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Effect of Physical State and Particle Size Distribution on Dissolution Enhancement of Nimodipine/PEG Solid Dispersions Prepared by Melt Mixing and Solvent Evaporation

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Abstract

The physical structure and polymorphism of nimodipine were studied by means of micro-Raman, WAXD, DSC, and SEM for cases of the pure drug and its solid dispersions in PEG 4000, prepared by both the hot-melt and solvent evaporation methods. The dissolution rates of nimodipine/PEG 4000 solid dispersions were also measured and discussed in terms of their physicochemical characteristics. Micro-Raman and WAXD revealed a significant amorphous portion of the drug in the samples prepared by the hot-melt method, and that saturation resulted in local crystallization of nimodipine forming, almost exclusively, modification I crystals (racemic compound). On the other hand, mainly modification II crystals (conglomerate) were observed in the solid dispersions prepared by the solvent evaporation method. However, in general, both drug forms may appear in the solid dispersions. SEM and HSM microscopy studies indicated that the drug particle size increased with drug content. The dissolution rates were substantially improved for nimodipine from its solid dispersions compared with the pure drug or physical mixtures. Among solid dispersions, those resulting from solvent coevaporation exhibited a little faster drug release at drug concentrations lower than 20 wt%. Drug amorphization is the main reason for this behavior. At higher drug content the dissolution rates became lower compared with the samples from melt, due to the drug crystallization in modification II, which results in higher crystallinity and increased particle size. Overall, the best results were found for low drug content, for which lower drug crystallinity and smaller particle size were observed.

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Introduction

Solid dispersions are dosage forms whereby the drug is dispersed in a biologically inert matrix. They can be used to increase the dissolution rate of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface,[1] as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example, decreasing the particle size of the drug powder, micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion.[2] The formulation of poorly soluble compounds for oral delivery now presents one of the greatest and most frequent challenges to formulation scientists in the pharmaceutical industry.[3-6]

Nimodipine, isopropyl(2-methoxyethyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridene-dicarboxylate, is a drug substance of the 1,4-dihydropyridene type that was developed by Bayer AG.[7] Nimodipine has been licensed in Germany since 1984 for the prevention and treatment of ischemic neurological deficits caused by spasm of cerebral vessels following subarachnoid hemorrhage.[8] According to Gruneberg et al[9,10] the substance is a racemic mixture of 2 optical antipodes and shows 2 polymorphic forms. Modification I (mod I) is a racemic compound and has a yellow color, whereas modification II (mod II) crystallizes as a conglomerate and it is almost white. Although the solubility of mod I in water at 25 and 37°C is double that of mod II (thermodynamically stable form), nimodipine is practically insoluble in water. Although it is a highly permeable drug (class 2 of the biopharmaceutical classification system

(BCS)), the rate-limiting step in its absorption is its dissolution rate in gastrointestinal fluids. Nimodipine exhibits low bioavailability after oral administration.[11]

The development of new formulations in which nimodipine is present in the crystalline form requires the investigation of the polymorphism in detail.[9-12] The improvement of its dissolution from its oral solid dosage form is an important consideration for enhancing bioavailability and therapeutic efficiency. To date there is only limited published work on solid dispersions of nimodipine. Urbanetz and Lippold[13] reported the dissolution properties and physicochemical characterization of solid dispersions of nimodipine and polyethylene glycol (PEG) 2000.

The preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients.[14-19] Methods for monitoring the stability of the amorphous state of the drug dispersed in the polymer have been explored for a long time. Wide-angle x-ray diffractometry (WAXD), differential scanning calorimetry (DSC), differential thermoanalysis, solution calorimetry, infrared spectroscopy, and Fourier Transform (FT)-Raman spectroscopy are used.[20-23]

Although solid dispersions of nimodipine in PEG 2000 have been studied, the solid structure and polymorphism of nimodipine in solid dispersions has not. Industrial nimodipine samples are in fact racemic mixtures of the 2 optical antipodes. If the homogeneous mixture of the optical antipodes cocrystallizes, the racemic compound is formed. If the antipodes are locally separated, crystallization results in a mixture of the crystals of the pure antipodes (conglomerate). Below 88°C the less soluble mod II is the most stable. The system is enantiotropic and crystals of mod I transform to mod II at room temperature. A goal would be to keep the drug in the amorphous phase or to prevent the transformation from mod I to mod II crystals.

In this work, solid dispersions of nimodipine in higher molecular weight PEG 4000 are prepared. The objective is to study the effect of the preparation method on the physical structure, meaning the transformation to the amorphous state and the polymorphism of the remaining crystalline drug in the solid dispersions and the resulting dissolution characteristics. Thus, the 2 usual methods for solid dispersion preparation, namely the hot-melt and the solvent method are used and 2 series of samples are prepared. Furthermore, the long-term stability of nimodipine in these formulations is investigated. Physicochemical characterization of the samples is performed by means of micro-Raman spectroscopy, wide-angle x-ray diffractometry (WAXD), DSC, hot-stage microscopy (HSM), and scanning electron microscopy (SEM). Micro-Raman spectroscopy is a new powerful tool for solid dispersion characterization. In this work, micro-Raman is used to study the crystalline phase (polymorphs) of the drug and also to characterize its amorphous phase. Micro-Raman mapping was used to examine the distribution of these phases and record topology over the solid dispersion sample volume. The results show that micro-Raman, in combination with the classical techniques for solid dispersion characterization, may reveal specific features of the samples, and may help to understand the relationship between the solid structure of the drug in solid dispersions and the dissolution improvement.

Materials and Methods

Materials and Equipment

Micronized nimodipine (Nimo) with an assay of 101.2% was supplied from Union Quimico Farmaceutica S.A. (UQUIFA) (Barcelona, Spain). It has a melting point of 125-128°C, aqueous solubility of ~0.5 mg/L, and it is freely soluble in ethanol. Its particle size distribution was determined using a Malvern Mastersizer S (633 nm) (Worcestershire, UK). Thus, the particle size was found to range from ~1 μm (or less) up to 29 μm (10% up to 1 μm, 50% between 1 and 9 μm, and 40% between 9 and 29 μm). PEG 4000 with a molecular weight of 3898 g/mol (calculated by OH end groups), T_m = 54°C (DSC analysis), moisture content less than 0.5% (thermogravimentric analysis (TGA)), and viscosity at 20°C and 50% relative humidity (RH) 118 mPas was obtained from CLARIANT (Sulzbach, Germany). Sodium lauryl sulfate (SLS) was obtained from COGNIS (Fino Mornasco, Italy). All other materials and reagents were of analytical grade of purity.

Methods

Preparation of solid dispersions

- Hot-melt method. Preliminary hot-stage microscopy tests showed that the temperature for complete dissolution of the nimodipine crystals in the melt of PEG increases with drug content and heating rate, similar to what was found in our previous study for felodipine.[24] Thus, physical mixtures of nimodipine and PEG were heated during stirring in a reaction tube immersed in an oil bath to 130°C under an Argon atmosphere and held to this temperature to ensure that the drug was completely melted and a homogeneous solution was obtained. Solid dispersions with Nimo/PEG 10/90, 20/80, 30/70, 40/60, 50/50, and 100/0 (control) weight ratios were prepared. Next, the tubes were immersed in a water bath to quench the melt. The prepared samples were stored at 25°C in desiccator.
- Solvent evaporation method. Proper volumes of 2 solutions, 1 of the drug (5 wt%) and 1 of the polymer PEG (5 wt%), in ethanol were mixed and the mixtures

were ultrasonicated for 10 minutes. The final solutions were poured onto aluminum plates and the solvent was left to evaporate in open air for 2 days. After complete removal of the solvent the solid dispersions were stored at 25°C in a desiccator. The solid dispersions had the same weight ratios as those prepared by the hot-melt method.

To evaluate the effect of long-term storage on the physical structure and the dissolution behavior, the solid dispersions were stored for 6 months at 25°C and 60% RH.

Differential scanning calorimetry

DSC studies of the prepared samples were conducted immediately after preparation as well as after storage for 6 months. A Perkin Elmer Pyris 1 DSC (Shelton, CT) equipped with an Intracooler 2P cooling accessory was used. Samples of 5 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 20°C/min or 100°C/min were applied with a nitrogen purge of 20 mL/min. Fast heating rates are preferred to prevent changes during scanning.[14]

Wide-angle x-ray diffractometry

WAXD study of the samples after storage for 10 days as well as after 6 months was performed over the range 2θ from 5 to 60°, at steps of 0.05°. A Philips PW1710 powder diffractometer (Eindhoven, The Netherlands), with CuK_α nickel-filtered radiation was used.

Scanning electron microscopy

The morphology of the samples was examined by an SEM system Jeol (JMS 840) (Tokyo, Japan). The films were covered with carbon coating to increase conductivity of the electron beam.

Micro-Raman spectroscopy

Raman studies were performed by using a Jobin-Yvon/Horiba micro-Raman Spectrometer (Model: Labram), equipped with a 632-nm He/Ne laser source, 1800 1/nm grating, and an Olympus BX41 microscope system (Edison, NJ). Collection of the spectra was performed at room temperature under the following conditions: ×100 microscope objective, 100-μm pinhole size, 300-μm slit width, and 20 seconds of exposure time. Each spectrum represents the average of 2 measurements. Sample profiling (2-dimensional mapping) was performed under the same conditions at a step increment of 0.5 μm in both x and y directions. The samples were first ground to fine powder with a mortar and pestle and then spread flat on a glass microscope slide.

Hot-stage microscopy

A polarizing optical microscope (Nikon, Optiphot-2 (Tokyo, Japan)) equipped with a Linkam THMS 600 (Surrey, UK) heating stage with a TP 91 control unit was used for HSM observations.

Dissolution testing

A dissolution apparatus I of USP (baskets) type Distek 2100C (North Brunswick, NJ) was used. An appropriate amount of solid dispersion with particle size 100 to 150 mesh, containing 30 mg of nimodipine was filled into a hard gelatin capsule. The capsules were pretested concerning their disintegration time in the dissolution medium. Their effect on the obtained dissolution rate was found to be negligible. The capsules were placed into the baskets before the initiation of the dissolution testing, which was performed at 37ºC and 100 rpm. To identify potential differences in the dissolution profile of the examined preparations, 1000 mL of aqueous solution containing 0.5% (wt/wt) of sodium lauryl sulfate was used. Samples were collected at 10, 20, 30, 45, 60, 90, 120, 180, 240, and 300 minutes using an automatic sampler type Distek Evolution 4300 and analyzed immediately after sampling, according to an appropriately validated UV method, at 353 nm, using a UV-Vis spectrophotometer type Shimadzu 1601 (Kyoto, Japan). Each test was performed in triplicate while the relative standard deviation (RSD) was found to be less than 3%.

Results and Discussion

Characterization of Pure Nimodipine

Before analyzing the findings for the solid dispersions, it is important to describe the behavior of the pure drug. In Figure 1A a series of WAXD patterns for nimodipine samples after various treatments is shown. In this figure the patterns of melt-quenched nimodipine samples after storage for 10 days or 6 months at room temperature can be seen. The patterns of nimodipine after crystallization from an ethanol solution and that corresponding to the original sample are also shown. Melt-quenched nimodipine after 10 days of storage showed very limited crystallinity. The amorphous broad peak and only some weak crystalline peaks were observed. However, after storage for 6 months at 25°C and 60% RH, the sample appears to be quite crystalline. The original sample, as well as that crystallized from solution, was highly crystalline. The original sample showed reflections of nimodipine crystal mod I, in contrast to those after solution crystallization or crystallization during long-term storage at room temperature after melt quenching, which showed reflections of the mod II. It is known that nimodipine shows 2 crystal modifications.[13] Although both modifications show essentially very similar reflections, there are

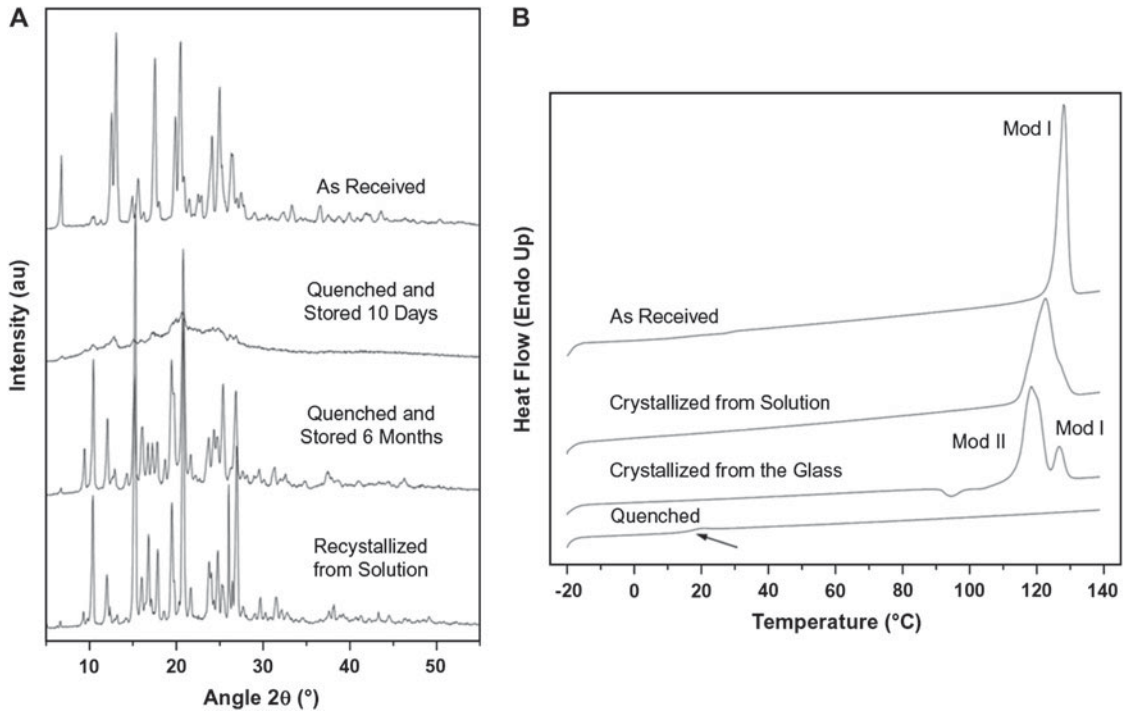

Figure 1. (A) WAXD patterns for nimodipine and (B) DSC thermograms of pure nimodipine samples.

some differences in the patterns at low angles 2θ; for example, characteristic peaks at 2θ = 6.7° for mod I, and at 2θ = 10.40° for mod II can be easily observed. Mod II is favored by crystallization at room temperature (as in our case), as well as by crystallization in the presence of solvent (isopropanol or ethanol) traces.[9,25] Thus, the above WAXD observations were in agreement with previously reported results.[9]

In accordance with the WAXD observations, the DSC trace of the original, as received, sample showed a melting peak at 126°C, corresponding to mod I. Solution-crystallized nimodipine showed a lower melting temperature consistent with mod II. However, the shoulder after the main peak is probably associated with melting of a few crystals of mod I. The sample crystallized from the glass for 6 months, showed a cold-crystallization peak during heating and double melting (Figure 1B). The main peak was the low temperature peak, associated with crystals of mod II, while the higher temperature peak most probably corresponds to mod I crystals generated by cold-crystallization during the scan since mod I crystals were not detected by WAXD.

Nimodipine was also rapidly cooled in the DSC pan and from the subsequent heating scan a glass transition temperature (T_g) of 20°C was measured. This is lower than the room (storage) temperature. For drugs, changes in physical structure like crystallization may occur not only above but also below the T_g.[26-29] The absence of crystallization during cooling from the melt, or during heating the quenched sample shows that nimodipine crystallizes slowly. However, crystallization of glassy nimodipine during storage at room temperature cannot be prevented, and leads to the less soluble mod II crystals.

The polymorhism of nimodipine was also studied by means of micro-Raman spectroscopy. A longstanding subject of chemical research is the relationship between the racemic and chiral crystals of 2 opposite and resolvable enantiomers (*d* and *l*). Of interest here are 3 crystal forms: the racemate or racemic compound, a crystal containing both *d* and *l* in the same unit cell; the enantiomorph, a chiral crystal of *d* or *l*; and the conglomerate, an equal-molar mixture of the *d* and *l* enantiomorphs. Crystal mod I of nimodipine refers to the racemic compound, and mod II refers to the conglomerate. The 2 modifications can be distinguished by means of vibrational spectroscopy as they exhibit different (Raman and infrared) spectra.[9] In the present study, the identification of crystal modifications by Raman spectroscopy became possible by using as criteria the intensities of the peaks observed at 1347 cm^{-1} and 1642 cm^{-1} (Figure 2). In a Raman spectrum, the intensity ratio $I_{1347} \div I_{1642}$ is greater than unity for mod I and the opposite is true for mod II. Moreover, this ratio is key in determining the physical state of the drug, as it also varies greatly between crystalline and amorphous states of the drug. In fact 4 distinct cases, 2 crystalline, the amorphous, and a transient, amorphouslike, state were observed for nimodipine. According to Grunenberg et al[9] the conglomerate is thermodynamically more stable below 88°C, while between 88°C and 126°C (melting) the most stable phase is the racemic compound, and at even higher temperatures the melt is favored. A lower critical temperature for

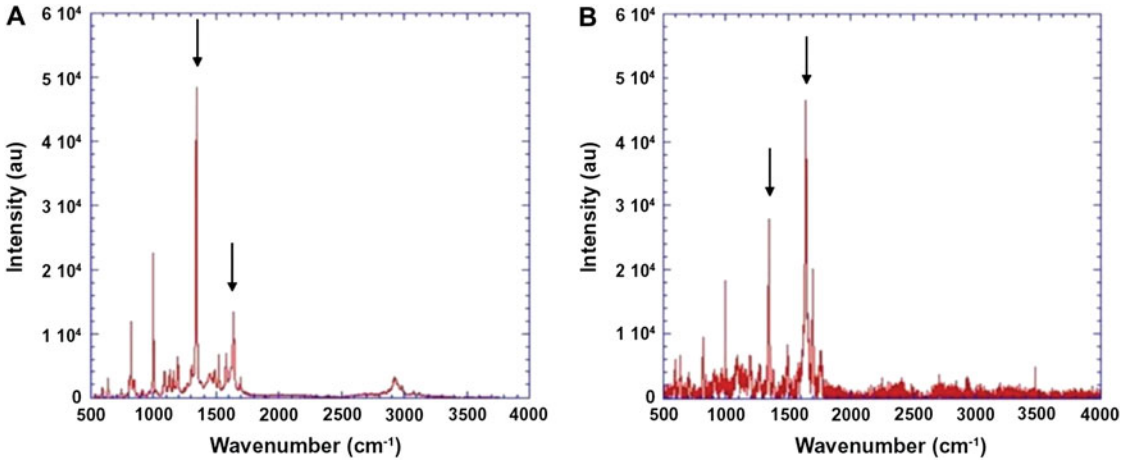

Figure 2. Raman spectra of nimodipine existing in different forms: (A) crystal of mod I; (B) crystal of mod II.

the mixture of the optical antipodes to be miscible is 88°C. Formation of racemic compound is by definition a result of crystallization of a homogeneous liquid mixture or a metastable homogeneous amorphous phase, while formation of conglomerate is associated with crystallization of metastable amorphous phase corresponding to a heterogeneous mixture of the antipodes below 88°C. This means that a segregation of the racemic mixture has occurred. Thus, the second amorphous phase observed corresponds to the heterogeneous mixture after such local segregation. To show the relation with the crystal modifications, the homogeneous amorphous form will be referred to as amorphous phase I, and the heterogeneous as amorphous phase II.

Little difference exists in the intensity ratios between amorphous phases I and II. However, for crystalline mod I, the band assignment at 1642 cm^{-1} (stretching vibration of the carbonyl bonds) is significantly suppressed resulting in an intensity ratio much larger than 1. For mod II, the band assignment at 1347 cm^{-1}, related to the vibrations of the C-NO_2 group, almost disappears and the intensity ratio is much smaller than unity. The variation of these intensity ratios is shown collectively in (Table 1). The tabulated mean values correspond to 100 measurements taken from each sample. It can be seen that there are distinct differences in the values of these intensity ratios; hence, the latter are deemed to be reliable criteria toward the determination of the physical state of the drug in its solid dispersions in PEG. It is important that PEG does not show any peak in the range of interest in the Raman spectra.

Solid Dispersions Prepared by Hot-Melt

The dissolution behavior of solid dispersions can be altered during storage because of changes in the drug's physicochemical characteristics. Drugs dispersed in crystalline form are expected to be less reactive than the amorphous or metastable polymorphic forms. Examination of the morphology of the drug and the polymer matrix in the solid dispersions is of primary importance. The WAXD patterns of the solid dispersions prepared by the hot-melt method were recorded after storage for 10 days and also after 6 months at 25°C and 60% RH (Figure 3). In both cases the patterns were almost identical, showing crystal reflections of both the drug and PEG. However, the peaks of crystalline nimodipine were weak especially for low drug loadings and this coupled with some curvature due to the amorphous halo proves significant amorphization of the drug. The samples reached their final physical structure within the first 10 days at 25°C, probably because of the low T_g. Besides, PEG crystallizes first and its crystals offer the solid surface for drug crystals to nucleate. The drug in the solid dispersions crystallized faster than the pure nimodipine after quenching to room temperature. Furthermore, the patterns showed that mainly nimodipine mod I crystals were formed, in contrast to what was anticipated. Pure nimodipine after slow crystallization below 88°C favors appearance of the less soluble mod II. This was almost prevented. Only in the patterns of the samples with high drug load a very weak peak at 2θ = 10.4° associated with a small portion of mod II crystals appeared. The crystallization process is governed by both thermodynamic and kinetic factors. Kinetic factors dominated crystallization of the drug crystallization in the solid dispersions. The stabilization of mod I crystals is also very important, since the pure drug transformation of mod I to mod II crystals occurs at room temperature. The interactions of the drug with the polymer chains probably lower the energy of the system, leading to stabilization of nimodipine, avoiding change in crystal modification.

Raman was used for assessing the spatial distribution and state of the drug in its solid dispersions with PEG. Micro-Raman mapping (XY scan) of the samples showed that the drug did not exist in ideal dispersion and that areas of crystalline mod I and mod II coexisted in the dispersions. An example can be seen in Figure 4 where mapped areas

Table 1. Intensity Ratios Corresponding to the 4 Types of Nimodipine Examined*

Phase	Structure	Peak 1 (cm^{-1})	Peak 2 (cm^{-1})	Intensity Ratio, R (= $I_1 \div I_2$)	
				Mean	SD
Mod I	Crystalline	1347–1348	1642–1643	3.67	0.58
I	Amorphous	1348–1351	1642–1644	1.22	0.17
II	Amorphous	1347–1350	1642–1644	0.83	0.074
Mod II	Crystalline	1347–1348	1643	0.171	0.035

*The columns labeled "Peak 1" and "Peak 2" indicate the wavenumber range of peak intensity for these 2 band assignments.

corresponding to solid dispersions from melt of (Figure 4A) Nimo/PEG 10/90 and (Figure 4B) Nimo/PEG 50/50 wt/wt are shown. The color map indicates the local value of the intensity ratio $I_{1347} \div I_{1642}$ in the sample. Red and yellow domains correspond to crystals of mod I, with lower and higher intensity respectively. Also, the variation in crystal size is large. In the sample containing 10-wt% nimodipine there are crystals with sizes ranging from 1 to 5 μm. These crystals are surrounded by amorphous material (green areas) in the form of a homogeneous mixture of the antipodes (amorphous phase I). Extended dispersion of these particles into PEG matrix shows that nimodipine exists in molecular dispersion in these areas. Also, light blue areas correspond to amorphous phase II of the drug. Furthermore, with increasing the content of nimodipine in the dispersions, the crystallinity increases in expense of the amount of heterogeneous amorphous phase I. In the sample with 50-wt% nimodipine, larger crystalline areas are detected (Figure 4B). However, the amorphous drug still dominates (green areas).

To estimate the particle size distribution of the drug in the solid dispersions, SEM microphotographs were taken (data not shown). Drug crystallites were observed, especially in the samples with high nimodipine content. Well-shaped crystalline particles with size 2 to 6 μm were observed in the Nimo/PEG 30/70 solid dispersion, while their maximum size increased in the 50/50 sample up to 10 μm The dissolution performance of a drug can be improved only if the particle size is reduced to less than 5 μm and, preferably, lower than 1 μm. Such low particle sizes are detected only in the samples containing 10- and 20-wt% nimodipine.

The dissolution profiles of nimodipine from the solid dispersions prepared by melting can be seen in Figure 5A. The release rates were faster compared with not only the pure

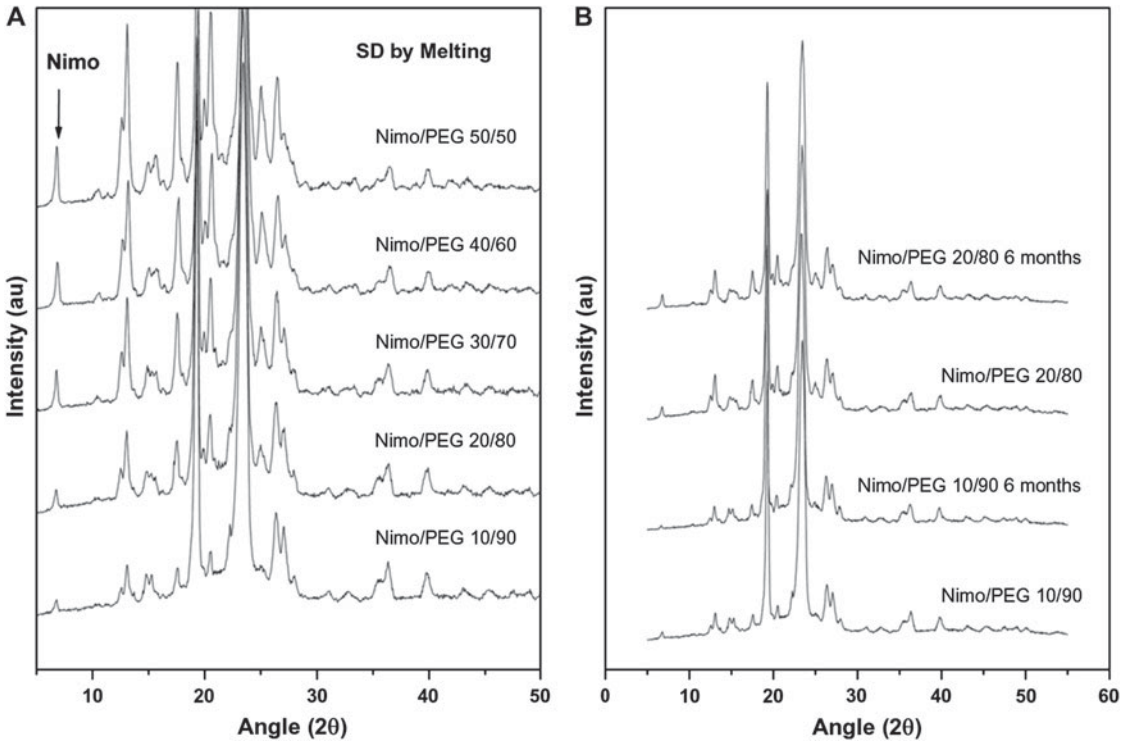

Figure 3. WAXD patterns for the Nimo/PEG solid dispersions prepared by melting (A) after quenching and (B) after long storage time (6 months).

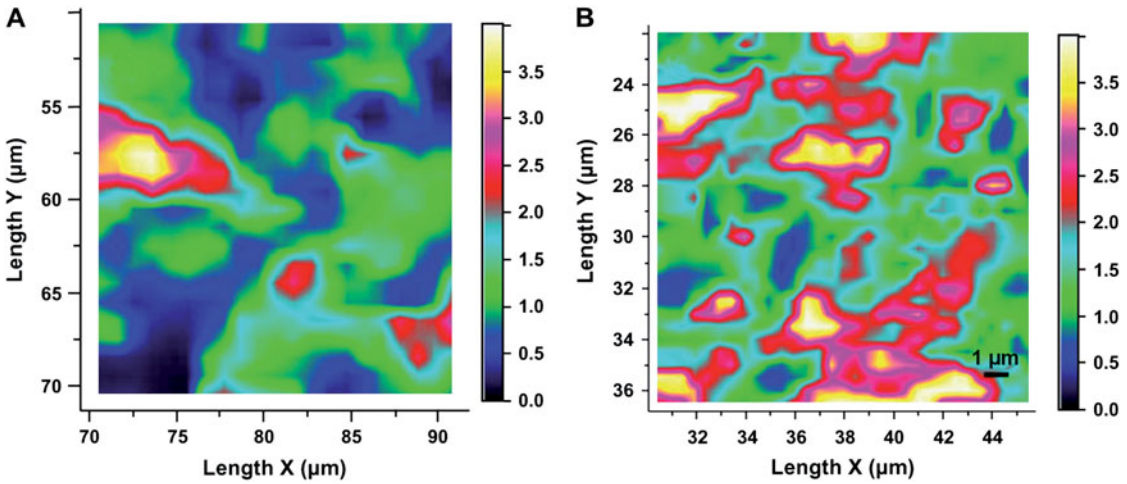

Figure 4. Micro-Raman XY scan of samples prepared by the melt method. (A) Nimo/PEG 10/90 and (B) Nimo/PEG 50/50. The color bar indicates spatial variation of the intensity ratio $I_{1347} \div I_{1642}$.

drug but also with the physical mixtures. The physical mixture (PM) with 50-wt% nimodipine content is used as reference in this figure. Almost a 100% release was obtained within 90 minutes from the solid dispersions with drug content up to 30 wt%. This increase in dissolution rates should be attributed to the amorphization of the drug and the particle size reduction. It is known that amorphous drug represents the most ideal case for fast dissolution.[18] Also, particle size reduction results in increased surface area available and thus acceleration of the dissolution. At last, especially in the case of low drug loadings in the solid dispersions, the presence of the water-soluble PEG results in improvement of the wetting characteristics of drugs with low aqueous solubility like nimodipine. However, for the solid dispersions with higher drug content, the increased drug crystallinity and larger particle size did not allow similar dissolution enhancement. For comparison, felodipine/polyvinylpyrrolidone (PVP) solid dispersions showed better results. But, apart from amorphization, the drug particle size was reduced to less than 250 nm.[30-33] It seems that the particle size is crucial for optimizing dissolution rates.

Solid Dispersions by the Solvent Method

To explore the effect of the preparation method on the physicochemical characteristics of the drug and mainly on its dissolution rates, a second series of solid dispersions was prepared by the so-called solvent evaporation method. In the WAXD patterns of these samples except from PEG peaks, the nimodipine crystal reflections appeared and they became stronger with increasing drug content. It is important that contrary to the solid dispersions by hot-melt, drug reflections corresponded to mod II. Only in the solid dispersion containing 10-wt% nimodipine a weak peak of mod I was recorded at $2\theta = 6.7°$, indicating a very small portion of mod I crystals. Furthermore, the samples prepared by solvent evaporation were white, while those from melt were yellow. The white color is related to crystal mod II, while the yellow color with mod I.[9] WAXD patterns of the samples after 6 months showed no increase in crystallinity or change in crystal modification of the drug. The latter was expected since mod II is the thermodynamically stable one below 88°C.

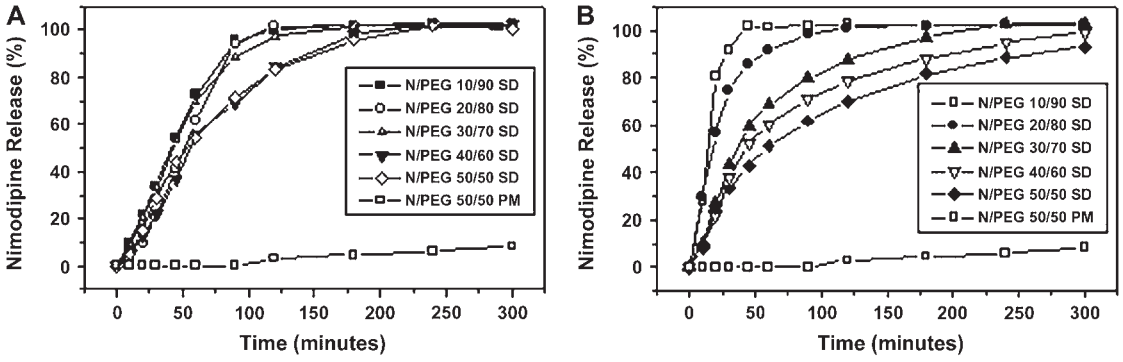

Figure 5. (A) Release profile for NIMO/PEG solid dispersions prepared by hot-melt. (B) Release profile for Nimo/PEG solid dispersions prepared using the solvent method.

Raman XY-maps for the 10/90 and 50/50 wt/wt samples resulted in images that were in complete contrast to those obtained from melt samples. The most notable difference is that the observed crystals are predominantly mod II. Moreover, for the same overall drug content, in the samples from solvent evaporation, both the crystallinity of the drug and also the average crystal size are larger than in samples from melt. Additionally, these crystals are surrounded by amorphous drug of phase II. Finally, crystals of mod I were observed only in the 10/90 sample, in accordance with WAXD.

In an attempt to assess the amount of each modification in the samples, Raman spectra were collected randomly from samples with surface area of ~1 cm^2 (100 point measurements per sample). Samples with 10-wt% and 50-wt% nimodipine prepared from melt and solutions were examined, using the $I_{1347} \div I_{1642}$ intensity ratio. The data are shown in (Table 2). Because of the relatively small number of point measurements per sample, the results are only indicative. However, they are in qualitative agreement with those obtained from Raman mapping and WAXD.

SEM microphotographs revealed existence of particles of ~5 μm or less in general in these dispersions, but the size increased with increasing drug content. Also, the HSM study revealed the presence of the drug particles in the melt of PEG. These dissolved with increasing temperature, similar to what was observed for samples from hot-melt. Both DSC and HSM observations showed a progressive dissolution of the drug in the polymer melt. The melting of the drug could be detected at high drug content, as a result of the saturation and larger particle size.

The dissolution study showed that the release rates of nimodipine from the solid dispersions from solvent evaporation were faster compared with the pure drug and the respective physical mixtures (Figure 5B). This is because the drug was effectively transformed to amorphous as one can see in Table 2. Also, the significant drug particle size reduction achieved, especially in the case of low drug loading, contributes to this improvement in dissolution rates.

The dissolution rates from solid dispersions from solvent evaporation are slower than those from melt for drug loadings exceeding 20 wt%. This is reasonable, since in the solid dispersions prepared by solvent evaporation the drug crystallinity and the particle size were larger especially for high drug content. For example, for the 50/50 samples, the crystallinity was 43% for that from solvent evaporation compared with 28% for the one from melt. Finally, another reason is that in the solid dispersions from solvent the crystalline drug existed in the less soluble mod II.

CONCLUSIONS

Characterization of various nimodipine samples prepared by different methods showed that both crystal forms, ie, racemic compound or conglomerate, may appear and the relative portions of the forms depend on the sample preparation conditions. Nimodipine shows a low T_g value (20°C) and crystallizes slowly during storage at room temperature.

Amorphization of the drug was achieved in Nimo/PEG solid dispersions, at least for low drug loadings. For higher drug content, recrystallization led to formation of mod I crystals in samples from melt, and to mod II crystals in samples from solvent evaporation. In the second case, higher crystallinity and larger drug particles were observed. Furthermore, in the solid dispersions the drug was stabilized, meaning that no extra transformation from amorphous to crystalline nimodipine was found after long-term storage. And in the case of the samples from melt the anticipated mod I to mod II crystal transformation was avoided. In general, a dissolution rate enhancement was found comparing to the pure nimodipine or the physical mixtures. The dissolution rates for solid dispersions prepared by the melt or the solvent method with drug content up to 20 wt% were similar. For higher drug content the samples from melt exhibited faster drug dissolution.

Micro-Raman proved to be a powerful tool for characterization of solid dispersions. It allowed detection of the drug distribution and also examination of the physical state and

Table 2. Influence of Drug Content and Preparation Method on the Distribution of Nimodipine in the Solid Dispersions*

	Solid Dispersion			
	Melt		Solution	
Mixture Composition	Nimo/PEG 10/90	Nimo/PEG 50/50	Nimo/PEG 10/90	Nimo/PEG 50/50
Mod I, Crystal	12	24	2	0
Amorphous phase I	79	62	16	10
Mod II, Crystal	0	4	11	43
Amorphous phase II	9	10	71	47
Total (/1 00)	100	100	100	100

*The tabulated results are based on 100 measurements per sample.
Nimo indicates nimodipine; PEG, polyethylene glycol.

polymorphism of nimodipine. It revealed differences not only in the crystalline state, but also in the amorphous state of the drug. These most probably are the result of segregation of the mixture of the optical antipodes of nimodipine.

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