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RESEARCH ARTICLE

Nimodipine (NM) tablets with high dissolution containing NM solid dispersions prepared by hot-melt extrusion

Fu Jijun, Xu Lishuang, Wang Xiaoli, Zhang Shu, Tao Xiaoguang, Zhao Xingna, He Haibing, and Tang Xing

Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, Liaoning, P. R. China

Abstract

Using a mixture of Eudragit® EPO and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA) (Kollidon VA64) as carriers, a nimodipine solid dispersion (NM-SD) was prepared by hot-melt extrusion (HME) to achieve high dissolution. The dissolution profiles in 900 mL 0.1 mol/L HCl showed that the drug release of NM-SD reached 90% in 1 h. Powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) were used to characterize the state of NM. The results obtained showed that NM was in an amorphous form in the solid dispersion (SD). NM-SD tablets (NM-T-SD) were compressed by wet granulation and direct compression, respectively. The stability of NM-T-SD was examined during a 2-month storage period (40°C, RH 75%). The results showed that the dissolution of NM-T-SD was slightly reduced after 2 months storage (40°C, RH 75%), which implied that aging occurred to some degree. However, no NM crystals could be observed by PXRD after 2 months storage for NM-T-SD (F_{11}) prepared by direct compression.

Keywords: Nimodipine, solid dispersions, hot-melt extrusion, dissolution, stability

Introduction

Dissolution plays an important role in the absorption of "low-solubility/high-permeability" drugs[1]. Improving the solubility and dissolution rate through formulation approaches is the most attractive option for increasing the release rate. Recently, a variety of methods have been used to enhance the solubility in water, such as solubilization, salt formation, the use of inclusion compounds based on cyclodextrin, and particle size reduction.

The solid dispersion (SD) method, by which a drug is molecularly dispersed in an amorphous state in carriers, is one of the most commonly used pharmaceutical methods to increase the aqueous solubility and bioavailability of poorly soluble drugs. This method is able to produce an increase in solubility within the SDs and, as the carrier dissolves, the drug comes into close contact with the dissolution medium[2].

SDs have been prepared by the hot-melt or solvent method. Hot-melt extrusion (HME) is essentially a combination of melting and mechanical preparation methods, and it has a number of advantages. First, it is a non-solvent technique, so it is not associated with the environmental, toxicological, and financial problems associated with the use of large solvent volumes. Second, drug degradation is decreased compared with the hot-melt method because of the increased input of mechanical energy[3] and the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed. Third, from a commercial point of view, HME can be carried out as a continuous process, thereby allowing efficient scale-up of production[4]. Last but not least, HME for the formation of SD allows the use of thermoplastic polymers that do not melt, such as PVP, which confer increased physical stability on amorphous systems[5]. Due to these advantages, a number of SDs have been developed using the HME process[6–12].

Due to the dissolution and absorption properties, nimodipine (NM; Figure 1) is classified in the Biopharmaceutics Classification Scheme as a class II drug, since it has a high permeability, but has a solubility in aqueous media which is insufficient for the whole dose to be dissolved in the

Address for Correspondence: Tang Xing, Department of Pharmaceutics, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, Liaoning, P. R. China. Tel: +86 24 23986343. Fax: +86 24 23911736. E-mail: tangpharm@yahoo.com.cn

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gastrointestinal fluids under normal conditions. Because of its poor aqueous solubility, NM has a low bioavailability and limited clinical efficacy. The purpose of the present work was to improve the dissolution and therefore, the bioavailability of the water-insoluble drug NM by HME. In the present study, NM-SD was produced by HME, in which the drug was present in the amorphous state in the carriers, mixtures of Eudragit® EPO and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA) (Kollidon VA64) (Figure 1). Tablets have a number of advantages: they are cost-effective, easy to produce, and convenient to take, so a stable NM-T-SD with a high dissolution was developed in the present study. Because of the sensitivity of SD to moisture, both wet granulation and direct compression were investigated to explore a practical technique for posttreatment of SD in the pharmaceutical industry. To investigate the stability of NM-T-SD, dissolution profiles were studied during 2 months of storage (40°C, RH 75%) and the results were explained by Fourier-transform infrared (FT-IR) and the T_g of SD.

Materials and methods

Materials

NM were obtained from Zhengzhou Ruikang Pharmaceutical Company (Zhengzhou, Henan, China). Kollidon VA64 (PVP/VA) and Ludipress® were a generous gift from BASF Chemical Company (Germany). Eudragit® EPO (ethyl acrylate, methyl methacrylate polymer) was purchased from Röhm (Germany). PVP K30 (Povidone K30) was supplied by Tianjin Bodi Chemical Co. Ltd. (Tianjin, China). Polyethylene glycol 6000 (PEG6000) was purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). CMS-Na (sodium starch glycolate) was purchased from Huzhou Zhanwang Chemical Company (Huzhou, China). Magnesium stearate was supplied by Shanghai Yuanji Chemical Ltd. (Shanghai, China). Talc

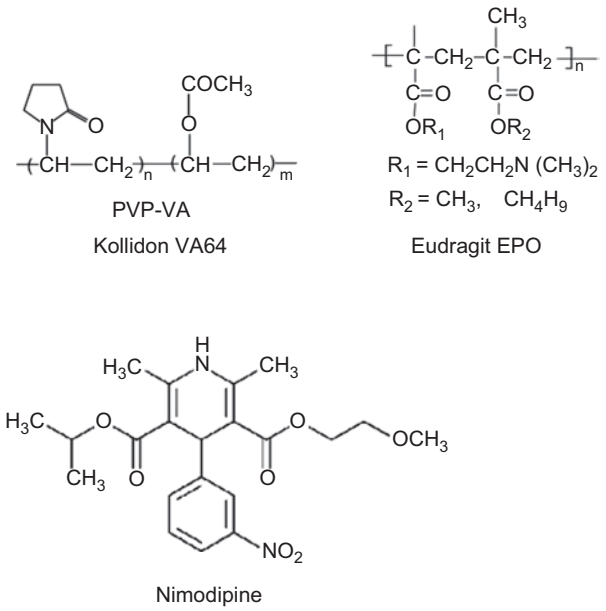

Figure 1. Molecular structures of the compounds and polymers.

was purchased from Guangxi Huashi Chemical Company (Guangxi, China). Lactose was purchased from NZMP Ltd. (Wellington, New Zealand). Opardry AMB was supplied by Colorcon Coating Technology Ltd. (Shanghai, China). Commercially available tablets of Nimotop®, used as a reference, were provided by Bayer Healthcare Company Ltd. (H200030010 Beijing, China). NM tablets, used as a reference, were purchased from The Central Pharmaceutical Co., Ltd. (H10910040 Tianjin, China) and Shanxi Yabao Pharmaceutical Group Co. Ltd. (H14022821 Shanxi, China). All other regents were either of analytical or chromatographic grade.

Methods

Preparation of NM-SD

NM, Eudragit® EPO and PVP/VA (Kollidon VA64) were accurately weighed and mixed by hand in a polyethylene bag for 10 min to obtain a homogeneous physical mixture (PM). The PM was then extruded using a Coperion KEYATE-20 (Nanjing, China) twin-screw extruder. The extruder consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. Materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw, and then extruded from the die. The temperatures of the extruder barrel zones and die were set as follows using external temperature controllers: Zone 1 = 120°C, Zone2 = 130°C, Zone3 = 130°C, Zone4 = 130°C, and Die = 80°C. The feed rate and screw rate were both set at 3.5 Hz. The extruded material was collected and allowed to cool at room temperature, and then milled using a laboratory cutting mill and, finally, passed through an 80-mesh sieve. The NM-SD formulations are summarized in Table 1.

Preparation of NM-T-SD containing NM-SD

Wet granulation

The tablet weight was set at 450 mg. After weighing and mixing SD_2 with excipients, the powder blends were granulated with 10% PVP K30 solution in 80% alcohol. The volume of PVP solution was set at 3.2 mL per 100 tablets. The powder blends were granulated by stirring, and then the wet granules were dried at 40°C in an oven, and the granules were compressed into tablets using a type TDP-5B single punch tablet press (Shanghai, China). Table 2 shows the composition of NM-T-SD.

Choice of fillers

The effect of lactose, PEG6000, and their mixtures on the dissolution of NM-T-SD was investigated. The PEG6000

Table 1. Formulations of nimodipine solid dispersion (NM-SD).

Formulation no.	NM (%)	Eudragit® EPO (%)	Kollidon VA64 (%)
SD_1	30	60	10
SD_2	25	65	10
SD_3	25	70	5
SD_4	25	60	15
SD_5	20	70	10

used had been pulverized and passed through an 80-mesh sieve.

Selection of the amount of disintegrants

In the present study, CMS-Na was chosen as the disintegrating agent. Formulations of NM-T-SD with different amounts of CMS-Na are illustrated in Table 2.

Selection of the type and dose of antiadherents

The effect of magnesium stearate and talc on the dissolution profiles of NM-T-SD was compared and the optimum dose was chosen. Formulations of NM-T-SD with different types and amounts of antiadherents are given in Table 2.

Direct compression tabletting

Formulations investigated for direct compression tabletting are shown in Table 3. First, PEG6000 was crushed to allow it to pass through a no. 40-mesh sieve, and then the ingredients (including lubricants) were weighed accurately and vigorously blended to obtain a uniform mixture and, finally, the powder blends were transferred into feeders and compressed into tablets.

Tablet coating

Opardry AMB was selected as the coating material because of its good waterproofing ability. The coating level of NM-T-SD was 3% (w/w) and coating was carried out using a type B200/400 coating pan (Baoji, Shanxi, China). In addition, 40% alcohol was selected as the solvent and the coating temperature was set at 40°C.

Hansen solubility parameter calculations

The Hansen solubility parameters of the drug and the polymers were calculated from their chemical structures using the Hoftyzer and Krevelen[13] method according to Equation (1).

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

The total solubility parameter (δ_t) is determined from the interactions between dispersion forces (δ_d), hydrogen bonding (δ_h), and polar interactions (δ_p) of the functional groups in the parent molecule. For polymeric excipients, determination of the solubility parameter was based on the average molecular weight. The units of the solubility parameters are $Mpa^{1/2}$, $(J/m^3)^{1/2}$.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) was used in the study to investigate the thermal decomposition of some drug/excipient mixtures to see if NM, Eudragit® EPO, and Kollidon VA64 could tolerate the high temperature during HME. TGA was also used to determine the moisture content of the melt extrudate. Weight loss up to 150°C was taken as dehydration and the weight change was equivalent to the moisture content. The TGA measurements were carried out using a Thermal Analyzer-60 WS and Thermogravimetric Analyzer -50 (Shimadzu, Japan). Samples were crimped in hermetic aluminum pans fitted with lids and each sample was heated from 30°C to 400°C, at a rate of 10°C per minute in an atmosphere of nitrogen.

Differential scanning calorimetry

Differential Scanning Calorimeter-60 and Thermal Analyzer-60 WS (Shimadzu, Japan) were used to characterize the thermal properties of different samples. Nitrogen was used as the purge gas at a flow rate of 40 mL/min. Samples were crimped in hermetic aluminum pans fitted with lids and then examined using a heating rate of 10°C/min from 30°C to 200°C.

Calculation of the glass transition temperature (T_g)

In the ternary systems, the T_g of the amorphous one-phase dispersion is calculated according to the Fox equation (Qi et al., 2008)[14]

Table 2. Formulations of nimodipine solid dispersion tablets (NM-T-SD) for wet granulation (mg per tablet).

Formulation no.	NM in SD_2	Lactose	PEG6000	CMS-Na	Kollidon VA64	Talc	Magnesium stearate
F_1	30	303	—	18	9	—	—
F_2	30	—	303	18	9	—	—
F_3	30	121.2	181.8	18	9	—	—
F_4	30	121.2	181.8	9	9	—	—
F_5	30	121.2	181.8	—	9	—	—
F_6	30	121.2	181.8	18	9	—	0.45
F_7	30	121.2	181.8	18	9	—	1.35
F_8	30	121.2	181.8	18	9	13.5	—
F_9	30	121.2	181.8	18	9	22.5	—

Table 3. Formulations of nimodipine solid dispersion tablets (NM-T-SD) for direct compression (mg per tablet).

Formulation no.	NM in SD_2	Ludipress®	PEG6000	CMS-Na	Talc	Kollidon VA64
F_{10}	30	151.5	151.5	18	22.5	9
F_{11}	30	181.8	121.2	18	22.5	9
F_{12}	30	212.1	90.9	18	22.5	9

$$1/T_{g123} = W_1/T_{g1} + W_2/T_{g2} + W_3/T_{g3} \quad (2)$$

With regard to the moisture present in the extrudate, Equation (2) should be modified as follows:

$$1/T_{g1234} = W_1/T_{g1} + W_2/T_{g2} + W_3/T_{g3} + W_4/T_{g4} \quad (3)$$

where W_1, W_2, W_3, and W_4 are the weight fractions of NM, Eudragit® EPO, Kollidon VA64, and water, respectively, and T_{g1}, T_{g2}, T_{g3}, and T_{g4} are the corresponding glass transition temperatures.

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) was performed using a D/Max-2400 X-ray Fluorescence Spectrometer (Rigaku, Japan) with a CuKa line as the source of radiation. Standard runs were carried out using a voltage of 56 kV, a current of 182 mA, and a scanning rate of 2° min^{-1} over a 2θ range of 3–45°.

Infrared spectroscopy

FT-IR spectra were obtained on a BRUKER IFS 55 FT-IR system using the KBr disk method. The scanning range was 4000–400 cm^{-1} and the resolution was 1 cm^{-1}.

Dissolution test

In this, 900 mL 0.1 mol/L HCl (pH 1.2) was chosen as the dissolution medium. The dissolution rate of NM under study was determined at 37°C using a ZRS-8G dissolution apparatus. The test was performed according to dissolution test method 2 as described in the China Pharmacopoeia (2005)[15] with a paddle rotation speed of 75 rpm. Samples equivalent to 30 mg drug were added to the dissolution apparatus, and test fluid was withdrawn after 5, 10, 20, 30, 45, and 60 min. Dissolution samples were subsequently passed through a 0.45 μm Millipore filter and then immediately assayed for NM by UV spectrophotometry at 356 nm to avoid recrystallization of the drug from the test fluid when the temperature became lower. In all experiments, the absorbance of the excipients at 356 nm was negligible.

Stability testing

The stability of NM-T-SD was tested during storage (40°C, RH 75%). NM-T-SD (F_9, F_{11}) were sealed tightly in commercial packing. The stability was evaluated in the following three ways: dissolution testing, differential scanning calorimetry (DSC), and PXRD. The parameters were the same as described above. NM-T-SD was tested after 1 and 2 months of storage.

Results and discussion

Miscibility study of NM with Eudragit® EPO and Kollidon VA64

In the present study, comparison of the solubility parameters of drug and excipient, and the experimental determination of miscibility by DSC were used to evaluate the miscibility of NM and the carriers.

Calculations of Hansen solubility parameters (δ)

Compounds with similar values of δ are likely to be miscible. It was demonstrated that compounds with a $\Delta\delta <$ 7.0 $Mpa^{1/2}$ were likely to be miscible[16]. When the $\Delta\delta >$10 $Mpa^{1/2}$, the compounds were likely to be immiscible.

Table 4 shows the solubility parameters of NM, Eudragit®, EPO, and Kollidon VA64. The small difference between the calculated solubility parameters of the polymers and NM indicated that NM is likely to be miscible with Eudragit® EPO and Kollidon VA64.

Thermal analysis of miscibility

In order to assess the behavior under thermal processing conditions, DSC has been applied to assess the processability of the drug:carrier PMs. Interestingly, the endothermic peak of NM in the pure drug and the PM is significantly different, as shown in Figure 2. The melting peak of the pure drug is typically sharp, whereas the endothermic peak in the PM becomes much broader. A significant reduction in melting temperature was also observed, with a peak temperature of 118°C in the PM compared with 129°C for the pure drug. The above phenomena were both caused by the gradual dissolution of NM in the carriers during the DSC heating ramp (Qi et al., 2008)[14] and provided strong evidence for the miscibility of NM with the mixtures of Eudragit® EPO and Kollidon VA64, which suggested that the mixtures would be an optimum carrier for NM-SD.

Thermogravimetric analysis

As shown in the weight loss profiles (Figure 3), all materials exhibited minimal weight loss up to temperatures of ~200°C and, at temperatures above 200°C, rapid decomposition of all materials was observed which indicated that the maximum processing temperature should not exceed 200°C for an extended period and the drug and carriers would not be destroyed by the

Table 4. Calculated solubility parameters of drug and polymers.

Compound	Solubility parameter δ_t ($Mpa^{1/2}$)	Difference $\Delta\delta$ ($Mpa^{1/2}$)
Nimodipine	20.7	—
Eudragit® EPO	18.9	1.8
Kollidon VA64	22.9	2.2

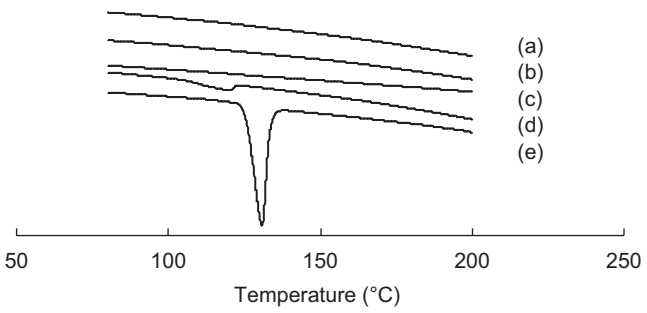

Figure 2. Differential scanning calorimetry (DSC) thermograms: (a) SD_2; (b) Kollidon VA64; (c) Eudragit® EPO; (d) physical mixture of SD_2; (e) pure nimodipine (NM).

high temperature during HME, offering the possibility of preparing SD by HME.

Estimation of glass transition temperature (T_g) using the Fox equation

The glass transition temperatures of water, NM, Eudragit® EPO, and Kollidon VA64 have been reported by other research groups[17–20] and these are shown in Table 5.

If one assumes complete dispersion of NM in the mixtures of polymers and there is no moisture in the SD prepared by HME, the calculated T_g value according to Equation (2) is 41.2°C for NM-SD_2. TGA showed that no water was present in the dispersions (figure not shown). The incorporation of water will generally lower T_g because water allows the polymer chain segments to have greater freedom. This phenomenon is known as plasticization and water is called as a plasticizer[4]. Because of the absence of water in SD_2, the T_g recalculated according to Equation (3) remained 41.2°C.

The T_g value calculated was not 40°C above the storage temperature (20–30°C) and, this suggested that there may be issues with the physical stability during long-term storage[21].

Physical characterization

Physical characterization of SD

Among the NM-SD formulations, SD_2 and its PM were studied by DSC and PXRD along with pure NM, Eudragit® EPO, and Kollidon VA64.

An indication of the amorphous state of NM in SD can be obtained by DSC. Figure 2 shows the DSC thermograms over the temperature range 80–200°C. The DSC recording of pure NM exhibits a sharp endothermic peak around 129°C, while SD_2 exhibited in a complete suppression of the drug fusion peak, indicating the amorphous state of NM in SD.

PXRD was used to confirm the loss of drug crystals, and the results are shown in Figure 4. Pure NM has several major peaks at 2θ angles within 30° (2θ angles of 6.5°, 12.3°, 12.8°, 17.3°, 19.7°, 20.3°, 20.8°, 21.3°, 23.9°, 24.8°, and 26.3°). In the PM, although these peaks became smaller, they were still present, indicating that the crystal state of NM did not change in the PM. After extrusion, no detectable diffraction peak of NM was observed, suggesting that NM was in an amorphous state in SD_2.

Physical characterization of NM-T-SD produced by wet granulation

As SD is easily destroyed by moisture and alcohol used during wet granulation, attention must be paid to whether NM in the tablets is still in an amorphous state. For this purpose, PXRD and DSC were employed to evaluate the state of NM in NM-T-SD made by wet granulation. The results are shown in Figures 5 and 6.

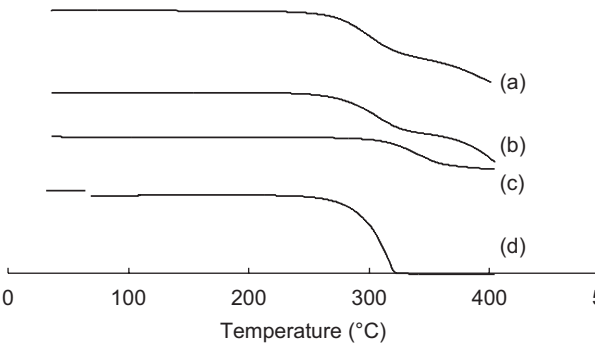

Figure 3. Thermogravimetric analysis (TGA): (a) physical mixture of SD_2; (b) Eudragit® EPO; (c) Kollidon VA64; (d) nimodipine (NM).

Table 5. Glass transition temperatures of different components.

Component	Water	Nimodipine	Eudragit® EPO	Kollidon VA64
T_g (°C)	−135.15	15.9	43.7	102

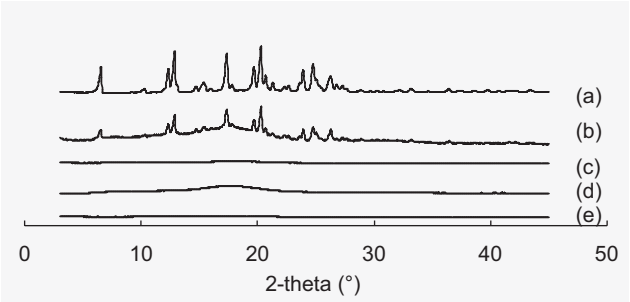

Figure 4. Powder X-ray diffraction (PXRD) patterns: (a) nimodipine (NM); (b) physical mixture of SD_2; (c) SD_2; (d) Eudragit® EPO; (e) Kollidon VA64.

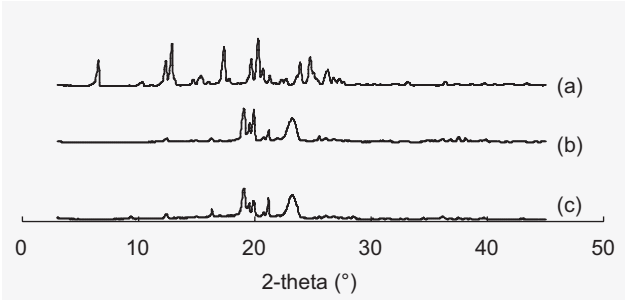

Figure 5. Powder X-ray diffraction (PXRD) patterns: (a) nimodipine (NM); (b) excipients of nimodipine solid dispersion tablets (NM-T-SD) (F_9); (c) NM-T-SD (F_9).

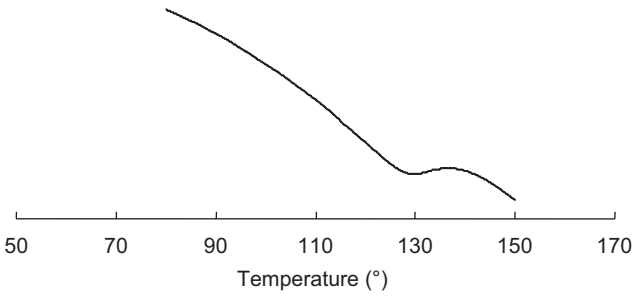

Figure 6. Differential scanning calorimetry (DSC) thermograms of nimodipine solid dispersion tablets (NM-T-SD) (F_9).

It can be seen from Figure 6 that a small endothermic peak was observed around 130°C in NM-T-SD, which means that SD was destroyed to some degree by water and alcohol during wet granulation. However, no detectable diffraction peak of NM was observed from the PXRD recordings. This phenomenon might be attributed to the higher sensitivity of DSC compared with PXRD[2].

FT-IR spectrometry

In order to study the possibility of an interaction of NM with Eudragit® EPO and Kollidon VA64 in the solid state, information was gathered using FT-IR spectroscopy. From the structures of NM, Eudragit® EPO, and Kollidon VA64 (Figure 1), it can be assumed that a possible interaction could occur between the secondary amine hydrogen atom of NM and the ester function of Eudragit® EPO and the amide function or ester function of Kollidon VA64. Thus, in this case any sign of interaction would be reflected by shifts in the C=O vibration, depending on its extent. H-bonding leads to a shift of the peak maxima toward a lower wave number (bathochromic shift) and very often the peak width is increased[22]. The infrared spectra of NM, Eudragit® EPO, Kollidon VA64, and the SD are shown in Figure 7. The position of the absorption bands of the ester function of Eudragit® EPO remained unchanged at 1732 cm^{-1} in SD. These results indicated the absence of a well-defined interaction of NM with Eudragit® EPO and Kollidon VA64.

In vitro dissolution

Dissolution from formulations of NM-SD

NM is a typical water-insoluble drug with an equilibrium solubility of 8.4 μg/mL in 0.1 mol/L HCl, 3.14 μg/mL in acetate buffer at pH 4.5, 3.86 μg/mL in purified water, 3.07 μg/mL in 0.9% NaCl aqueous, 3.19 μg/mL in phosphate buffer at pH 6.8 and 7.13 μg/mL in phosphate buffer at pH 7.2 at 37°C[23].

The dissolution profiles of NM from a PM of NM-SD_2, the five formulations of SD, and pure drug in 900 mL 0.1 mol/L HCl are shown in Figure 8.

It can be seen clearly from the curve that, after 1 h, the dissolution of the pure NM and PM of NM-SD_2 was no more than 10%, while the dissolution from the five formulations of SD were all 80% and over in 10 min. This proved that after HME, NM had been transformed into an amorphous state in the carriers, which markedly increased the solubility and wettability of the drug. So from the above results, it can be concluded that HME is an effective method to improve the dissolution of water-insoluble drugs.

It also can be inferred from the dissolution profiles that, after 5–10 min, dissolution of all five formulations of NM-SD was reduced and, after 1 h, the dissolution fell to about 40–60%. That is because after >80% of NM was released, the drug was present in supersaturated form in the dissolution medium, which means that NM is not stable in the dissolution medium. So it easily recrystallizes when stirred. However, this phenomenon might not reflect the behavior of the drug in the gastrointestinal tract, as dissolution *in vitro* was not carried out under sink conditions, while NM was taken up immediately after release from NM-T-SD *in vivo* because of its high permeability. So, as long as the peak time of the dissolution curve is delayed to some degree to ensure there was enough time for NM to uptake, recrystallization *in vivo* might be avoided and a high bioavailability could be achieved.

Comparing NM-SD_1 with NM-SD_2, NM-SD_3, and NM-SD_4, it can be seen that when drug was loaded in SD there was a reduction, from 30% to 25%, and the drug release increased from 85% to 90%. This is because there is a limited ability of carriers to dissolve NM, and the carriers could not dissolve all the drug when NM loaded in SD was 30%, so some of the NM was loaded in SD as crystals and the drug release was lower than SD_2, SD_3, and SD_4, in which the percentage of NM in SD was 25%. When the NM loaded in SD fell further, from 25% to 20%, the drug release did not increase further because all the NM in SD was already in an amorphous form when the drug loading was 25%. In a word, reducing the drug loading further was not necessary. The more SD there is in the formulation, the more difficult it is to compress into tablets because of the high viscosity of SD and its sensitivity to moisture and when a high carrier/drug ratio must be used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a

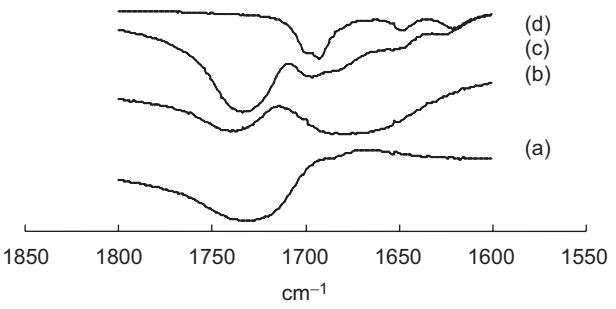

Figure 7. Fourier-transform infrared (FT-IR) spectra: (a) Eudragit® EPO; (b) Kollidon VA64; (c) nimodipine solid dispersion (NM-SD_2); (d) NM.

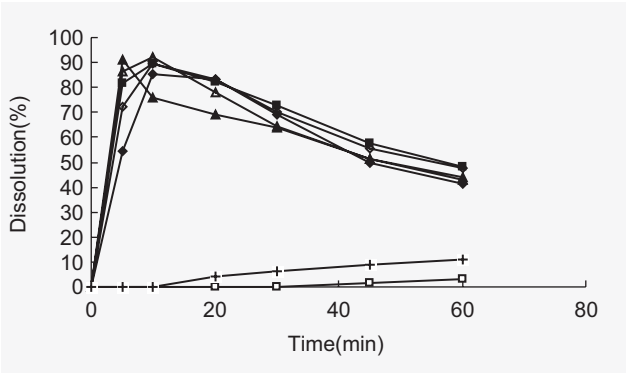

Figure 8. Drug dissolution profile in 0.1 mol/L HCl ($n=3$): (♦) SD_1; (■) SD_2; (▲) SD_3; (△) SD_4; (◊) SD_5; (□) pure nimodipine (NM); (+) physical mixture of nimodipine solid dispersion (NM-SD_2).

tablet or capsule that can be easily swallowed and, so, the drug loading was fixed at 25%.

Comparing SD_2, SD_3, and SD_4, it was found that when the percentage of Kollidon VA64 was 10%, the rate of recrystallization was slower than for formulations in which the percentage of Kollidon VA64 was 5% and 15%. As Kollidon VA64 is the copolymer of PVP and VA, it has properties similar to a surfactant, with PVP as the hydrophilic part and VA as the hydrophobic part. Accordingly, it was possible to inhibit the drug recrystallization to some degree. As the amount of Kollidon VA64 used in SD increased from 5% to 10%, the surface active effect was enhanced, resulting in a lower rate of recrystallization. However, when the amount of Kollidon VA64 used increased further to 15%, the rate of recrystallization increased instead of slowing down further. This is because the softening point of Kollidon VA64 is too high (about 180°C) to melt completely during HME (120–130°C) and, as a result, the viscosity was high, preventing uniform mixing with other ingredients, which resulted in a lower drug release. The more Kollidon VA64 used, the greater was this effect. When the percentage of Kollidon VA64 in SD was 15%, this effect exceeded the surface active effect of Kollidon VA64 and, so, the drug release was lower than SD_2 in which the percentage of Kollidon VA64 was 10%. After investigating the above parameters, formulation of SD_2 was chosen in the end. High polymer viscosity has been reported to limit the miscibility of nifedipine and HPMC in DSC studies[24]. Regarding the solubility parameter, the difference between NM and Kollidon VA64 is 2.2 $MPa^{1/2}$, and, in theory, an amorphous dispersion is likely to result when the components are melt-extruded. However, it must be borne in mind that the viscosity of the excipient may limit the drug/excipient ratio that can be extruded as viscosity is not taken into account when calculating solubility parameters. The present study provided strong evidence to support this point.

Dissolution behavior of NM-T-SD made by wet granulation

Although after HME, dissolution of NM was markedly increased to about 90%, SD cannot be administrated to patients directly for two reasons. First, SD is quite sensitive to moisture, and if it was not present in dosage forms, such as tablets, pellets, and so on, it would not be stable, lumps will form due to water uptake of SD, resulting in a marked dissolution reduction, either because of recrystallization of the drug or because of the change in the physical state of the carriers[25]. Second, although the permeability of NM is high and the drug will be taken up quickly once it is released, a period of time is needed for the drug released to pass from the stomach into the small intestine. Moreover, during this short period of time, recrystallization of drug could not occur until the effective absorption region was reached. So, from this point of view, SD needs to be incorporated in dosage forms to lower the rate of recrystallization.

Wet granulation is a widely used method to manufacture tablets. Although SD developed by all methods are sensitive to moisture, alcohol, and other solvents, wet granulation was still tried to make a comparison with direct compression. Kollidon VA64 was used in the formulations as it helped the formation of granules because of its high viscosity.

Selection of diluents

It can be seen from Figure 9 that when lactose was used as a diluent, the tablets disintegrated immediately after coming into contact with the dissolution medium and the drug release was about 90% after just 5 min. However, because of supersaturation, the curve declined quickly to <30% after 1 h. Taking this point into account, this kind of dissolution behavior is not ideal. When PEG6000 was used as a filler, the peak time of the dissolution curve was delayed to 30 min. As the melting point of PEG6000 was low, when compressed into tablets, PEG6000 melted to some degree and blocked the pores through which water entered the tablets and the tablets simply eroded instead of disintegrating and, so, the peak time of the dissolution curve was delayed. After half an hour, the drug release was about 80% and the drug release measured after 1 h was higher than F_1, slightly >40%. However, taking stability into account, if the amount of PEG6000 used was too high and, because of its low melting point (about 60°C), the tablets manufactured according to F_2 may not be stable during storage. So, some changes needed to be made to reduce the amount of PEG6000 used in the formulation. From the above results, PEG6000/lactose 60:40 was studied. From the dissolution curve of F_3, it can be seen that the peak time was 20 min when slightly >80% was achieved and, after 1 h, the drug release was still above 45%. Finally, based on the above two reasons, F_3 was chosen for the subsequent investigation.

Choice of the amount of disintegrants

From Figure 9, it can be seen that when the amount of disintegrants was only 2% of the tablet weight or no

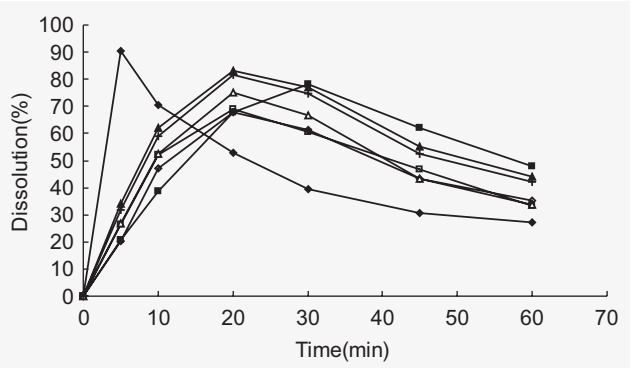

Figure 9. Dissolution profiles of nimodipine solid dispersion tablets (NM-T-SD) in 0.1 mol/L HCl (n=3) (♦) F_1; (■) F_2; (▲) F_3; (◊) F_4; (□) F_5; (△) F_7; (+) F_9.

integrating agent was used, the dissolution behaviors were similar, with the drug release being <70% and only slightly >30% after 1 h. However, when the amount of CMS-Na used was 4% of the tablet weight, the drug release was not <80%, and the maximum dissolution was close to that of SD_2, which means that more disintegrating agent is not needed. So, the amount of CMS-Na was set at 4% of the tablet weight.

Choice of the type and amount of antiadherents

As SD manufactured by HME has a high viscosity, after the granules were compressed into tablets, there was a lot of adhesion to punches and dies and, thus, automatic production could not be carried out. In order to avoid this, lubricants should be added to the granules and blended to a uniform state before being compressed into tablets. Magnesium stearate and talc are commonly used as lubricating agents in the pharmaceutical industries. Magnesium stearate is well-known for its strong lubricating activity, but it may reduce the drug release. Talc is said to have no effect on dissolution although the dose used may be high. The aim of this part of the investigation was to compare the effect of magnesium stearate and talc on the dissolution profiles of NM-T-SD and to choose the optimum dose.

For F_6 and F_8, when the amount of magnesium stearate and talc used was only 0.1% and 3%, respectively, adhesion to punches and dies could not be avoided and, thus, continuous production could not be achieved. From Figure 9, it can be seen that when magnesium stearate was used as an antiadherent, the drug release was markedly reduced although the ability to avoid sticking was high, as indicated by the fact that the amount used was only 0.3%. Although much more talc (5%) needed to be used to avoid sticking compared with magnesium stearate, the dissolution behavior of F_9 was similar to F_3, in which no antiadherents were used. So, it was concluded that talc had no marked effect on the dissolution behavior. Based on the above reasons, F_9 was selected for the subsequent investigations.

Dissolution profiles of NM-T-SD made by direct compression

Direct compression tabletting is an increasingly widely used method in the modern pharmaceutical industry. It has numerous advantages over wet granulation, for example, the procedure is solvent-free and, thus, it is environmental-friendly. Most important of all, it has a great advantage in that the amorphous state of NM in carriers is not adversely affected by moisture or alcohol since no solvents are used. Apart from the above advantages, there are also a few disadvantages. For example, direct compression will cause greater damage to punches and dies. Furthermore, the flowability that ensures automatic and continuous tabletting is a great challenge for direct compression tabletting. To make sure the flowability of the powder blends is high enough for direct compression, a great number of granules must be present in the powder blends. So, Ludipress® was used instead of lactose, and the flaky PEG6000 was pulverized and passed through a 40-mesh sieve.

Another challenge faced by direct compression is content uniformity. To make sure the tablets made by direct compression have a good content uniformity, the powder mixture must be blended until a uniform state is reached and no significant delamination happens during direct compression. The content uniformity of NM-T-SD manufactured according to formulation F_{11} was tested, and the RSD of the contents was found to be 2.24%, which met the requirement of the China Pharmacopoeia (2005)[15].

The dissolution behavior of NM-T-SD (F_{10}, F_{11}, F_{12}) is illustrated in Figure 10. From the curve, it can be seen that the peak time of F_{11} was 20 min and the drug release reached 90%, while the measured drug release declined to just over 45% after 1 h. The dissolution behavior of F_{11} was better than that of F_{10} and F_{12}, so F_{11} was chosen for the subsequent study.

Dissolution profiles of NM-T-SD made by wet granulation and direct compression after coating compared with that of commercially available NM tablets

The dissolution profiles of the five kinds of tablets are shown in Figure 11. The dissolution profile of NM-T-S was the lowest of all, with no more than 10% within 1 h. It can be seen from the curve that the dissolution behaviors of F_9 and F_{11} after coating were similar. The drug release in both cases was >80% in 20 min, and then it declined to about 40% after 1 h. What's more, as shown in Figures 9–11, the dissolution profiles of F_9 and F_{11} after coating were similar to that of the uncoated, indicating that great influence of the coating on dissolution behaviors was absent. The dissolution behavior of NM-T-C in the first 10 min was similar to these two, and then declined to about 35% after 1 h. The dissolution behavior of Nimotop® was quite different from the above three in that, after reaching a maximum dissolution at 30 min, no dramatic decrease happened during the following 30 min and it remained at about 60%. This finding proves that recrystallization was effectively inhibited in the case of Nimotop®. Actually, DSC graph of Nimotop® exhibited a straight line, without

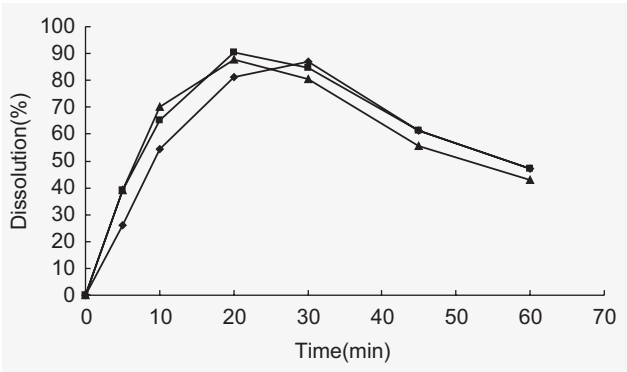

Figure 10. Dissolution profiles of nimodipine solid dispersion tablets (NM-T-SD) made by direct compression in 0.1 mol/L HCl ($n=3$). (♦) F_{10} (Ludipress®/PEG6000 50:50); (■) F_{11} (Ludipress®/PEG6000 60:40); (▲) F_{12} (Ludipress®/PEG6000 70:30).

the endothermic peak of NM, indicating the amorphous state of NM in the product (data not shown). Although, in the present study, this could not be achieved, it might not affect the bioavailability greatly as long as the uptake of NM was complete in about 20 min since NM was released from NM-T-SD.

Dissolution profiles of Nimotop® and NM-T-SD (F_{11}) in different media

The dissolution profiles of Nimotop® and NM-T-SD (F_{11}) in different media are shown in Figures 12 and 13. It can be seen clearly from the figures that the dissolution behavior of Nimotop® was not influenced by pH, while that of F_{11} was highly pH-dependent. NM exhibited no release from F_{11} at pH 6.8 and in purified water. This phenomenon could be attributed to the high pH-dependence of Eudragit® EPO, which does not dissolve in solutions with a pH above 5.0. In NM-SD_2, molecules of Eudragit® EPO surrounded NM closely so, when exposed to media with a pH above 5.0, the surrounding molecules of Eudragit® EPO did not dissolve and consequently, NM could not be released.

However, the high pH-dependence of F_{11} might not affect the absorption of NM *in vivo*, since tablets usually stay in the stomach where the pH is normally lower than 5.0 for no less than half an hour and, during this period, NM could be released from the dosage forms almost completely as indicated by the dissolution behavior *in vitro* and then carried down into the small intestine where it would be taken up.

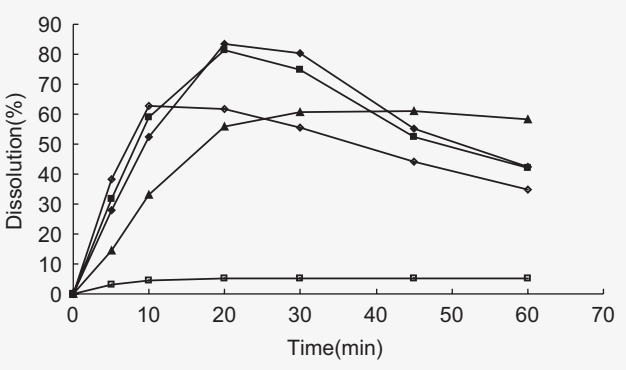

Figure 11. Dissolution profiles of nimodipine solid dispersion tablets (NM-T-SD) made by wet granulation and direct compression after coating compared with that of the commercial available NM tablets in 0.1 mol/L HCl ($n=3$). (♦) F_{11} (direct compression); (■) F_9 (wet granulation); (▲) Nimotop®; (◊) nimodipine tablets produced by the Central Pharmaceutical Co., Ltd. (H1091040 Tianjin, China); (□) Nimodipine tablets produced by Shanxi Yabao Pharmaceutical Group Co. Ltd. (H14022821 Shanxi, China).

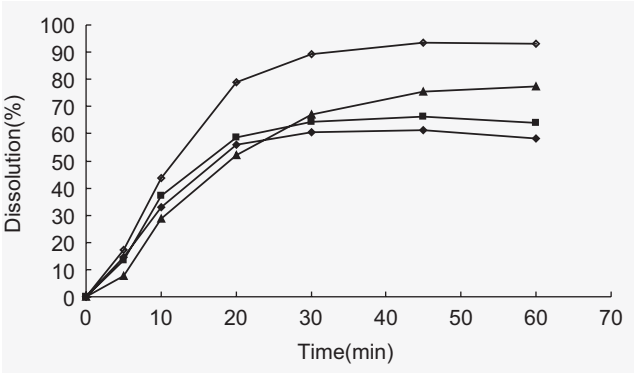

Figure 12. Dissolution profiles of Nimotop® in different media ($n=3$). (♦) 0.1 mol/L HCl; (■) acetate buffer at pH 4.5; (▲) phosphate buffer at pH 6.8; (◊) purified water.

Stability testing

For immediate-release dosage forms prepared by SD, there are three challenging problems to be overcome, scale-up, posttreatment, and stability. Many methods of preparing SD are not suitable for large-scale production in the pharmaceutical industry, either for reasons of difficulty in scale-up, posttreatment, or general instability. By combining the technology of HME and direct compression tabletting, problems related to scale-up and posttreatment have been overcome. So, the stability of NM-T-SD made by HME should be investigated in detail.

Stability is of critical importance for immediate-release dosage forms made by SD technology since SD is easily destroyed by moisture. After storage for a few months, recrystallization may occur and the drug release will be lowered, resulting in a lower bioavailability *in vivo*. To study the stability of NM-T-SD made by wet granulation and direct compression, dissolution testing and physical characterization were carried out after storage for 1 and 2 months (40°C, RH 75%).

Dissolution testing after storage

The results of dissolution testing of NM-T-SD made by wet granulation and direct compression in 900 mL 0.1 mol/L HCl after storage are shown in Figures 14 and 15. It can be seen clearly that after storage, the drug release was lower, but still above 70%, while the rate of dissolution was slower, with the peak time delayed from 20 to 30 min for NM-T-SD made by wet granulation. The physical

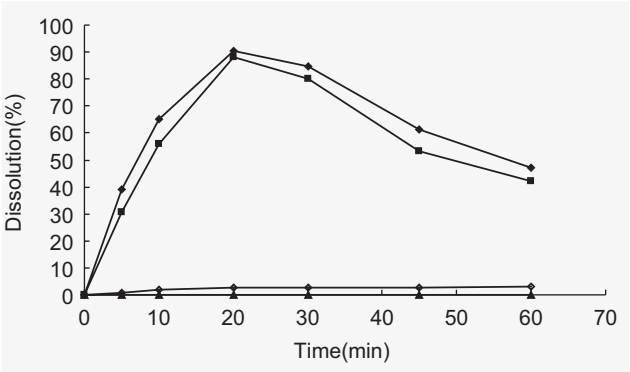

Figure 13. Dissolution profiles of nimodipine solid dispersion tablets (NM-T-SD) (F_{11}) in different media ($n=3$). (♦) 0.1 mol/L HCl at pH 1.2; (■) acetate buffer at pH 4.5; (▲) phosphate buffer at pH 6.8; (◊) purified water.

characteristics were investigated to see if the crystalline state of NM changed during storage.

Physical characteristics after storage

The PXRD recordings of NM-T-SD made by wet granulation and direct compression after storage for 1 and 2 months are shown in Figures 16 and 17.

It can be seen clearly from Figure 16 that the diffraction peak at the 2θ angle of 20.8° became larger after storage for F_9 and the endothermic peak around 130°C is still present in DSC thermograms (data not shown), indicating that the state of NM was gradually changed from the amorphous to the crystal form to some degree.

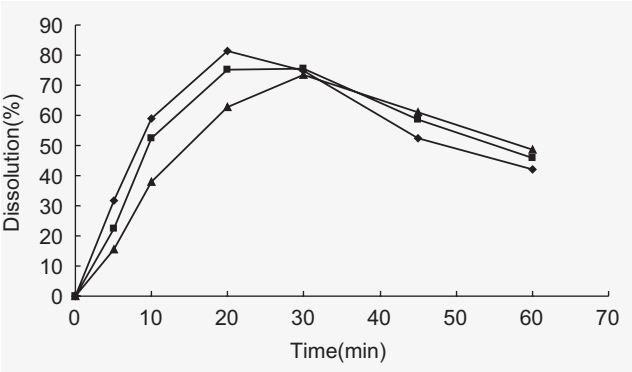

Figure 14. Dissolution testing of nimodipine solid dispersion tablets (NM-T-SD) (F_9) in 0.1 mol/L HCl ($n = 3$). (♦) Before storage; (■) storage for 1 month; (▲) storage for 2 months.

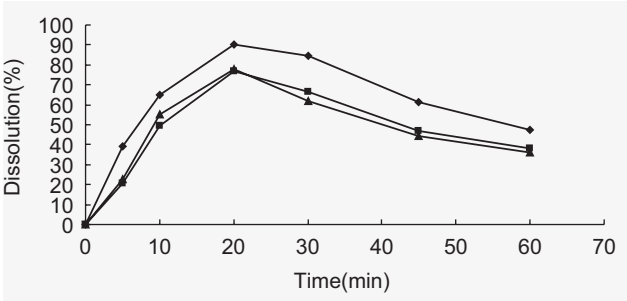

Figure 15. Dissolution testing of nimodipine solid dispersion tablets (NM-T-SD) (F_{11}) in 0.1 mol/L HCl ($n = 3$). (♦) Before storage; (■) storage for 1 month; (▲) storage for 2 months.

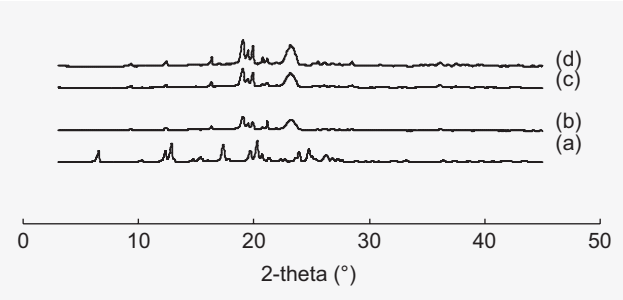

Figure 16. Powder X-ray diffraction (PXRD) patterns of F_9 after storage. (a) Pure nimodipine (NM); (b) nimodipine solid dispersion tablets (NM-T-SD) before storage; (c) NM-T-SD after storage for 1 month; (d) NM-T-SD after storage for 2 months.

Figure 17 shows that the amorphous state of NM in SD is not destroyed during compression and coating for NM-T-SD (F_{11}) made by HME combined with direct compression, and crystals of NM did not appear during storage (40°C, RH 75%), which proved the good stability of NM-T-SD (F_{11}) prepared by HME combined with direct compression. DSC was not employed to characterize the state of NM as excipients of NM-T-SD (F_{11}) could interfere with the measurement.

From all the above results, it is clear that recrystallization occurs after storage of NM-T-SD (F_9) and this is perhaps catalyzed by the seed-crystals formed during wet granulation while the state of NM was still PXRD amorphous after storage of F_{11}, and the results showed that NM-T-SD made by direct compression is more stable than that made by wet granulation. However, the drug release of both NM-T-SD made by wet granulation and direct compression declined after storage, which indicated that aging occurred during storage of NM-T-SD (F_{11}). From another point of view, compared with the dissolution behavior of Nimotop®, as the drug release of NM-T-SD (F_{11}) after storage for 2 months was still above 70%, the degree of aging was slight and acceptable.

With respect to the physical stability of the amorphous state, it is generally accepted that recrystallization is dependent on the molecular mobility and the degree of supersaturation of the solute in the matrix[26]. As the molecular mobility increases, the risk of crystallization also increases. Usually, the addition of a polymer with a high T_g is sufficient to prevent crystallization. The protective effect of the polymer can be caused by two factors: an antiplasticizing effect of the polymer or interactions between the drug and the polymer, or a combination of both. An antiplasticizing effect of the polymer may contribute significantly by increasing the temperature at which the molecular mobility becomes significant with respect to recrystallization. In addition, the resulting system will exhibit high viscosity at room temperature, hence impairing crystallization[5]. As described above, there were no interactions between NM and the carriers and the T_g of NM-SD_2 was not 40°C above storage temperature (40°C) and, NM-SD_2 might not be stable during

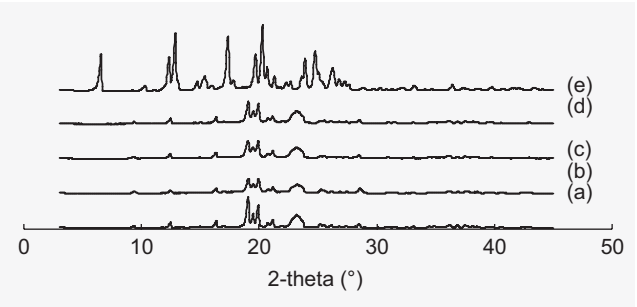

Figure 17. Powder X-ray diffraction (PXRD) patterns of F_{11} after storage. (a) Excipients of nimodipine solid dispersion tablets (NM-T-SD); (b) NM-T-SD before storage; (c) NM-T-SD after storage for 1 month; (d) NM-T-SD after storage for 2 months; (e) pure NM.

storage (40°C, RH 75%)[21]. Aging of NM-T-SD (F_{11}) to some degree was also detected in this study.

Conclusions

In vitro dissolution of the water-insoluble drug NM was greatly enhanced by HME in the present study. DSC and PXRD have proved that NM is present in the carriers in an amorphous form. NM-T-SD was made by wet granulation and direct compression. Recrystallization occurred to some degree during wet granulation and became worse after storage while the state of NM was still totally PXRD amorphous during storage in the case of NM-T-SD made by direct compression, although dissolution *in vitro* was slightly slower and lower, which indicated that some aging had occurred. So, attention must be paid to develop NM-T-SD with a higher stability and the bioavailability of the NM-T-SD should be tested *in vivo* in subsequent investigations[27].

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Declaration of interest

The authors report no declarations of interest.

References

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res, 12:413–420.
2. Leuner C, Dressman J. (2000). Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 50:47–60.
3. Forster A, Rades T, Hempenstall J. (2002). Selection of suitable drug and excipient candidates to prepare glass solutions by melt extrusion for immediate release oral formulations. Pharm Technol Eur, 14:27–37.
4. Chokshi RJ, Sandhu HK, Iyer RM, Shah NH, Malick AW, Zia H. (2005). Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion process as a means to manufacture solid dispersion/solution. J Pharm Sci, 94:2463–2474.
5. Van den Mooter G, Wuyts M, Blaton N, Busson R, Grobet P, Augustijns P et al. (2001). Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur J Pharm Sci, 12:261–269.
6. Breitenbach, J. (2003). Pharmaceutical Extrusion Technology. Marcel Dekker: New York.
7. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK et al. (2007). Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm, 33:909–926.
8. He H, Yang R, Tang X. (2010). *In vitro* and *in vivo* evaluation of fenofibrate solid dispersion prepared by hot-melt extrusion. Drug Dev Ind Pharm, 36:681–687.
9. Patterson JE, James MB, Forster AH, Rades T. (2008). Melt extrusion and spray drying of carbamazepine and dipyridamole with polyvinylpyrrolidone/vinyl acetate copolymers. Drug Dev Ind Pharm, 34:95–106.
10. Repka MA, Battu SK, Upadhye SB, Thumma S, Crowley MM, Zhang F et al. (2007). Pharmaceutical applications of hot-melt extrusion: Part II. Drug Dev Ind Pharm, 33:1043–1057.
11. Trey SM, Wicks DA, Mididoddi PK, Repka MA. (2007). Delivery of itraconazole from extruded HPC films. Drug Dev Ind Pharm, 33:727–735.
12. Yang R, Wang Y, Zheng X, Meng J, Tang X, Zhang X. (2008). Preparation and evaluation of ketoprofen hot-melt extruded enteric and sustained-release tablets. Drug Dev Ind Pharm, 34:83–89.
13. Hoftyzer PJ, Krevelen DWV. (1976). Properties of Polymers. Elsevier: Amsterdam.
14. Qi S, Gryczke A, Belton P, Craig DQ. (2008). Characterisation of solid dispersions of paracetamol and EUDRAGIT E prepared by hot-melt extrusion using thermal, microthermal and spectroscopic analysis. Int J Pharm, 354:158–167.
15. China Pharmacopeia, Beijing, 2005, pp. 166-167.
16. Greenhalgh DJ, Williams AC, Timmins P, York P. (1999). Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci, 88:1182–1190.
17. Goddeeris C, Willems T, Houthoofd K, Martens JA, Van den Mooter G. (2008). Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit E100. Eur J Pharm Biopharm, 70:861–868.
18. Matsumoto T, Zografi G. (1999). Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm Res, 16:1722–1728.
19. Roos YH. (1997). Frozen state transitions in relation to freeze drying. J Thermal Anal, 48:535–544.
20. Zheng X, Yang R, Tang X, Zheng L. (2007). Part I: characterization of solid dispersions of nimodipine prepared by hot-melt extrusion. Drug Dev Ind Pharm, 33:791–802.
21. Hancock BC, Zografi G. (1997). Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci, 86:1–12.
22. Weuts I, Kempen D, Decorte A, Verreck G, Peeters J, Brewster M et al. (2004). Phase behaviour analysis of solid dispersions of loperamide and two structurally related compounds with the polymers PVP-K30 and PVP-VA64. Eur J Pharm Sci, 22:375–385.
23. Sun Y, Rui Y, Wenliang Z, Tang X. (2008). Nimodipine semi-solid capsules containing solid dispersion for improving dissolution. Int J Pharm, 359:144–149.
24. Suzuki H, Sunada H. (1998). Comparison of nicotinamide, ethylurea and polyethylene glycol as carriers for nifedipine solid dispersions systems. Chem Pharm Bull, 46:482–487.
25. Damian F, Blaton N, Kinget R, Van den Mooter G. (2002). Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire 44/14 and PVP K30. Int J Pharm, 244:87–98.
26. Weuts I, Kempen D, Decorte A, Verreck G, Peeters J, Brewster M et al. (2005). Physical stability of the amorphous state of loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64. Eur J Pharm Sci, 25:313–320.
27. Fu J-J, Zhang L-L, Guan T-T, Tang X, He H-B. (2010). Stable nimodipine tablets with high availability containing NM-SD prepared by hot-melt extrusion. Powder Technol, 204:214–221.