolution (Tables 2 and 4). The dissolution profiles of N1, N2, N3, and N4 from SD10 were comparable. This could be aptly explained by the method of preparation of solid dispersions, whereby almost all drug particles were dissolved in the molten PEG 3350. Keeping all processing parameters constant, the size of drug particles recrystallized from the matrix would be similar and not governed by the initial geometry of nifedipine.

At 30% w/w nifedipine, the drug particles were not completely dissolved in the molten polymeric carrier. With the exception of N4, the size of the drug particles embedded in the solid dispersion was smaller than that of the pure drug, but to a lesser extent than that prepared using a lower nifedipine:PEG 3350 ratio (Table 4). Interestingly, the N4 particles embedded in the solid dispersion were larger than those of the pure drug. Pure N4 had the smallest particle size. In accordance to a modified Ostwald relationship of particle size and solubility by Freundlich as follows:

$$\frac{RT}{M}\ln\frac{S_2}{S_1} \equiv \frac{4\sigma}{\rho}\left(\frac{1}{d_2}-\frac{1}{d_1}\right) \quad (1)$$

where S_1 and S_2 are the solubility values of particles with diameter d_1 and d_2, respectively, σ is the surface energy, M is the molecular weight, T is the absolute temperature, ρ is the density, and R is the gas constant. The smaller drug particles were envisaged to be more soluble in molten polymeric carrier when preparing the solid dispersion. For a given weight of nifedipine, the population of pure N4 particles would numerically be largest. A larger number of undissolved N4 nuclei could thus be available as seeds in molten PEG 3350 for recrystallization of dissolved nifedipine during the solidification stage. The smaller N4 particles which had previously dissolved rapidly when heated were recrystallized on cooling as a result of a greater saturation level of drug as well as the availability of a larger population of undissolved seeds in molten PEG 3350. Thus, there was coarsening of N4 particles. The similar observation was noted in solid dispersion carrying a high load of fine griseofulvin particles, particularly when the solid dispersion was prepared by means of a solvent method (Sjökvist & Nyström, 1988).

Expectedly, the $T_{30\,\mathrm{min}}$ of SD30 was lower than that of SD10 for all batches of nifedipine. SD30 N4 possessed a higher $T_{30\,\mathrm{min}}$ value than that of the pure drug in spite of its larger drug particle size (Tables 2 and 4). The results suggested that PEG 3350 could be employed to prevent aggregation of nifedipine particles, in addition to size reduction of drug particles, through the formation of solid dispersions. A Pearson's correlation study of $T_{30\,\mathrm{min}}$ values versus final particle size of nifedipine in the solid dispersions indicated that the extent of nifedipine dissolution was significantly affected by drug particle size as in the case of interactive mixture ($r > -0.8$, $p < .05$).

X-Ray Diffraction and DSC Analysis

PEG 3350, IM0, and SD0 had similar DSC melting peak temperatures and endothermic specific heats (Table 3). Apparently, the thermal characteristics of the polymeric carrier were not affected by the preparation processes of interactive mixtures and solid dispersions. Pure nifedipine (N1 to N4), PEG 3350, IM0, and SD0 melted at 169.68 ± 0.07°C, 55.18 ± 0.05°C, 55.29 ± 0.07°C, and 55.37 ± 0.14°C, respectively. Blends of nifedipine and PEG 3350 in interactive mixture and solid dispersion gave rise to a single melting endotherm at about 52.97°C to 54.31°C, indicating interaction between PEG 3350 and drug. The melting peak temperatures of PEG 3350 in nifedipine-loaded interactive mixtures and solid dispersions were lower than those of PEG 3350, IM0, and SD0 (Table 3; One-Way ANOVA, $p < .05$). The lowering of the melting peak temperature was attributed to the disruption of the PEG 3350 matrix by dissolved and/or dispersed nifedipine. Practically, the melting peak temperature and endothermic enthalpy were lower in the case of solid dispersion than those of interactive mixture (Table 3). The extent of disruption of the PEG 3350 matrix by nifedipine during the preparation process of solid dispersion was greater than those of the interactive mixture. The X-ray diffraction study showed that the I_N values (2θ: 11.76°) of interactive mixtures were consistently higher than that of the corresponding solid dispersions (Table 5). The crystallinity of nifedipine was generally higher in interactive mixtures than in solid dispersions. The drug crystals could have converted to molecularly dispersed entities in solid dispersion, thereby reducing the level of nifedipine crystallinity and enhancing the interaction of PEG 3350 matrix with nifedipine in solid

TABLE 5
Crystallinity Levels of Nifedipine, I_N, in the Interactive Mixtures and Solid Dispersions

	Interactive Mixture		Solid Dispersion	
Batch of Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine	10% w/w Nifedipine	30% w/w Nifedipine
N1	1225 ± 86	2419 ± 373	881 ± 191	2389 ± 139
N2	1216 ± 61	2343 ± 101	1052 ± 109	2413 ± 75
N3	1095 ± 59	2421 ± 121	1078 ± 16	2362 ± 168
N4	1209 ± 14	2347 ± 121	1064 ± 35	2482 ± 144

dispersions as shown by the DSC study. Unlike drug particle size, a Pearson's correlation study of $T_{30\,min}$ values versus nifedipine crystallinity in interactive mixtures and solid dispersions containing 10% w/w and 30% w/w of drug, respectively, indicated that the dissolution profile of nifedipine was not significantly governed by the crystallinity of the embedded drug particles (Interactive mixture: $r < -0.4$, $p > .05$; solid dispersion: $r < 0.6$, $p > .05$).

Comparison Between Interactive Mixture and Solid Dispersion

The extent of dissolution of nifedipine from interactive mixture and solid dispersion was mainly governed by the final particle size of the drug. Practically, smaller drug particles brought about an increase in T_{30min} value. The solid dispersion was more effective as a rapid drug delivery system when compared with the interactive mixture. Nonetheless, the difference in effectiveness between the solid dispersion and interactive mixture became smaller when fine nifedipine particles or a high nifedipine:PEG 3350 ratio was employed in the preparation of the drug delivery system. At 30% w/w nifedipine loading, the extent of drug dissolution was lower in solid dispersion than in interactive mixture where fine drug particles were concerned. Drug coarsening was noted in the preparation of solid dispersion. This limits the use of solid dispersion as an enhanced-release carrier to low dose formulations. Unlike solid dispersion, the interactive mixture could accommodate a higher drug load with respect to its drug dissolution enhancement capacity when fine drug particles were incorporated in the formulation. The extent of nifedipine dissolution can be promoted without subjecting the drug to any heating process and the influences of drug coarsening.

CONCLUSIONS

Micronization itself does not enhance but rather results in poorer nifedipine dissolution. The use of micronized nifedipine required the transformation of drug particles into an interactive mixture or solid dispersion using PEG 3350 as the carrier in enhancement of drug dissolution. Practically, the extent of drug dissolution of an interactive mixture or a solid dispersion was mainly promoted through the use of smaller drug particles or reducing the size of drug particles during the process of product preparation. In comparison with the interactive mixture, the solid dispersion was more effective as a rapid drug delivery system, as the size of a given batch of drug particles was markedly reduced by the molten PEG 3350 during the preparation process of solid dispersion. Nonetheless, the extent of drug dissolution was lower in the solid dispersion than in the interactive mixture when a high load of fine drug particles was used as the starting material. This was attributed to drug coarsening in the preparation of the solid dispersion. This limits the use of solid dispersion as an enhanced-release carrier to low dose formulations. Unlike solid dispersion, the interactive mixture could accommodate a high load of fine drug particles without compromising its capacity to enhance the extent of drug dissolution. The extent of nifedipine dissolution of an interactive mixture can be promoted without subjecting the drug to any heating process and drug coarsening.

REFERENCES

Betageri, G. V., & Dipali, S. R. (1995). Preparation and in vitro dissolution profiles of tolazamide-polyethylene glycol solid dispersions. *Drug Dev. Ind. Pharm., 21*, 1347–1352.

Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci., 60*, 1281–1302.

Chutimaworapan, S., Ritthidej, G. C., Yonemochi, E., Oguchi, T., & Yamamoto, K. (2000). Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions. *Drug Dev. Ind. Pharm., 26*, 1141–1150.

Doshi, D. H., Ravis, W. R., & Betageri, G. V. (1997). Carbamazepine and polyethylene glycol solid dispersions: Preparation, in vitro dissolution, and characterization. *Drug Dev. Ind. Pharm., 23*, 1167–1176.

Goldberg, A. H., Gibaldi, M., & Kanig, J. L. (1966a). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II: Experimental evaluation of eutectic mixture: Urea-acetaminophen system. *J. Pharm. Sci., 55*, 482–487.

Goldberg, A. H., Gibaldi, M., & Kanig, J. L. (1966b). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III: Experimental evaluation of griseofulvin-succinic acid solution. *J. Pharm. Sci., 55*, 487–492.

Hickey, A. J., & Ganderton, D. (2001). Size reduction and classification. In A. J. Hickey & D. Ganderton (Eds.), *Pharmaceutical Process Engineering* (pp. 174–197). New York: Marcel Dekker.

Jachowicz, R., Nürnberg, E., & Hoppe, R. (1993). Solid dispersions of oxazepam. *Int. J. Pharm., 99*, 321–325.

Jachowicz, R., Nürnberg, E., & Hoppe, R. (1997). Enhanced release of oxazepam from tablets containing solid dispersions. *Int. J. Pharm., 159*, 149–158.

Joshi, H. M., Tejwani, R. W., Davidovich, M., Sahasrabudhe, V. P., Jemal, M., Bathala, M. S., Varia, S. A., & Serajuddin, A. T. M. (2004). Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. *Int. J. Pharm., 269*, 251–258.

Karavas, E., Ktistis, G., Xenakis, A., & Georgarakis, E. (2005). Miscibility behavior and formation mechanism of stabilized felodipine-polyvinylpyrrolidone amorphous solid dispersions. *Drug Dev. Ind. Pharm., 31*, 473–489.

Karavas, E., Georgarakis, E., Sigalas, M. P., Avgoustakis, K., & Bikiaris, D. (2007). Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug-polymer interactions. *Eur. J. Pharm. Biopharm., 66*, 334–347.

Kerć, J., Srćić, S., & Kofler, B. (1998). Alternative solvent-free preparation methods for felodipine surface solid dispersions. *Drug. Dev. Ind. Pharm., 24*, 359–363.

Lin, C.-W., & Cham, T.-M. (1996). Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions. *Int. J. Pharm., 127*, 261–272.

Lin, S. L., Menig, J., & Lachman, L. (1968). Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water-insoluble drugs. *J. Pharm. Sci., 57*, 2143–2148.

Liu, C., Wu, J., Shi, B., Zhang, Y., Gao, T., & Pei, Y. (2006). Enhancing the bioavailability of cyclosporine A using solid dispersion containing polyoxyethylene (40) stearate. *Drug Dev. Ind. Pharm., 32*, 115–123.

Nilsson, P., Westerberg, M., & Nyström, C. (1988). Physicochemical aspects of drug release. V. The importance of surface coverage and compaction on drug dissolution from ordered mixtures. *Int. J. Pharm., 45*, 111–121.

Nyström, C., & Westerberg, M. (1986). The use of ordered mixtures for improving the dissolution rate of low solubility compounds. *J. Pharm. Pharmacol., 38*, 161–165.

Parrott, E. L. (1974). Milling in pharmaceutical solids. *J. Pharm. Sci., 63*, 813–829.

Rabasco, A. M., Ginés, J. M., Fernández-Arévalo, M., & Holgado, M. A. (1991). Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions. *Int. J. Pharm., 67*, 201–205.

Ren, F., Jing, Q., Tang, Y., Shen, Y., Chen, J., Gao, F., & Cui, J. (2006). Characteristics of bicalutamide solid dispersions and improvement of the dissolution. *Drug Dev. Ind. Pharm., 32*, 967–972.

Save, T., & Venkitachalam, P. (1992). Studies on solid dispersions of nifedipine. *Drug Dev. Ind. Pharm., 18*, 1663–1679.

Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull., 9*, 866–872.

Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci., 88*, 1058–1066.

Sheu, M.-T., Yeh, C.-M., & Sokoloski, T. D. (1994). Characterization and dissolution of fenofibrate solid dispersion systems. *Int. J. Pharm., 103*, 137–146.

Sjökvist, E., & Nyström, C. (1988). Physicochemical aspects of drug release. VI. Drug dissolution rate from solid particulate dispersions and the importance of carrier and drug particle properties. *Int. J. Pharm., 47*, 51–66.

Sjökvist, E., Nyström, C., & Aldén, M. (1991). Physicochemical aspects of drug release. XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions. *Int. J. Pharm., 69*, 53–62.

Sjökvist Saers, E., Nyström, C., & Aldén, M. (1993). Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. *Int. J. Pharm., 90*, 105–118.

Sjökvist, E., Nyström, C., Aldén, M., & Caram-Lelham, N. (1992). Physicochemical aspects of drug release. XIV. The effects of some ionic and non-ionic surfactants on properties of a sparingly soluble drug in solid dispersions. *Int. J. Pharm., 79*, 123–133.

Sugimoto, I., Kuchiki, A., Nakagawa, H., Tohgo, K., Kondo, S., Iwane, I., & Takahashi, K. (1980). Dissolution and absorption of nifedipine from nifedipine-polyvinylpyrrolidone coprecipitate. *Drug Dev. Ind. Pharm., 6*, 137–160.

Vippagunta, S. R., Maul, K. A., Tallavajhala, S., & Grant, D. J. W. (2002). Solid-state characterization of nifedipine solid dispersions. *Int. J. Pharm., 236*, 111–123.

Westerberg, M., Jonsson, B., & Nyström, C. (1986). Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures. *Int. J. Pharm., 28*, 23–31.

Westerberg, M., & Nyström, C. (1991). Physicochemical aspects of drug release. XII. The effect of some carrier particle properties and lubricant admixture on drug dissolution from tableted ordered mixtures. *Int. J. Pharm., 69*, 129–141.

Westerberg, M., & Nyström, C. (1993). Physicochemical aspects of drug release. XVII. The effect of drug surface area coverage to carrier materials on drug dissolution from ordered mixtures. *Int. J. Pharm. 90*, 1–17.