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Solid State and Dissolution Rate Characterization of Co-Ground Mixtures of Nifedipine and Hydrophilic Carriers

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ABSTRACT Co-ground powders of the poorly water-soluble drug nifedipine and a hydrophilic carrier, [partially hydrolyzed gelatin (PHG), polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), urea or Pluronic F108] were prepared in order to improve the dissolution rate of nifedipine. The effects of type of grinding equipment, grinding time, and type of hydrophilic carrier on the crystallinity of nifedipine (x-ray diffraction and differential scanning calorimetry) on the interaction between drug and carriers (differential scanning calorimetry), on the particle size and appearance (scanning electron microscopy), on the wettability (contact angle measurements), and on the drug release were investigated. Grinding nifedipine together with these carriers improved the dissolution rate. PHG-ground mixtures resulted in the fastest dissolution rate followed by PVP, SDS, HPMC, Pluronic, urea, and PEG. This effect was not only due to particle size reduction, which increased in the order PHG<PEG=SDS<Pluronic<drug<urea<HPMC<PVP, but also resulted from the ability of some carriers (PVP and HPMC) to prevent reaggregation of the finely divided drug particles. PVP, HPMC, and PHG formed a powder with amorphous drug. The carriers improved the wettability of the ground products in the order HPMC<drug<urea<PVP<SDS<PHG<PEG<Pluronic. Differential scanning calorimetry (DSC) measurements gave valuable information about the nature of drug crystallinity and the interactions with the carriers within the ground mixtures.

KEYWORDS Co-ground mixtures, Dissolution rate enhancement, Hydrophilic carriers, Nifedipine, Poorly soluble drugs

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INTRODUCTION

Nifedipine [4-(2-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethyl-1,4-dihydropyridine] is a calcium channel blocker widely used for the treatment of hypertension and angina pectoris. It is a weakly basic drug (pK_a=3.93),

photosensitive (Gambaro et al., 1985), poorly water-soluble [10 μg/ml in water at 37°C] (Friedrich, 2004), and is usually supplied as yellow crystals having a melting range of 172–174°C (Burger & Koller, 1996). These authors have described two metastable polymorphs as well as four different solvates crystallized from 1,4-dioxane. Low and irregular bioavailability following oral administration of nifedipine was reported (Ali, 1989; Pabst et al., 1986).

Considerable efforts have been undertaken to enhance the dissolution rate of nifedipine. These included the preparation of solid dispersions with polyvinylpyrrolidone (Sugimoto et al., 1981), PEG 6000 (Lin & Cham, 1996), hydroxypropyl-β-cyclodextrin, poloxamer 407 (Chutimaworapan et al., 2000), or a mixture of poloxamer 188 and gelucire 50/13 (Vippagunta et al., 2000). Solid dispersions, which are generally prepared by melting or solvent methods, pose several challenges. Finely dispersed drug particles in solid dispersion systems are usually in the thermodynamically unstable amorphic form. This could lead to crystallization upon storage, especially under humid conditions (Kawano et al., 1985; Sugimoto et al., 1981), resulting in changes in drug dissolution/bioavailability. Problems of the melting technique are the limited number of low temperature melting water-soluble carriers and the possibility of thermal drug degradation. The solvent methods suffer from the undesirable environmental impact of many organic solvents and their potential toxic and carcinogenic effects.

Micronization of drug powders results in a considerable decrease of particle size. However, the product tends to agglomerate, which leads to a considerable reduction of specific surface area and formation of a cohesive powder with poor flow properties (Arias-Blanco et al., 1996; Mura et al., 2002).

Co-grinding of poorly soluble drugs with hydrophilic carriers is an interesting technique for the production of micronized and stable drug particles. Many authors have reported on the use of this method for the enhancement of dissolution rates of various drugs. Examples include digoxin, spironolactone, estradiol (Florence & Salole, 1976), ketoprofen (Mura et al., 2001), indomethacin (Etman & Nada, 1999), and phenytoin (Nada, 1997; Yamamoto et al., 1976). Sugimoto et al. (1998) reported on the wet co-grinding of nifedipine with a mixture of PEG 6000 and HPMC in the presence of a small amount of water and the higher dissolution rate of this technique when compared to a spray-dried product of the same composition.

The objective of the present study was the size reduction of nifedipine and improvement of the rate of dissolution by co-grinding with hydrophilic materials, namely partially hydrolyzed gelatin (PHG), sodium dodecyl sulfate (SDS), urea, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and poloxamer (Pluronic F108). The samples were evaluated by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder x-ray diffractometry, powder wettability, and drug release.

MATERIALS AND METHODS

Materials

Nifedipine (purchased at Sigma-Aldrich Laborchemikalien GmbH, Seelze, Germany), polyvinylpyrrolidone (PVP 30, Kollidon® 30), copolymer of ethylene oxide and propylene oxide (Pluronic, Pluronic® F108 NF), polyethylene glycol (PEG, Lutrol® E 4000) (BASF AG, Ludwigshafen, Germany), hydroxypropyl methycellulose (HPMC, Methocel® K15M) (Colorcon Ltd, Orpington, UK), partially hydrolyzed gelatin (PHG) (DGF Stoess, Eberbach/Baden, Germany), sodium dodecyl sulfate (SDS, Texapon®) (Henkel KGaA, Düsseldorf, Germany) and urea (Merck KGaA, Darmstadt, Germany). Other materials were supplied by the manufacturer.

Preparation of Physical (PM) and Ground Mixtures (GM)

Nifedipine and mixtures with each carrier (1.0 g drug and 3.0 g carrier) were ground using a metal ball mill (MBM) (Fritsch Laborette, Fritsch GmbH, Idar-Oberstein, Germany) and a teflon ball mill (TBM) (mixer mill MM 2000, Retsch, Hemer, Germany), respectively. The MBM consisted of a 40 ml jar and four metal balls and the TBM of a 10 ml jar with cover and cooling attachment and two teflon coated balls. Liquid nitrogen was used to cool the teflon jar. Test samples were ground at 70 rpm for 30, 60, or 120 min at ambient conditions. The physical mixtures were prepared by gentle mixing with a spatula in a porcelain mortar for 5 min.

Powder X-Ray Diffractometry

Pure drug, physical mixtures, and ground mixtures were measured by wide angle x-ray diffractometry on a Philips PW 1830 x-ray generator with a copper anode (Cu Kα radiation, $\lambda = 0.15418$ nm, 40 kV), fixed with a Philips PW 1710 diffraction control unit (Philips Industrial and Electro-acoustic Systems Divisions, Almelo, The Netherlands). The radiation scattered in the crystalline regions of the samples was measured with a vertical goniometer (Philips PW 1820, Philips Industrial and Electro acoustic Systems Division, Almelo, The Netherlands). Patterns were obtained using a step width of 0.02°C with a detector resolution in 2θ (diffraction angle) between 4° and 40° at ambient temperature.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry studies were performed using a Mettler DSC 821e (Mettler, Toledo, Giessen, Germany). Samples (5–7 mg) were weighed in 40 µl aluminium pans with perforated covers. DSC scans were recorded at a heating rate of 10°C/min from 25°C to 180°C with a nitrogen flow rate of 80 ml/min. The values of the transitions were derived from the computed extrapolated peak maximum, onset and offset temperature, and the enthalpy values (ΔH) were calculated from the area under the melting peak using the STAR^e Software (Mettler, Toledo, Giessen, Germany). The peak width was calculated as the width at the middle of the peak height by the STAR^e Software. The peak symmetry was the ratio of the width of onset to midpoint temperature/width of midpoint to offset temperature.

Scanning Electron Microscopy (SEM)

The shape and surface characteristics of the ground mixtures were studied by SEM. The particles were coated with gold-palladium and then observed with an electron microscope (Philips SEM 515, PW 6703, Philips Industrial Electronics, Kassel, Germany) at ambient temperature.

Particle Size Measurements

The particle size was determined by laser light scattering including polarization intensity differential scattering technology (PIDS) (Coulter LS 230, powder module, Coulter Electronics, Krefeld, Germany). The relative frequency of the diameter of the particles was obtained by calculations based on volume distribution. The particle size at 90% of total fraction was used as particle size. The values were the average of three measurements.

Contact Angle Measurements

The mixtures were compressed to flat-faced tablets (diameter: 13 mm, weight: 300 mg) with a hydraulic press (P/N 25.011, Specac, Orpington, England) at 10 KN for 5 sec. The compressed tablet was placed onto an adjustable platform of the contact angle goniometer (Krüss G1 Goniometer, Hamburg, Germany). Using a micro-syringe, 2 µl distilled water was applied onto the mixture. The contact angles were measured 30 seconds after wetting the samples ($n = 6$).

Dissolution Studies

Dissolution studies were performed with freshly prepared blends containing 5 mg drug in 500 ml 0.1 N HCl at 37°C in a horizontal shaker at 75 rpm (GFL 3033, Gesellschaft für Labortechnik mbH, Burgwedel, Germany) ($n = 2$). The dissolution studies were performed under non-sink conditions, therefore the dissolution curves levelled off. The drug concentration was detected spectrophotometrically at $\lambda = 238$ nm (UV 2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA). Absorbance of the carriers at $\lambda = 238$ nm was negligible. Samples were withdrawn with a filter syringe and replaced by fresh solvent. All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

RESULTS AND DISCUSSIONS

Co-grinding is a relatively simple and effective method to prepare a drug delivery system with an enhanced dissolution rate (Shakhtshneider et al., 1996; Sugimoto et al., 1998). This approach of dissolution

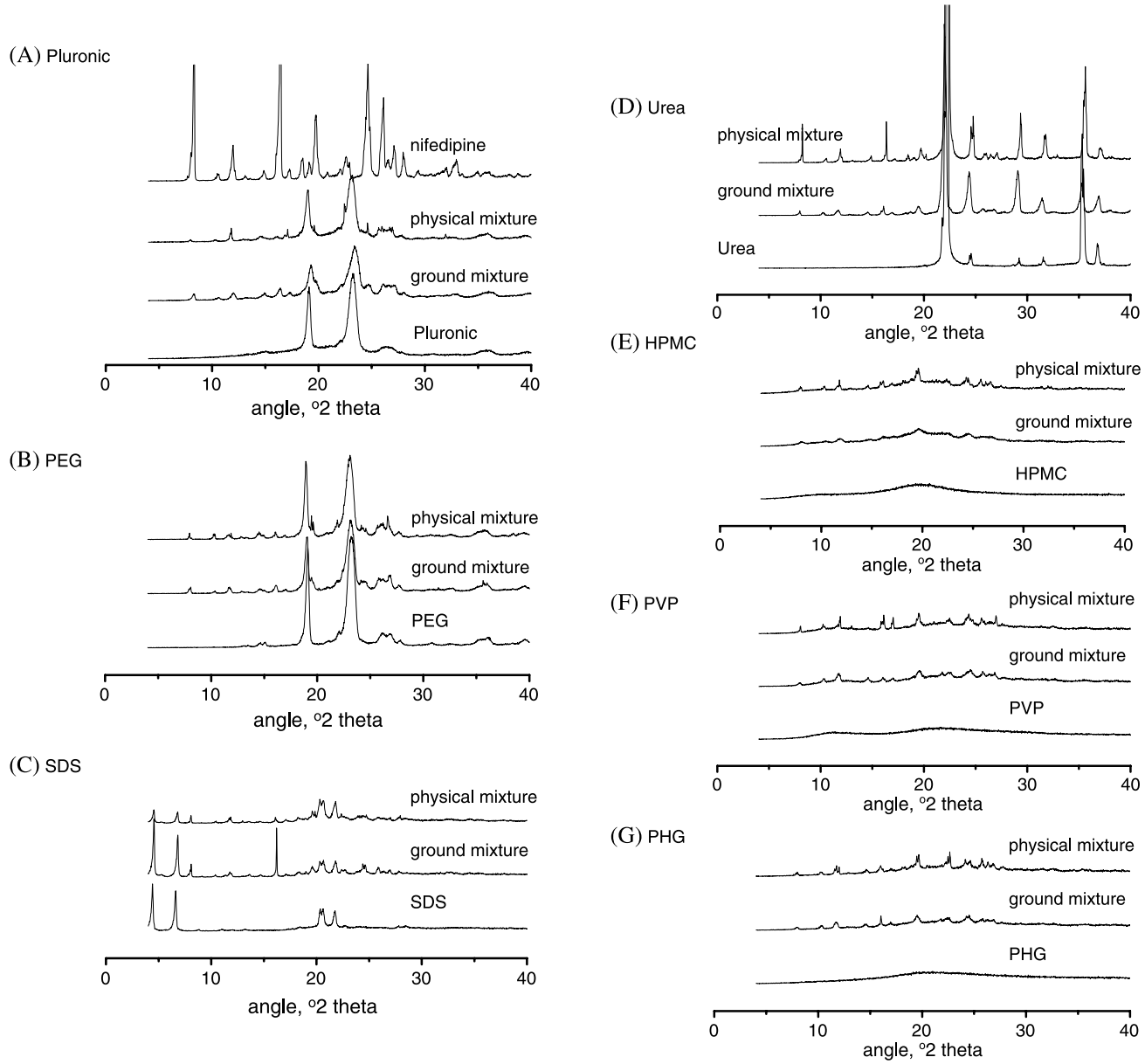

FIGURE 1 **X-Ray Patterns of Nifedipine, Hydrophilic Carriers, Physical Mixtures, and Ground Mixtures which were Milled with the MBM: (A) Pluronic, (B) PEG, (C) SDS, (D) Urea, (E) HPMC, (F) PVP, (G) PHG (Drug:Carrier Ratio, 1:3 w/w).**

rate improvement is caused by 1) solubilizing effects of the additives, 2) reducing the particle size of the drug, and 3) the presence of the amorphous form of the drug.

First, x-ray diffraction studies were undertaken to investigate the effect of grinding on the amorphous/crystalline drug ratio within the mixtures. Crystallinity of nifedipine was indicated by the presence of multiple sharp peaks, whereby the major two peaks appeared at 16° and 8° 2θ, respectively (Fig. 1A). The hydrophilic carriers, Pluronic, PEG, SDS, and urea also showed some crystallinity (Fig. 1A–D). The x-ray diffraction patterns of ground mixtures of nifedipine with Pluronic, PEG, SDS, and urea indicated the characteristic peaks of the carriers, while the characteristic peaks of nifedipine were of significantly lower intensity. Nifedipine therefore existed in a less crystalline state in the ground mixtures with Pluronic, PEG, and urea when compared to the corresponding physical mixtures (Fig. 1A, B, D). Ground mixtures with SDS indicated a higher crystallinity compared to the physical mixture (Fig. 1C). On the contrary, a halo diffraction pattern was obtained with the amorphous carrier HPMC (Fig. 1E). Small peaks were observed for

ground mixture with the amorphous PVP and PHG (Fig. 1F and G). Physical mixtures with these amorphous carriers showed a higher degree of crystallinity than the ground mixtures (Fig. 1E–G). DSC-studies were performed on the individual components and on freshly prepared ground and physical mixtures in order to study the interactions between nifedipine and the carriers in the solid state (Fig. 2, Table 1). Nifedipine exhibited a single sharp melting endotherm at 171°C. Similarly, PEG, Pluronic, and urea showed single sharp peaks at 60°C, 59°C, and 137°C, respectively (Fig. 2A and B). In contrast, SDS demonstrated a small endotherm with peak temperature at 63°C and a broad endotherm at 105°C, respectively (Fig. 2B). The glass transition temperature (Tg) of PVP was defined at 179°C, whereas the big bump around 75°C demonstrated evaporation of absorbed water (Fig. 2A) (Friedrich, 2004). The Tg of the amorphous HPMC could not be detected, but it was reported to be approximately 162°C (McPhillips et al., 1999). DSC-thermograms of the ground mixtures with Pluronic and PEG did not show distinctive peaks of nifedipine (Fig. 2A), indicating the complete dissolution of nifedipine in these polymers below the melting temperature of nifedipine. Hence, these mixtures formed monotectics during the DSC-heating process. Similar to the x-ray data, the DSC-data showed the reduced crystallinity of nifedipine and a depressed melting point with the other hydrophilic carriers.

The peak symmetry was calculated in order to get information about the extent of interactions between nifedipine and the carriers (Table 1) (Kim et al., 1985). The peak symmetry of mixtures with PEG and Pluronic could not be calculated because nifedipine was dissolved in the carrier melts. The peak symmetry exhibited variable degrees of change, depending on the type of polymer, method of treatment, possible drug-carrier interactions, as well as the ratio of amorphous/crystalline components. The extent of drug-excipient interactions and the transformation of crystalline to amorphous drug are higher with a higher variation of the peak symmetry between physical and ground mixtures. The peak symmetry of the melting transition in the ground mixtures increased because of the decreased interparticular spaces resulting from the grinding effect, and probably because of increased surfaces available for interactions between nifedipine and carrier. The heating process affected this peak symmetry and melting point depression depending on the type of carrier and its interactions with the drug. In general, the peak symmetry of the drug peak in the ground mixture was higher than in the corresponding physical mixtures, except for the PVP mixtures (Table 1). The thermograms of the untreated drug (peak symmetry ratio=2) and its physical mixture with PHG (peak symmetry ratio=2) and with SDS (peak symmetry ratio=1), to which the drug was less bound, were symmetrical (Table 1). Physical mixtures with urea (peak symmetry ratio=0.3, melting point depression=12.4°C) and with HPMC (peak symmetry ratio=0.7, melting point depression=2.5°C) showed less symmetric melting peaks of nifedipine. These peak symmetry data and melting point depressions indicated interactions caused by simple mixing in a mortar. The melting peak of nifedipine disappeared or appeared as broad peak in case of drug molecules bound to the carrier in the solid state, e.g., for the physical and ground mixtures with PVP (Monkhouse & Lach, 1972) (Fig. 2A). The interaction potential in the case of nifedipine is caused mainly by hydrogen bonding between the H-donor group of nifedipine and the carbonyl group of the pyrrole ring of PVP (Forster et al., 2001). Likewise, formation of H-bonds could be suggested for the nifedipine/PEG and nifedipine/HPMC systems, as previously reported for PEG (Maraqa et al., 1995) and HPMC (Cilurzo et al., 2002) solid dispersions. The drug melting endotherm was less asymmetric with SDS or urea after grinding in the TBM than in the MBM (Fig. 2B). Similar results were obtained with the other carriers. The lower ΔH values (area under the melting transition) indicated also the increased interactions and miscibility between drug and carrier in the order of drug>PM SDS>PM Urea>GM SDS>GM Urea>GM PHG>PM PHG>PM PVP>PM HPMC>GM HPMC>GM PVP. The absence of the melting transition peak in presence of PEG and Pluronic indicated the complete miscibility of drug with the carrier (Table 1).

The DSC data supported the use of the MBM, where higher interactions between nifedipine and the carriers within the same grinding time were obtained (Fig. 2B). The higher interactions were mainly caused by the higher forces obtained with the harder material of the metal mill compared to the teflon ball mill.

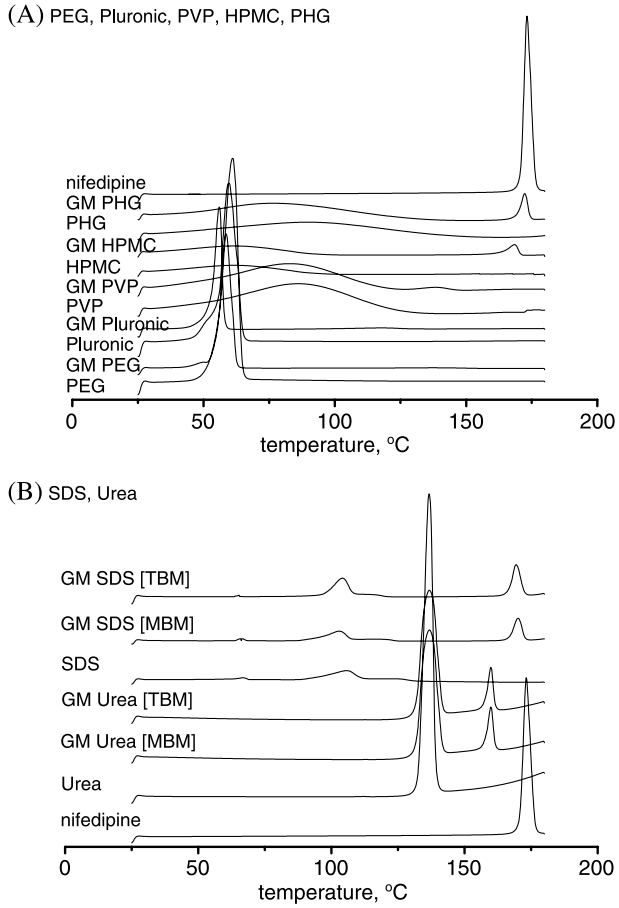

FIGURE 2 **DSC Thermograms of Nifedipine, Hydrophilic Carriers, and Ground Mixtures (GM): (A) PEG, Pluronic, PVP, HPMC, PHG (MBM), (B) Urea and SDS (MBM or TBM) (Drug:Carrier Ratio, 1:3 w/w).**

Besides the partially amorphous nature of nifedipine, the reduced particle size of the drug within the ground mixtures could also enhance the dissolution rate. Co-grinding of nifedipine crystals with the different carriers resulted in a particle size reduction into the lower μm size range (Fig. 3). The initial drug particles were rectangular crystals with a smooth and compact surface; 90% of the particles were smaller than 50 μm (data not shown). Round-shaped microparticles were obtained for ground mixtures with PEG (Fig. 3A) and Pluronic (similar to PEG, photograph not shown). Ninety percent of the tested total fraction of nifedipine/PEG particles were smaller than 45 μm and of the nifedipine/Pluronic particles were smaller than 49 μm. Drug particles were transformed to smaller crystalline structures, which are finely dispersed and surrounded by the PHG and SDS particles (Fig. 3B and C). Ninety percent of the nifedipine/PHG particles were smaller than 41 μm and 90% of the nifedipine/SDS particles were smaller than 45 μm. Nifedipine/urea particles had spherical shape and 90% of the particles were smaller than 123 μm (Fig. 3D). The drug particles were partially covered by particles of PEG, Pluronic, and urea (Fig. 3A and D). However, the larger particles of nifedipine/urea could be detrimental for dissolution. The nifedipine/HPMC particles were large and the drug was completely covered by HPMC. Ninety percent of these particles were smaller than 387 μm (Fig. 3E). Nifedipine/PVP formed particles with an average size of 411 μm covered by a net-like film of the carrier (Fig. 3F). This covering of the particles could prevent reaggregation of the

TABLE 1 **Heat of Fusion (ΔH), Peak Temperature, Onset Temperature, Offset Temperature, Peak Width, and Peak Symmetry of Ground Mixtures (Milled with the MBM), Physical Mixtures, and Untreated Nifedipine**

Mixture	ΔH (J/g)	Peak temperature (°C)	Onset temperature (°C)	Offset temperature (°C)	Peak width (°C)	Peak symmetry
PHG—ground mixture	23.6	171.5	160.4	176.8	3.6	2.2
PHG—physical mixture	19.8	169.3	156.3	173.0	4.8	2.0
Urea—ground mixture	24.5	159.3	151.9	163.6	5.3	1.7
Urea—physical mixture	26.5	158.7	156.3	165.8	3.9	0.3
SDS—ground mixture	25.5	169.9	163.4	174.3	3.4	1.3
SDS—physical mixture	31.9	169.0	161.2	179.1	4.1	1.0
PVP—ground mixture	7.1	143.6	129.2	153.5	12.7	1.8
PVP—physical mixture	19.3	170.4	148.9	173.4	5.8	6.0
HPMC—ground mixture	18.2	171.6	158.9	178.2	2.9	1.7
HPMC—physical mixture	19.2	168.6	151.5	172.4	4.7	0.7
Nifedipine	109.2	171.1	167.7	178.3	3.1	2.0

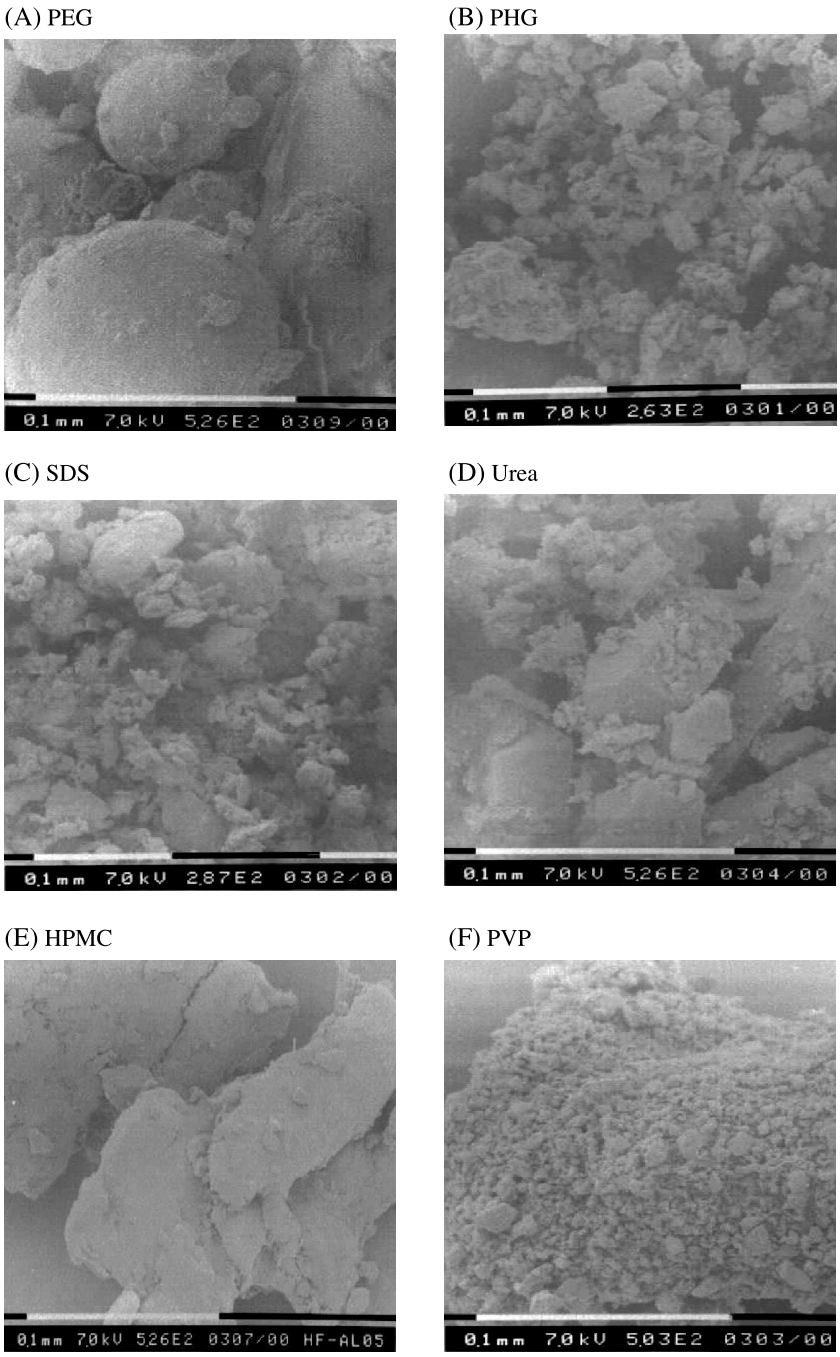

FIGURE 3 **Scanning Electron Micrographs of Ground Mixtures (Milled with the MBM) of Nifedipine with (A) PEG, (B) PHG, (C) SDS, (D) Urea, (E) HPMC, (F) PVP (Drug:Carrier Ratio, 1:3 w/w).**

initially finely ground drug particles, which could affect the drug release positively.

Finally, the drug release was investigated. Initial trials were performed to determine the optimum milling time. The dissolution rate increased with increased grinding time, but grinding times in excess of 30 min did not further increase the dissolution rates of the ground nifedipine/PVP mixtures probably because of the increase of surface free energy and subsequent aggregation of the particles (Fig. 4). A treatment of the powder for 120 min actually decreased the dissolution rate. Grinding of the drug also resulted in an increase in dissolution rate, but not to the extent as with the PVP mixture. Grinding of pure nifedipine for 120 min led to electrostatically charged particles, which agglomerated, resulting in a decreased drug release. A satisfactory dissolution rate and minimal heat stress were therefore

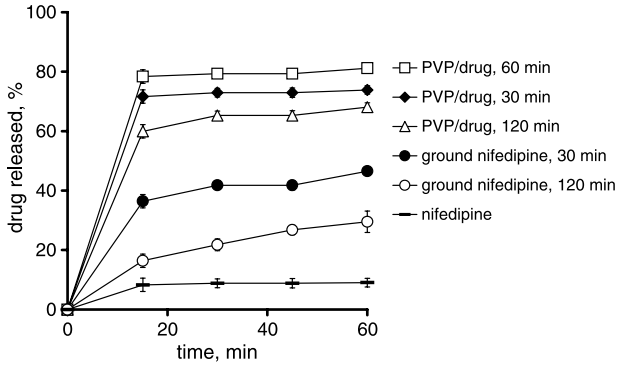

FIGURE 4 **Effect of Grinding Time on the Dissolution of Nifedipine and Ground Mixtures with PVP (Milled with the MBM) (Drug:Carrier Ratio, 1:3 w/w).**

obtained with ground mixtures with a grinding time of 30 min.

Besides milling time, the influence of two types of milling jars made from either teflon (TBM) or from steel (MBM) on the grinding efficiency as determined by drug dissolution was investigated (Fig. 5A–C). First, irrespective of the milling equipment, the release of the drug from the physical mixtures was significantly slower than from the corresponding ground mixtures because of the lower crystallinity of nifedipine in the ground mixture (Figs. 1 and 5) and the weak interparticular bondings with the carrier in the physical mixtures. In general, mixtures ground with the MBM showed faster drug release profiles than mixtures ground with the TBM. The dissolution rate of the mixtures ground with the MBM was approximately four times higher with PVP, three times higher with PHG and urea, two times higher with PEG, and one time higher with HPMC when compared to the ground mixtures milled with the TBM. The milling equipment had little influence on the release from the SDS mixture (Fig. 5C). Only the TBM-treatment of

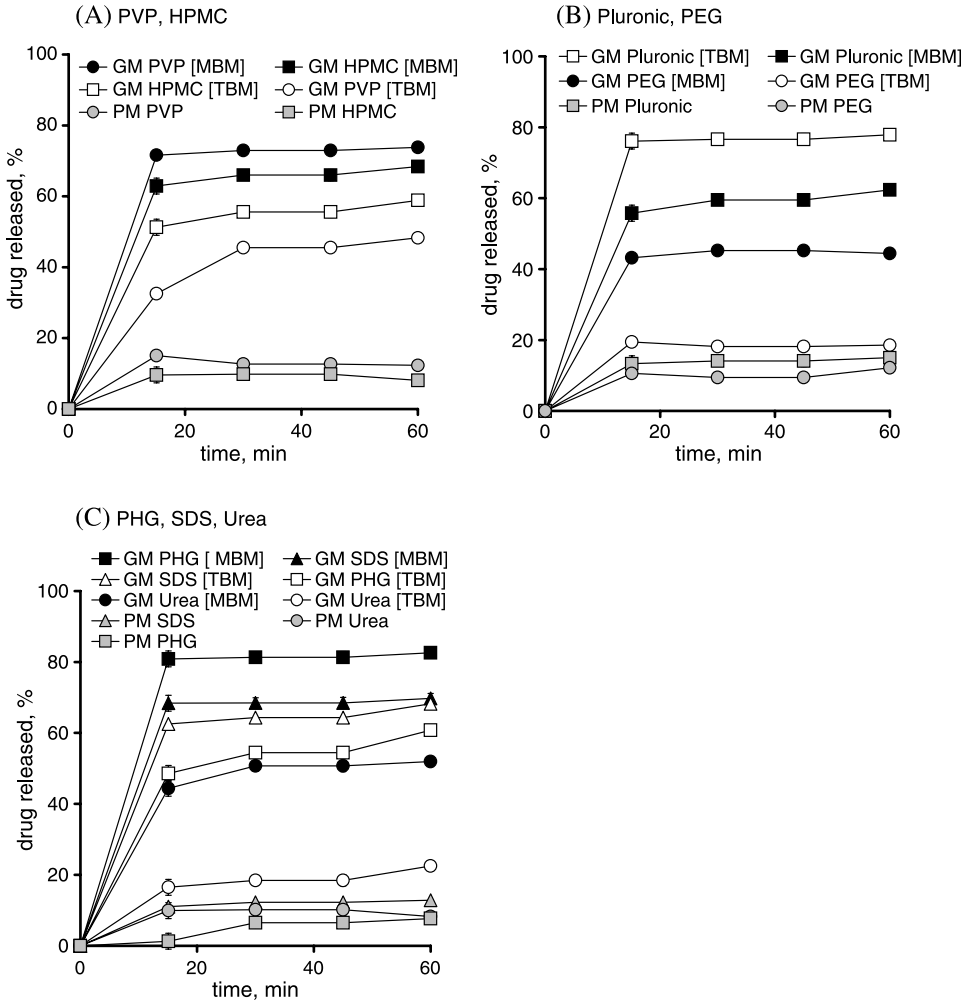

FIGURE 5 **Drug Release from the Physical Mixtures (PM) and Ground Mixtures (GM) Milled with Either the MBM or the TBM: (A) HPMC and PVP, (B) Pluronic and PEG, (C) SDS, PHG and Urea (Drug:Carrier Ratio, 1:3 w/w).**

nifedipine with Pluronic resulted in an improved dissolution rate when compared to mixture prepared with the MBM (Fig. 5B). This was probably due to the higher temperatures obtained during the milling process within the MBM than with the cooled TBM. The higher heat formation within the MBM could potentially liquify the Pluronic particles, which could result either in a partial fusion of the drug with the carrier resulting in a more stable product or in the formation of larger particles and agglomerates. Hence, the stainless steel jar (MBM) was used for most studies since the resultant products had faster dissolution rates (Figs. 4 and 5).

The rank order of dissolution rate enhancement of the different hydrophilic carriers was in the order of PHG > PVP > SDS > HPMC > Pluronic > urea > PEG (Fig. 6). Ground mixtures with PHG as carrier had the highest dissolution rate (approximately 8 times higher than that of nifedipine), which was caused by the partially amorphous nature of the drug (Fig. 1G), the decreased particle size and thus increased surface area (Fig. 3B), and the improved wettability reflected by a contact angle of only 32° when compared to 51° of the untreated nifedipine particles (Table 2). The enhanced drug dissolution rate from ground mixtures with HBMC and PVP could be attributed to the stabilization of the partially amorphous drug particles by the surrounding carriers despite the larger particle sizes and less improved wettabilities (Figs. 1E, 1F, 3E, 3F, 6, Table 2). In addition, PVP and HPMC could inhibit the recrystallization of the partially amorphous drug in the dissolution fluid immediately after starting

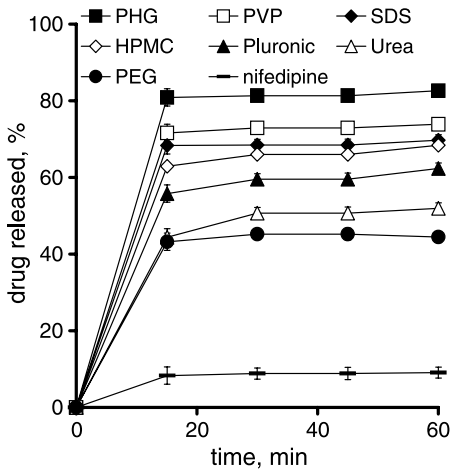

FIGURE 6 **Effect of Hydrophilic Carriers on the Nifedipine Release from Ground Mixtures (Drug:Carrier Ratio, 1:3 w/w; Milled with the MBM).**

TABLE 2 **Contact Angles of Compressed Ground Mixtures (Milled with the MBM)**

Sample	Contact angle, °
Nifedipine	51.3 ± 2.3
PHG/drug	33.3 ± 2.6
HPMC/drug	53.5 ± 1.2
PVP/drug	44.2 ± 5.1
SDS/drug	36.1 ± 2.8
Pluronic/drug	26.6 ± 2.0
PEG/drug	27.3 ± 2.1
Urea/drug	45.8 ± 0.9

of the dissolution test (Aso et al., 1996). The ground mixture with SDS was one of the mixtures with the fastest dissolution rate despite of the highest degree of crystallinity of nifedipine compared to ground mixtures with PHG, PVP, and HPMC (Figs. 1C and 6). Sodium dodecyl sulfate could have directly increased the dissolution rate by wetting and solubilization effects (Table 2). A possible stronger solubilization effect could operate in the diffusion layer immediately surrounding the drug particles in the early stages of dissolution since the carrier rapidly dissolved completely. Ground mixtures with Pluronic, urea, and PEG showed the slowest dissolution rates, however, they were still approximately 4–5 times higher than with pure nifedipine (Fig. 6). The slower dissolution rate of the ground mixtures with urea compared to the other ground mixtures could be explained by the poor wettability, higher degree of crystallinity, and large particle size of nifedipine (Table 2, Figs. 1D and 3D). Ground mixtures with Pluronic and PEG exhibited the smallest contact angles (Table 2). A fast dissolution rate could be expected, but the higher crystallinity of nifedipine in these formulations resulted in lower dissolution rates (Fig. 1A and B).

CONCLUSION

Grinding nifedipine with hydrophilic carriers improved the dissolution rate to variable extents. This effect was not only due to particle size reduction (PHG < PEG = SDS < Pluronic < drug < Urea < HPMC < PVP), but also resulted from the ability of these carriers to prevent reaggregation of the finely divided drug particles, to improve wettability (HPMC < drug < Urea < PVP < SDS < PHG < PEG), and to inhibit recrystallization during dissolution (PVP, HPMC). PHG proved to be superior in increasing the

dissolution rate followed by PVP, SDS, HPMC, Pluronic, Urea, and PEG. Data from DSC thermographs (ΔH, melting range, and peak symmetry) gave valuable information about drug crystallinity and the strong interactions with the carriers urea, HPMC, PVP, SDS, and PHG within the ground mixtures.

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