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Part I: Characterization of Solid Dispersions of Nimodipine Prepared by Hot-melt Extrusion

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ABSTRACT The purpose of this study was to prepare and characterize solid dispersions of nimodipine with hydroxypropyl methylcellulose (HPMC, Methocel E5), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA, Plasdone S630®), and ethyl acrylate, methyl methacrylate polymer (Eudragit® EPO). The goal was to investigate whether the solid dispersion prepared by hot-melt extrusion can improve the dissolution rate of nimodipine. The dissolution results indicated that three polymers are suitable carriers to enhance the in vitro dissolution rate of nimodipine in pH 4.5 medium. The solubility research and solubility parameters calculation was corresponded with dissolution data. XRPD and DSC data showed that the crystallinity was not observed in hot-melt extrudates. NMD acted as a plasticizer for PVP/VA and EPO and was miscible with the polymers as well as 10% NMD-HPMC systems, because a single T_g was observed in these extrudates. However, two $T_g s$ were observed in the 30 and 50% NMD-HPMC samples, indicating phase separation. The weakening and shift of the N–H stretching vibration of the secondary amine groups of nimodipine as determined by FT-IR proved hydrogen bonding between the drug and polymers in the solid dispersion.

KEYWORDS Nimodipine, Solid dispersion, Hot-melt extrusion, Solubility parameters

INTRODUCTION

The solubility and permeability behaviors of a drug are the key determinants of its oral bioavailability. For many compounds, solubility has presented a challenge to the development of suitable formulations for oral administration. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

The most attractive option for increasing the release rate is improvement of the solubility and dissolution rate through formulation approaches. The solid dispersion method, by which a drug is molecularly dispersed, as an amorphous

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state in a carrier, is one of the most commonly employed pharmaceutical approaches to increase solubility and bioavailability of poorly soluble drugs (Leuner and Dressman, 2000). Solid dispersions have been prepared by hot spin mixing (Dittgen et al, 1995), spray drying (Jung et al, 1999), co-evaporation, co-precipitation (Sekikawa et al, 1978), freeze-drying (Sekikawa et al, 1983), roll-mixing or co-milling (Murali Mohan Babu et al, 2002a; Murali Mohan Babu et al, 2002b), and supercritical fluid processing (SFP) (Gong et al, 2005).

Hot-melt extrusion is an alternative method to manufacture solid dispersions that is becoming more widely utilized in the production of drug delivery systems. This technique was introduced to the pharmaceutical field relatively recently as an alternative manufacturing method for solvent-related processes (Breitenbach, 2002; Prapaitrakul et al, 1991). The essential advantages of the melt extrusion process are its solvent-free formation process and dust-free processing environment. There are various problems related to the use of solvent-based processes (environmental pollution, explosion proofing, and residual organic solvent), and the measures to counteract these problems can be challenging. The same logic holds for dust contamination. In addition to the environmental and economical benefit, hot-melt extrusion allows for a continuous production process. The drug/polymer dispersions can be milled, sieved, and encapsulated directly after extrusion. Furthermore, the melt extrusion process offers the chance to convert drugs to the amorphous state or more often to dissolve the drugs in the matrix polymer. Therefore it is capable of handling actives of different particle sizes, as well as amorphous solids or other polymorphic forms, and leading to the same product. A number of solid dispersions have been developed using melt extrusion processes (Breitenbach, 2003). The studies have shown that melt extrusion is a promising method to enhance the water solubility of poorly water-soluble drugs such as itraconazole (Rambali et al, 2003; Six et al, 2003a; Six et al, 2003b; Six et al, 2005), indomethacin, nifedipine, tolbutamide, lacidipine (Forster et al, 2001a; Forster et al, 2001b), nitrendipine (Wang et al, 2005), and 17-beta estradiol (Hulsmann et al, 2000; Hulsmann et al, 2001).

Nimodipine is a dihydropyridine calcium channel blocker, used in the treatment of senile dementia and in the prophylaxis of the vascular hemierania

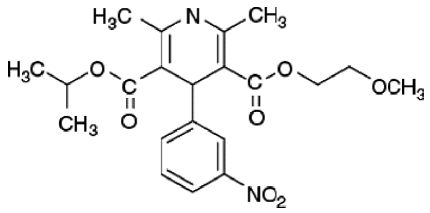

FIGURE 1 Structural formula of nimodipine.

(Manhold, 1985). The molecular structure of nimodipine is illustrated in Fig. 1. The drug is practically insoluble in water and exists in the solid form as yellow crystals. Additionally, the drug often shows low and irregular bioavailability following oral administration due to its low solubility (Grunenberg et al., 1995).

In the present study, solid dispersions of nimodipine with HPMC, Eudragit® EPO, and PVP/VA were prepared using hot-melt extrusion. The dissolution properties and physicochemical properties of the solid dispersions were investigated and compared with their physical mixtures.

MATERIALS AND METHODS

Materials

Nimodipine (NMD) was purchased from Tianjin Zhongyang Pharmaceutical Company (Tianjin, China). Methocel E5 (hydroxypropyl methylcellulose, HPMC, type 2910 E5, 5 cp viscosity, Dow) was kindly provided by Colorcon (West Point, PA), Eudragit® EPO (ethyl acrylate, methyl methacrylate polymer) from Röhm (Darmstadt, Germany), and Plasdone S630® (polyvinylpyrrolidone/vinyl acetate copolymer, PVP/VA) from ISP (Wayne, NJ). All other reagents were analytical grade.

Methods

Preparation of Physical Mixture

NMD (passed through 150 μm screen) and HPMC, Eudragit® EPO or PVP/VA were accurately weighed and mixed by hand in a polyethylene bag for 10 min to obtain a homogenous physical mixture.

Preparation of Amorphous Drug

Amorphous drug samples were prepared by melting the drug in stainless steel beakers on a hotplate equilibrated to 150°C. Melts were rapidly cooled by partially

submerging the beaker into ice-cooled water. The resulting mass was then pulverized by light grinding in a mortar.

Preparation of Solid Dispersion by Hot-melt Extrusion

Solid dispersions consisted of NMD with a polymeric carrier (HPMC, Eudragit® EPO or PVP/VA) and were prepared by hot-melt extrusion using a co-rotating twin-screw extruder TE-20 32:1 (Coperion Keya CO., China). The concentration of drug in the dispersions was 10, 30 or 50% (w/w). The extruder configuration 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 feed rate was fixed at 60 rpm and the screw rate was set at 40 rpm. The five temperature zones were set at 100, 130, 130, 140, 145°C from feeder to die for both Eudragit® EPO and PVP/VA, and 100, 140, 170, 170, 175°C for HPMC. The extrudates were collected after cooling at ambient temperature, milled using a laboratory-cutting mill and then sieved through a 180 μm screen.

X-ray Powder Diffraction (XRPD) Analysis

XRPD was performed using a type D/Max-2400 diffractometer (Rigaku Instrument, Japan). The samples were exposed to *CuKa* radiation under 56 kV and 182 mA over the 2-theta range from 3 to 45° in increments of 0.5°/min every 0.04°. The extrudates were ground into a fine powder before analysis.

Differential Scanning Calorimetry (DSC) Analysis

DSC (DSC 60, Shimadzu) was used to characterize the thermal properties of the drug, polymer, physical mixtures, and hot-melt extrudates. The DSC was performed in the first run because the systems were the extrudates. T_g was determined by the middle point of the heat capacily shift. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 mL/min. Samples weighing 10 ± 5 mg were crimped in hermetic aluminum pans with lids and then analyzed using a heating rate of 10°C/min. All of the experiments are triplicated.

Fourier Transformation-infrared Spectroscopy (FT-IR) Analysis

FT-IR Spectroscopy was performed using a Bruker IFS-55 (Germany) and the KBr method in the 4000–450 cm^{-1} region at 4 cm^{-1} resolution and 16 scans per spectrum. The powder samples were dispersed as a 5% w/w mix in KBr and scanned immediately after mixing. Mixtures were prepared in duplicate.

Scanning Electron Microscopy (SEM) Analysis

SEM was used to study the surface morphology of the hot-melt extrudates. The samples were mounted on an aluminum stage using adhesive carbon tape and placed in a low humidity chamber prior to analysis. Samples were coated with gold–palladium, and microscopy was performed using a LEO Supra 35 operating at an accelerating voltage of 5 kV.

Phase Solubility Study

Excess NMD was added to pH 4.5 acetate buffer containing 0.05% sodium dodecyl sulfate (SDS). The resulting suspensions were sonicated for 2 h and then shaken at 100 cycles per minute at 37°C for 72 h in a thermostatically controlled water bath since these conditions were previously shown to be sufficient for achieving equilibrium solubility. Samples were then passed through a 0.45 μm Millipore membrane filter, and the filtrates were suitably diluted and analyzed using HPLC. The HPLC method is described in the dissolution testing section.

Calculation of Hansen Solubility Parameters

The Hansen solubility parameters of the drug and the polymers were calculated from their chemical structures using the Hoftyzer and van Krevelen method (Hoftyzer and Krevelen, 1976) according to Eq. (1).

$$\delta_t^2 = \delta_{\mathrm{d}}^2 + \delta_p^2 + \delta_h^2 \tag{1}$$

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 $MPa^{1/2}$, $(J\ m^{-3})^{1/2}$ or $(cal\ cm^{-3})^{1/2}$, where 1 $(cal\ cm^{-3})^{1/2}$ is equivalent to 2.0421 $MPa^{1/2}$.

Dissolution Testing

The dissolution rate of NMD under study was determined at 37°C in 900 mL of dissolution medium using a ZRS-8G dissolution apparatus. The test was performed according to dissolution test method 2 as described in the Chinese Pharmacopoeia with a paddle rotation speed of 75 rpm. The dissolution media used was pH 4.5 acetate buffer containing 0.05% (w/v) sodium dodecyl sulfate (SDS). Samples equivalent to 20 mg of drug were added to the dissolution apparatus, and test fluid was withdrawn after 5, 10, 15, 30, 45, and 60 min. Dissolution samples subsequently were passed through a 0.45 μm Millipore filter and then assayed for NMD by HPLC. All tests were performed in triplicate.

The HPLC system consisted of an L-7100 HPLC pump, a L-7200 autosampler equipped with a 100 μL loop, a L-7420 UV detector set at 237 nm and an D-7000 interface (Hitachi, Japan). UV signals were monitored and peaks integrated using D-7000 HSM software. Chromatographic separations were performed at room temperature using a C_{18} column (Diamonsil, 5μm, 4.6 mm × 250 mm, Dikma, China) guarded with a refillable precolumn (C_{18}, 2.0 mm × 20 mm, Alltech) and a flow rate of 1.0 mL/min. The mobile phase consisted of methanol:acetonitrile:water (38:37:27, v/v) and was filtered through a 0.45 μm membrane filter and degassed by ultrasonication before use. These conditions resulted in a typical elution time for NMD of 9.30 min.

Khan (1975) suggested dissolution efficiency (DE) as a suitable parameter for evaluation of in vitro dissolution data. DE_{10}, DE_{30}, and DE_{60} values were calculated from dissolution data and used to evaluate the dissolution rate. The differences between DE values were statistically evaluated by calculating analysis of variance (ANOVA) based on a model independent method. Results with P-values < 0.01 were considered statistically significant.

RESULTS AND DISCUSSION

Thermal Analysis by Differential Scanning Calorimetry

DSC was used to analyze the glass transition temperature (T_g) of drug and polymer binary mixtures and extrudates (Forster et al, 2001). The study of T_g allows the evaluation of miscibility of drug in polymer. A single T_g at an intermediate temperature between the T_g of both drug and polymer is evidence of miscibility and thus helps in predicting the physical nature of the melt extrudate as a single or two phase system. Thus, calculation of solubility parameters and DSC studies complement each other to access drug miscibility with polymers. Additionally, DSC investigations are useful since the T_g or melting temperature aid in determining applicable extrusion conditions such as heating zones temperatures.

Based on Gordon–Taylor equation, if drug and polymer are miscible, the mixture will show a single T_g that ranges between the T_g of pure components and depends on the relative proportion of each component. The T_g of the mixtures can be predicted using the Gordon–Taylor (GT) equation.

$$T_g = \frac{W_1 \times T_{g1} + K \times W_2 \times T_{g2}}{W_1 + K \times W_2} \tag{2}$$

$$K = \frac{Tg_1 \times \rho_1}{Tg_2 \times \rho_2} \tag{3}$$

where T_{g1} and T_{g2} are the glass transition temperatures of the components, W_1 and W_2 are the weight fractions and K is calculated from the T_g and density of the amorphous components.

DSC results of NMD, polymers, physical mixes and melt extrudates are presented in Table. 1. A DSC thermogram of pure NMD showed a sharp melting peak temperature at 130°C with a fusion enthalpy (ΔH) of about 92.60 J/g, whereas amorphous Eudragit® EPO, PVP/VA, and HPMC exhibited a T_g at 43.87, 110.57, and 158.31°C, respectively.

All the physical mixtures exhibited melting peaks of NMD with a slightly decreasing melting temperature and ΔH as the ratio of carrier increased. In contrast, no drug melting endotherm was observed in the EPO and PVP/VA dispersions prepared by melt extrusion. The solid dispersions only exhibited a single T_g that decreased with increasing drug concentration. Thus, NMD acted as a plasticizer for PVP/VA and EPO and was miscible with the polymers at 10–50% drug loading. In the NMD-HPMC systems, a single T_g was observed in the 10% drug loading extrudate, indicating

TABLE 1 **Melting endotherm and glass transition temperatures for NMD, polymers, physical mixtures and extrudates**

Compound	Solubility Paramerter δ_t (MPa$^{1/2}$)	Difference $\Delta\delta_t$(MPa$^{1/2}$)
NMD	20.7	?
HPMC	22.4	1.7
Eudragit® EPO	18.9	1.8
PVP/VA	22.7	2

	NMD Concentration (w/w)			
Polymer	10%	30%	50%	100%
PVP/VA	99.81	78.94	69.69	5.32
Eudragit® EPO	15.76	15.83	13.81	5.32
HPMC	15.32	17.95	16.98	5.32

Formulations	Melting Temperature in Physicaln Mixtures (°C)	ΔH of NMD in Physical Mixtures (J/g)	*T* g in Hot-melt Extrudates (°C)	*T* g Calcurated by Gordon - Taylor equation (°C)
	NMD System (% NMD)			

miscibility. However, two $T_g s$ were observed in the 30 and 50% NMD samples, indicating phase separation. NMD was present in the amorphous state in all studied solid dispersions as no melting endotherm was observed. It was suggested that the mixtures systems should be miscible which can result in drug dissolved in soft polymer. Solubility parameter was a possible method to predict the miscibility, but we also should consider the viscosity of the polymers. The polymers were soft and melt at the operation temperature for PVP/VA and EPO, while HPMC was only soft. So the extrusion process made drug PVP/VA and EPO systems homogenous in contrast to HPMC as two phases with two Tg. The comparison of calculated Tg and the detected have been listed on the table 1.

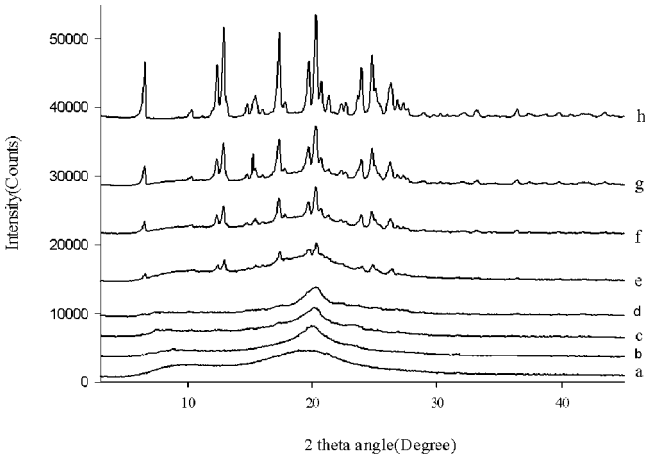

FIGURE 2 **Powder XRPD patterns of NMD-HPMC solid dispersion (SD) and physical mixtures (PM) systems: (a) HPMC (b) 10% NMD SD (c) 30% NMD SD (d) 50% NMD SD (e) 10% NMD PM (f) 30% NMD PM (g) 50% NMD PM.**

X-ray Powder Diffraction

XRPD is the standard technique for studying the crystalline or amorphous nature of drugs in solid dispersions and solid solutions. XRPD patterns of NMD, polymers, physical mixtures, and extrudates are presented in Fig. 2, 3 and 4. NMD has distinct crystalline peaks at 2θ angles of 6.5, 12.8, 17.3, 20.2, and 24.8° and a series of smaller peaks at 2θ angles of 12.3, 19.7, 20.6, 21.3, 23.9, and 26.3°. The diffraction patterns of the physical mixtures of drug and polymers exhibited most NMD crystalline peaks (2θ angles 6.5, 12.3, 12,8, 17.3, 19.7, 20.2, 23.9, 24.7, and 26.3°), but at a lower intensity. The attenuation of NMD-derived diffraction peaks with increasing carrier ratio can be explained by the decreasing concentration of drug in the physical mixture. The presence of drug peaks supported the DSC investigations, which found that the drug was crystalline in the binary mixtures. XRPD of extrudates revealed the absence of drug peaks, indicating that NMD was present in an amorphous form in the extrudates for all drug/polymer systems and ratios

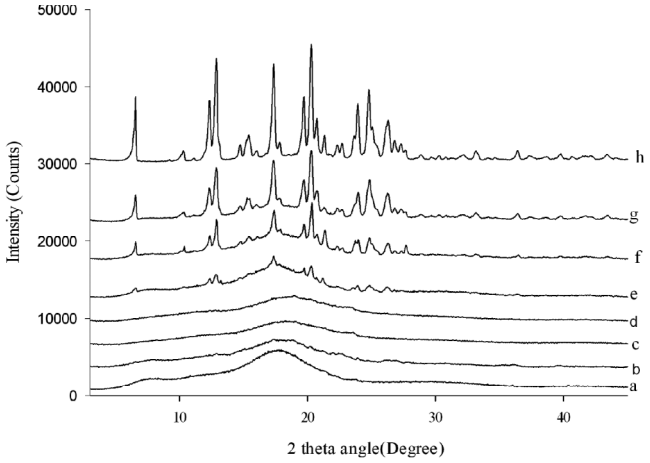

FIGURE 3 **Powder XRPD patterns of NMD- Eudragit® EPO solid dispersion (SD) and physical mixtures (PM) systems. (a) Eudragit® EP O (b) 10% NMD SD (c) 30% NMD SD (d) 50% NMD SD (e) 10% NMD PM (f) 30% NMD PM (g) 50% NMD PM (h) pure NMD.**

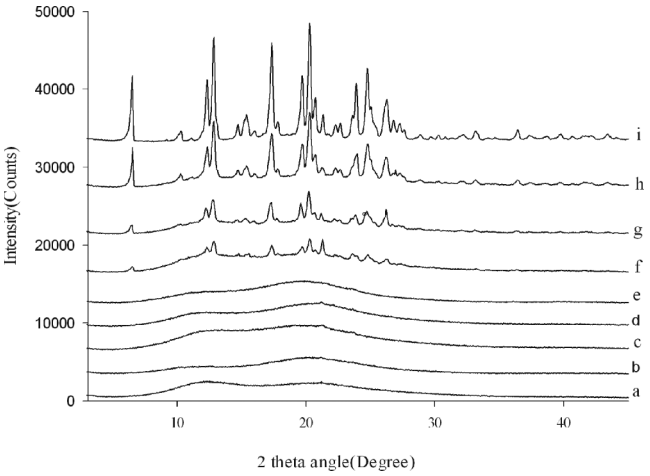

FIGURE 4 **Powder XRPD patterns of NMD-PVP/VA solid dispersion (SD) and physical mixtures (PM) systems. (a) PVP/VA (b) amorphous NMD (c) 10% NMD SD (d) 30% NMD SD (e) 50% NMD SD (f) 10% NMD PM (g) 30% NMD PM (h) 50% NMD PM (i) pure NMD.**

studied. This observation confirmed the formation of amorphous solid dispersions and supported the conclusions of thermal analysis.

FT-IR Spectrometry

PFT-IR was used to study intermolecular interactions between NMD and constituents of the solid dispersions. The FT-IR spectra of the hot-melt extrudates were compared to the spectra of crystalline drug substance, polymers and drug/polymer physical mixtures in Fig. 5, 6, and 7. The bands of interest in the NMD-containing FT-IR spectra are the N–H stretching vibrations in the secondary amine groups and the C = O stretch in the esteric groups. In crystalline NMD, these bands are at 3298 and at 1695 cm^{-1}, respectively. In the case of amorphous NMD, these bands broadened and shifted to higher wave numbers. The morphological change and the shift of these bands to free N–H and C = O regions can be attributed to the rupture of

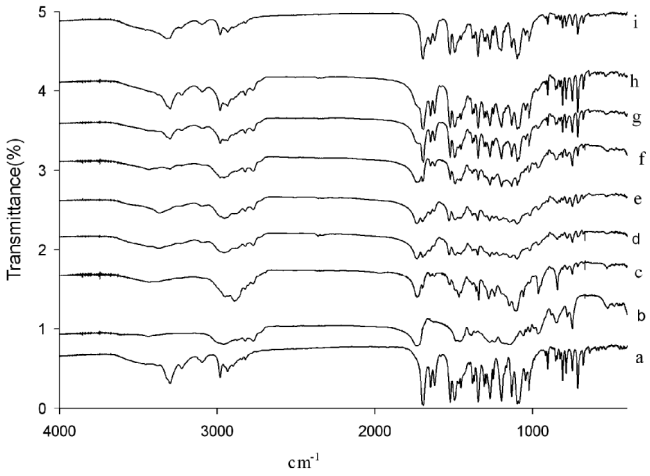

FIGURE 5 **FT-IR spectra of NMD-Eudragit® EPO solid dispersion (SD) and physical mixtures (PM) systems. (a) pure NMD (b) Eudragit® EPO (c) 10% NMD SD (d) 30% NMD SD (e) 510% NMD SD (f) 10% NMD PM (g) 30% NMD PM (h) 50% NMD PM (i) amorphous NMD.**

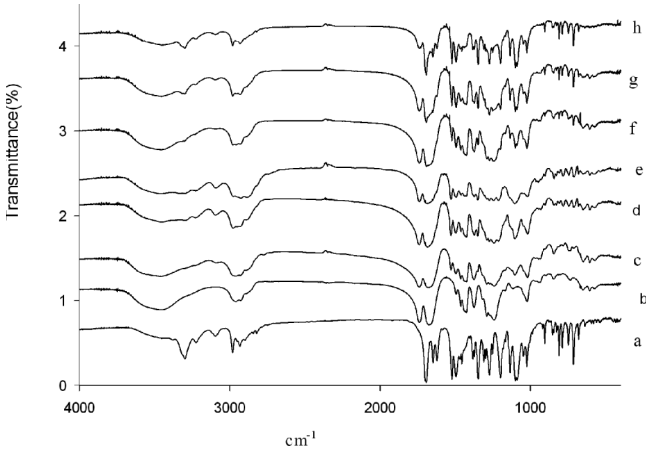

FIGURE 6 **FT-IR spectra of NMD-PVP/VA solid dispersion (SD) and physical mixtures (PM) systems. (a) pure NMD (b) PVP/VA (c) 10% NMD SD (d) 30% NMD SD (e) 50% NMD SD (f) 10% NMD PM (g) 30% NMD PM (h) 50% NMD PM.**

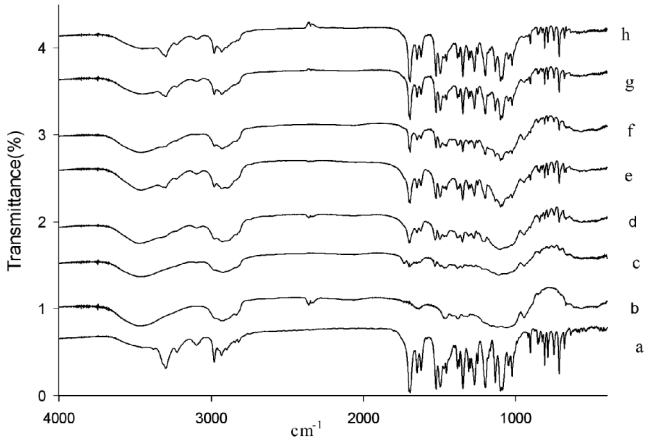

FIGURE 7 **FT-IR spectra of NMD-HPMC solid dispersion (SD) and physical mixtures (PM) systems. (a) pure NMD (b) HPMC (c) 10% NMD SD (d) 30% NMD SD (e) 50% NMD SD (f) 10% NMD PM (g) 30% NMD PM (h) 50% NMD PM.**

intermolecular hydrogen bonding observed in the crystalline state between the two functional groups. The physical mixtures of drug and different carriers resulted in spectra closely resembling the addition of the individual components, and the intensities of characteristic absorption bands were in direct linear proportion to the concentrations of the ingredients. Meanwhile, the corresponding absorption band did not shift.

In Fig. 5, the characteristic secondary amide group (N–H) stretching vibration at 3298.0 cm^{-1} for NMD alone was not observed in the FT–IR spectra of solid dispersions containing drug and Eudragit® EPO. The band around 1731 cm^{-1}, representing the stretching vibration of the carboxyl groups of Eudragit® EPO, appeared to be significantly broader in the solid dispersion than in the physical mixtures. The differences in the IR spectra were attributed to hydrogen bonding between the secondary amine groups of NMD and the carboxyl groups of Eudragit® EPO after solid dispersion formation.

Figure 6 shows the FT-IR spectra for pure NMD, PVP/VA, drug-PVP/VA physical mixtures, and drug-PVP/VA extrudates. In comparison to the physical mixture, the spectra of extrudates showed a significant change at 3298 cm^{-1}. This change was related to weakening or removal of the N-H stretching vibrations and was also exhibited by the NMD-Eudragit® EPO extrudates. It is strong evidence of hydrogen bonding between the drug and polymer via the secondary amine group of the drug. The absorption band observed at 1695 cm^{-1}, which was assigned to the C = O bond stretching vibration of NMD, was shifted to 1679 cm^{-1} in the solid dispersion at 10% drug loading.

From the FT-IR spectra of HPMC (Fig. 7), the absorption observed at 3460 cm^{-1} was assigned to the stretching vibration of the hydroxyl groups. The NMD N-H stretching vibration disappeared at the lowest NMD levels (10%) in the hot-melt extrudates, but it became evident at the 30% drug loaded level and grew in intensity with increasing percentage of loaded NMD. This change in the FT-IR pattern indicated possible immiscibility of NMD and HPMC at high drug loading. Nevertheless, the intensities of the N–H stretching vibration in extrudates were much weaker than in physical mixtures at the same drug load level. This finding suggested that the drug/HPMC solid dispersions prepared by melt extrusion resulted in hydrogen bonding between the secondary amine groups of NMD and the hydroxyl groups of HPMC. The interaction in the HPMC dispersion was probably much weaker than in extrudates prepared with Eudragit® EPO or PVP/VA since there were almost no N–H stretching vibrations with these carriers. And less miscibility of the drug-HPMC system were observed through reduced hydrogen bonding ability of the hydroxyl groups compared to the carbonyl group of the other carriers.

The reduction or disappearance of N–H stretching in the extrudates is strong evidence of H-bonding between the drug and these polymers. Another possible reason for the loss of the N–H stretch is due to photodegradative dehydrogenation of the light-sensitive drug (Teraoka et al, 1999). However, no changes were seen in the N–H stretch of physical mixtures, and the NMD samples were protected from light during sample preparation and storage.

Scanning Electron Microscopy

SEM was used to examine the surface morphology of the drug and extrudates (Fig. 8). The particle morphology of NMD is illustrated in Fig. 8j. The extrudates containing PVP/VA and Eudragit® EPO exhibited drug crystals on the extrudate surface at 50 and 30% drug loading, but the number of crystals decreased with drug load. No drug crystals were observed at 10% NMD loading. NMD crystals were observed on the surface of HPMC extrudates at all

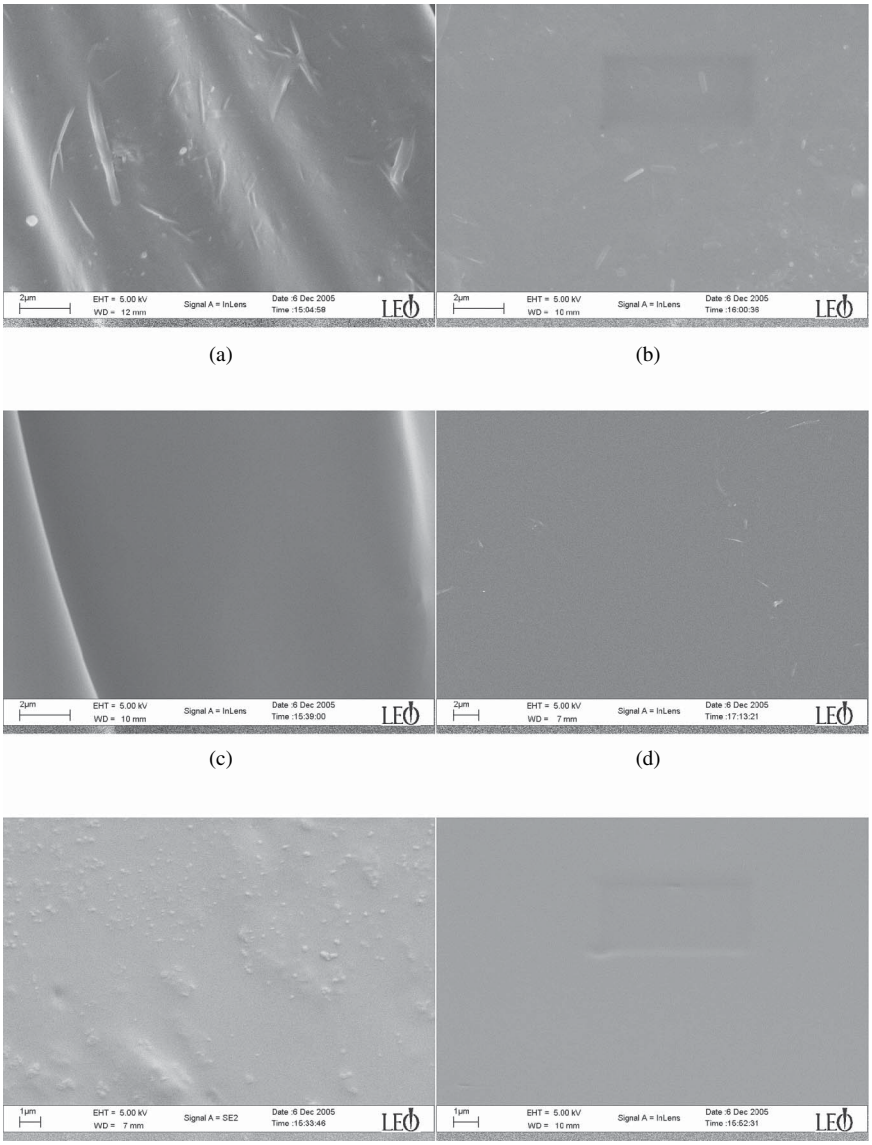

FIGURE 8 **SEM micrograph of the surface morphology of pure NMD and hot-melt extrudates containing NMD. (a) NMD:PVP/VA (50:50) (b) NMD:PVP/VA (30:70) (c) NMD:PVP/VA (10:90) (d) NMD:Eudragit® EPO (50:50) (e) NMD:Eudragit® EPO (30:70) (f) NMD:Eudragit® EPO (10:90) (g) NMD:HPMC (50:50) (h) NMD:HPMC (30:70) (i) NMD:HPMC (10:90) (j) SEM micrograph of the surface morphology of NMD.**

drug concentrations, indicating that NMD is less miscible with HPMC than PVP/VA and Eudragit® EPO. Thus, the SEM observations were more sensitive to the presence of drug/polymer immiscibility than the DSC and XRPD investigations.

Phase Solubility Studies

The water solubility of NMD as a function of PVP/VA concentration is given in Table 2, and the data show that the increase in NMD solubility was linear with respect to the weight fraction of polymer. The solubility increase was approximately 20 fold with 90% PVP/VA compared to pure drug. The increase in solubility in the presence of PVP/VA can be attributed to micellular solubilization. Addition of Eudragit® EPO increased solubility 3 fold compared to pure NMD. Similar observations were obtained with HPMC.

Solubility Parameter Calculations

Solubility parameters (δ_t) have been used successfully to predict the miscibility of drugs with excipients and polymers in solid dispersions (Forster et al.,

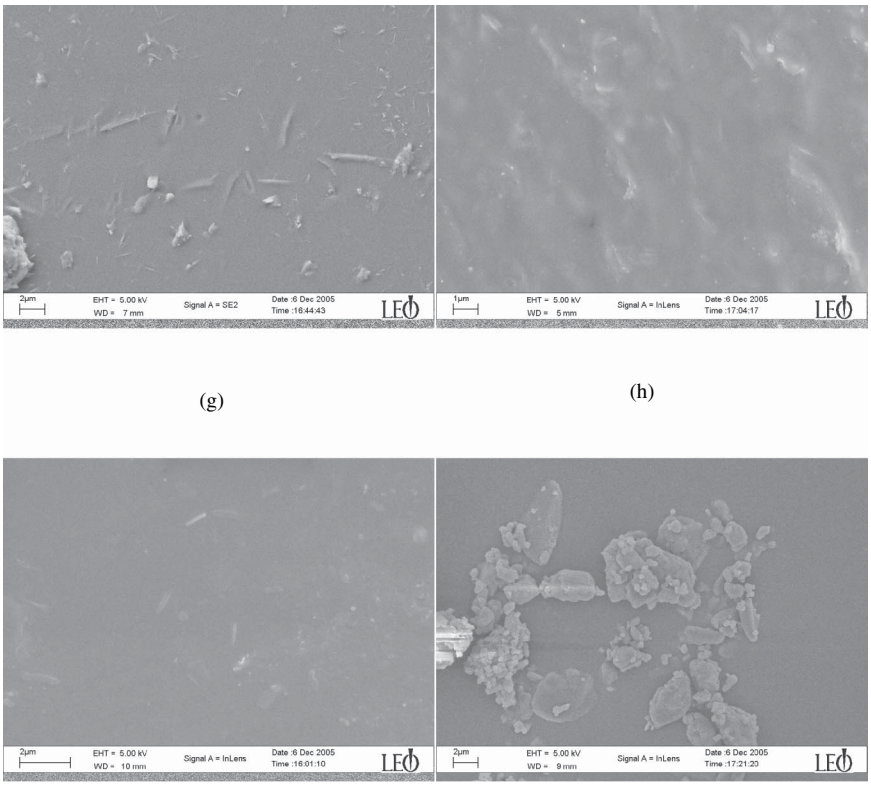

FIGURE 8 **(Continued).**

TABLE 2 **Solubility data for NMD water-carrier systems at pH 4.5 acetate buffers containing 0.05% SDS at 37°C**

	NMD Concentration (w/w)			
Polymer	10%	30%	50%	100%
PVP/VA	99.81	78.94	69.69	5.32
Eudragit® EPO	15.76	15.83	13.81	5.32
HPMC	15.32	17.95	16.98	5.32

2001b; Greenhalgh et al., 1999; Hancock et al., 1997; Suzuki and Sunada, 1997, 1998). Hildebrand and Scott first used the term solubility parameter; and the Hildebrand solubility parameter is defined as the square root of the cohesive energy density:

$$\delta^2 = \mathrm{E/V} \tag{4}$$

where V is the molar volume of the pure solvent or matrix and E is its energy of vaporization. Greenhalgh (Greenhalgh et al, 1999) later suggested that interactions between polar (δ_p) and hydrogen bonding groups (δ_h) significantly affect solubility and should be incorporated into the estimation of the solubility parameter that previously only accounted for dispersive forces (δ_d). This parameter provided insight into the balance of polar and non-polar forces operating between adjacent atoms/molecules and between material surfaces. The difference between the solubility parameters (δ_d) of two materials gives an estimation of the likelihood that they will be miscible. Compounds with similar values for δ_t are likely to be miscible because the energy of mixing from intramolecular interactions is balanced with the energy of mixing from intermolecular interactions. Greenhalgh demonstrated that compounds with $\Delta\delta_t < 7$ MPa$^{1/2}$ were likely to be miscible and compounds with $\Delta\delta_t > 10$ MPa$^{1/2}$ were likely to be immiscible (Greenhalgh et al, 1999).

Table 3 shows the solubility parameters and interaction parameters calculated for NMD, PVP/VA, HPMC, and Eudragit® EPO. The difference between the calculated solubility parameters of the polymers and the drug indicate that NMD is likely miscible with PVP/VA and Eudragit® EPO. Thus, the Hansen solubility parameter calculated using the method of Hoftyzer and

TABLE 3 **Calculated solubility parameters of drug and polymers**

Compound	Solubility Paramerter δ_t (MPa$^{1/2}$)	Difference $\Delta\delta_t$ (MPa$^{1/2}$)
NMD	20.7	—
HPMC	22.4	1.7
Eudragit® EPO	18.9	1.8
PVP/VA	22.7	2

van Krevelen supports miscibility between NMD with PVP/VA and Eudragit EPO as observed by DSC, XRPD, and FT-IR. However, it does not predict the lower miscibility observed with HPMC than the other polymers. Thus, it must be borne in mind that other excipient properties such as arrangement and viscosity cannot be predicted by the solubility parameter and may limit drug/excipient miscibility. Despite the limitations of this approach, solubility parameters provide a simple and generic capability for rational selection of carriers in the preparation of solid dispersions, but solubility parameter calculations should be combined with analysis using thermal methods before extrusion.

Dissolution Testing

Dissolution profiles of NMD from NMD-HPMC, NMD–Eudragit® EPO, and NMD-PVP/VA systems in pH 4.5 acetate buffer containing 0.05% (w/v) SDS are shown in Figs. 9, 10 and 11, respectively. The corresponding values of DE_{10}, DE_{30}, and DE_{60} are given in Table 4. The dissolution rate of NMD from Eudragit® EPO extrudates was higher than those in physical mixtures when the contents of NMD were 30 and 50%, however, a significant decrease in the dissolution of NMD was observed in the case of the solid dispersions compared with physical mixtures at the 10% drug loading level ($p < 0.01$). After 1 hr only 1% of the drug was released from the 10% NMD extrudates. Compared to the NMD alone and preparations containing different polymers, the lower dissolution rate of the drug from the extrudates can be explained by the insolubility of the polymer in the dissolution

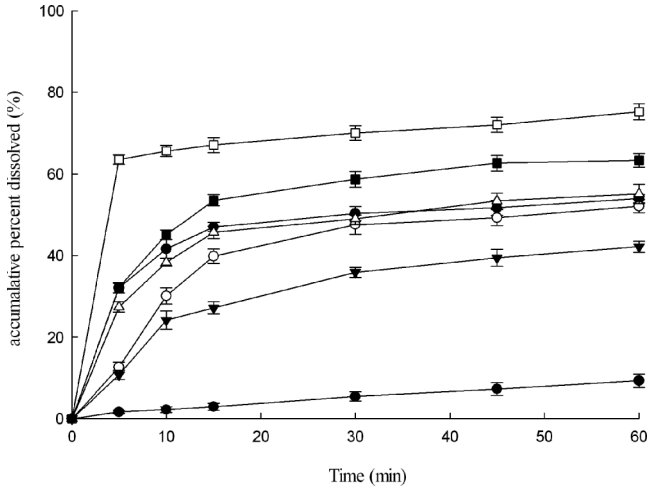

FIGURE 9 **Dissolution profiles of NMD-HPMC systems in pH 4.5 acetate buffer containg 0.05% (w/v) of SDS. (■) 10% NMD SD (□) 30% NMD SD (□) 50% NMD SD (□) 50% NMD PM (○) 30% NMD PM (▼) 10% NMD PM (•) pure NMD (mean ± *S.D.*, *n* = 3).**

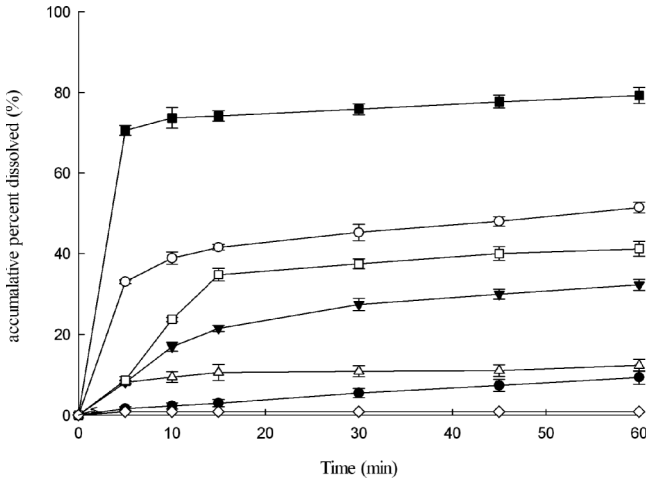

FIGURE 10 **Dissolution profiles of NMD-Eudragit® EPO systems in pH 4.5 acetate buffer containing 0.05% (w/v) of SDS. (□) 30% NMD SD (□) 10% NMD SD (■) 50% NMD SD (○) 50% NMD PM (▼) 30% NMD PM (□) 10% NMD PM (•) pure NMD (mean ± *S.D.*, *n* = 3).**

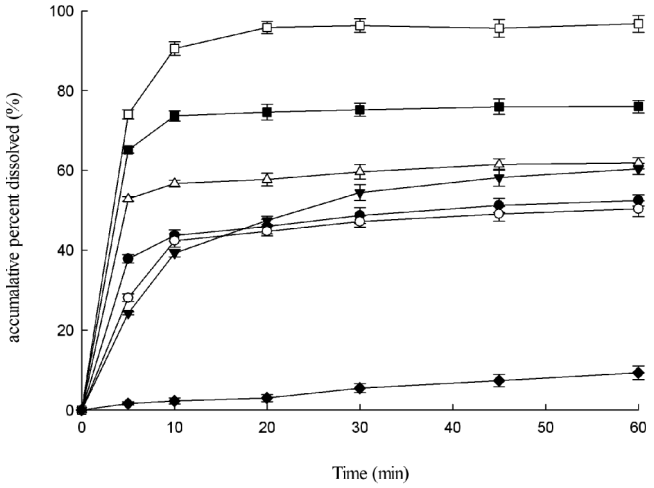

FIGURE 11 **Dissolution profiles of NMD-PVP/VA systems in pH 4.5 acetate buffer containg 0.05% (w/v) of SDS. (□) 50% NMD SD (■) 30% NMD SD (□) 10% NMD SD (•) 50% NMD PM (○) 30% NMD PM (▼) 10% NMD PM (□) pure NMD (mean ± *S.D.*, *n* = 3).**

TABLE 4 Dissolution efficiency values (mean ± S.D.) of NMD and various physical mixtures (PM) and solid dispersions (SD)

Carrier	%NMD	DE_{10}	DE_{30}	DE_{60}
NMD	100%	1.40±0.11	2.76±0.23	5.07±0.65
PVP/VA	PM 50%	29.38±0.43	41.01±0.39	45.57±0.33
	PM 30%	24.88±0.46	36.91±1.01	43.19±0.53
	PM 10%	22.06±0.45	38.81±0.20	48.45±0.35
	SD 50%	39.61±0.84	51.19±0.82	55.71±0.80
	SD 30%	50.90±0.17	67.42±0.67	71.25±0.30
	SD 10%	59.57±0.15	82.26±0.65	88.49±0.91
HPMC	PM 50%	26.72±0.42	39.85±1.01	45.86±1.43
	PM 30%	13.97±1.05	31.02±1.06	40.43±1.01
	PM 10%	11.19±0.42	22.26±0.55	30.78±0.52
	SD 50%	23.29±1.22	37.55±1.54	45.15±0.57
	SD 30%	27.34±0.40	44.27±0.36	53.05±0.18
	SD 10%	48.41±0.33	61.80±0.67	67.16±0.49
Eudragit® EPO	PM 50%	26.12±0.21	35.89±0.64	41.39±0.88
	PM 30%	4.15±0.13	14.95±0.38	22.44±0.39
	PM 10%	8.28±0.14	8.60±0.96	9.01±0.93
	SD 50%	54.94±1.24	67.81±0.23	72.39±0.20
	SD 30%	10.88±0.53	25.86±0.64	32.59±0.27
	SD 10%	0.61±0.02	0.83±0.05	0.97±0.14

medium (pH 4.5). The delay and decrease in drug release rate was greater with extrudates than physical mixtures. Additionally, increased polymer content led to further decreases in drug release rate.

The mechanism of drug release in this case depended on the penetration of the dissolution medium into the extrudates followed by dissolution and subsequent diffusion of the drug through the polymeric matrix. Since the dissolution of solid dispersion was predominantly diffusion-controlled, the high viscosity of this carrier was presumably the main factor that control drug dissolution rate. The diffusion coefficient of the drug was largely decreased, resulting in the low dissolution rate of the drug from solid dispersions compared to the physical mixtures. The high polymer concentration formulations exhibited slower drug release because the polymer further inhibited the diffusion of water in the matrix.

All studied solid dispersions of NMD with PVP/VA and HPMC exhibited enhanced dissolution rates compared to NMD alone or in physical mixtures with the polymer ($p < 0.01$). Significant differences were also observed between the DE values of NMD and all extruded preparations. Good linear relationship was observed between the concentration of these carries and DE_{10}, DE_{30}, and DE_{60} up to 90% w/w concentration of polymer. Thus, it was concluded that the solid dispersions of NMD with PVP/VA and HPMC markedly enhanced drug dissolution and that the enhancement of dissolution rate was influenced by the drug/polymer ratio. Concerning the dissolution tests, the findings of faster dissolution of higher drug levels in some polymer systems could be contributed to possibility of channel formation during dissolution. The enhancement of NMD dissolution rate by the solid dispersion technique compared to that of the pure drug can be attributed to the solubilization effect of the carrier in addition to improved wettability and dispersibility of the drug from the dispersion.

CONCLUSIONS

The results of this study demonstrated that solid dispersions containing nimodipine and HPMC, PVP/VA or Eudragit® EPO can be successfully prepared by the hot-melt extrusion process. Eudragit® EPO and PVP/VA showed better miscibility with nimodipine than HPMC as indicated by XRPD, DSC, and SEM. Results from IR spectroscopy concluded that there was well-defined interaction between nimodipine and the polymers. The weakening and shift of the N–H stretching vibration of the secondary amine groups of nimodipine proved hydrogen bonding between nimodipine and the carriers after extrusion.

Increased aqueous solubility was observed in nimodipine mixtures with all three polymers, and solid

dispersions prepared by hot-melt extrusion with the hydrophilic polymers PVP/VA and HPMC resulted in greater dissolution rate over physical mixtures or pure drug. Extrudates containing Eudragit® EPO with 10% drug loading showed slower drug release rates due to low solubility of polymer in the dissolution medium. NMD-PVP/VA might be the most appropriate system to manufacture the solid dispersion.

Thus, through proper selection of a polymeric carrier solid dispersions of nimodipine can be prepared by hot-melt extrusion to improve the dissolution properties of the poorly water-soluble drug. Further work is warranted to determine if the oral bioavailability of nimodipine is increased for the solid dispersions with enhanced dissolution characteristics.

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