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Part II: Bioavailability in Beagle Dogs of Nimodipine Solid Dispersions Prepared by Hot-Melt Extrusion

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ABSTRACT The aim of the present work was to investigate the in vitro dissolution properties and oral bioavailability of three solid dispersions of nimodipine. The solid dispersions were compared with pure nimodipine, their physical mixtures, and the marketed drug product Nimotop®. Nimodipine solid dispersions were prepared by a hot-melt extrusion process with hydroxypropyl methylcellulose (HPMC, Methocel E5), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA, Plasdone S630®), and ethyl acrylate, methyl methacrylate polymer (Eudragit® EPO). Previous studies of XRPD and DSC data showed that the crystallinity was not observed in hot-melt extrudates, 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. The dissolution profiles of the three dispersion systems showed that the release was improved compared with the unmanipulated drug. Drug plasma concentrations were determined by HPLC, and pharmacokinetic parameters were calculated after orally administering each preparation containing 60 mg of nimodipine. The mean bioavailability of nimodipine was comparable after administration of the Eudragit® EPO solid dispersion and Nimotop®, but the HPMC and PVP/VA dispersions exhibited much lower bioavailability. However, the AUC0–12 hr values of all three solid dispersions were significantly higher than physical mixtures with the same carriers and nimodipine powder.

KEYWORDS Nimodipine, Solid dispersion, Hot-melt extrusion, Dissolution, Bioavailability

INTRODUCTION

The solubility and permeability behaviors of a drug are the key determinants of the drug's 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

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potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble drugs for oral delivery is now one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Nimodipine is a dihydropyridine calcium channel blocker used in the treatment of senile dementia and in the prophylaxis of the vascular hemierania (Manhold, 1985). The molecular structure of nimodipine is illustrated in Fig. 1. The drug is practically insoluble in water and exists in the form of yellow crystals. Due to the low aqueous solubility and the poor absorption of nimodipine after oral administration, nimodipine often shows low and irregular bioavailability (Grunenberg et al., 1995). Since the dissolution rate of such drugs is the absorption limiting step, the formulation of solid dispersions can be used to enhance the dissolution characteristics of poorly soluble drugs and hence improve their oral bioavailability (Craig, 2002; Leuner and Dressman, 2000). The distribution of the drug in the carrier, sometimes at the molecular level, together with the enhanced wettability and microenvironment created by the carrier may increase both drug solubility and dissolution rate. Attempts have been made to modify the dissolution characteristics of nimodipine by decreasing particle size, coprecipitation, comixing, and preparation of solid dispersions (Murali Mohan Babu et al., 2002a; Murali Mohan Babu et al., 2002b), however, few authors have similarly reported on the in vivo performance of solid dispersions (Emara et al., 2002; Murali Mohan Babu et al., 2002a).

Hot-melt extrusion is an alternative method to manufacture solid dispersions and is becoming widely utilized in the production of drug delivery systems (Breitenbach, 2002). This technique was introduced to the pharmaceutical field relatively recently as an alternative manufacturing method for solvent-related processes. A number of solid dispersions have been developed using melt extrusion processes. Studies have shown that melt-extrusion is a promising method to enhance the water solubility of poorly water-soluble drugs such as itraconazole (Six et al., 2003a; Six et al., 2003b; Verreck et al., 2003; Six et al., 2005), indomethacin, nifedipine, tolbutamide, lacidipine (Forster et al., 2001a; Forster et al., 2001b), and nitrendipine 17-β estradiol (Hulsmann et al., 2000; Hulsmann et al., 2001).

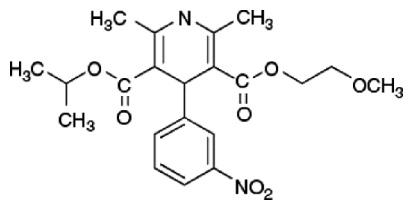

FIGURE 1 Structural formula of nimodipine.

In the previous study, solid dispersions of nimodipine with HPMC, Eudragit® EPO, and PVP/VA were prepared using hot-melt extrusion, and in vitro dissolution data showed the potential of melt extruded solid dispersions for improving drug absorption. The aim of the present study was to investigate the in vivo properties of capsules prepared with melt-extruded solid dispersions of nimodipine in comparison to commercially available Nimotop® tablets.

MATERIAL AND METHODS

Materials

Nimodipine (NMD) was purchased from Tianjin Zhongyang Pharmaceutical Company (Tianjin, China). Hydroxypropyl methylcellulose (HPMC) type 2910 E5 (5 cp viscosity, Methocel, Dow) was kindly provided by Colorcon, Eudragit® EPO by Röhm (Germany) and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA) (Plasdone S630®) by ISP. Microcrystalline cellulose (MCC) was purchased from Huzhou Zhanwang (China).

Preparation of Physical Mixture (PM)

NMD (passed through a 180 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 homogeneous physical mixture. 60 mg of nimodipine powder and physical mixtures containing 60 mg of NMD were mixed with 100 mg of MCC and filled into size 0 capsules.

Preparation of Solid Dispersions (SD)

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 extruder configuration consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. 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.

All solid dispersions were assessed with differential scanning calorimetry and X-ray powder diffraction (XRPD) in order to determine the presence or absence of crystalline drug in the solid dispersions. Solid dispersions containing 60 mg of NMD were mixed with 100 mg of MCC and filled into size 0 capsules.

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 according to the 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 NMD 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 the tests were performed in triplicate.

The HPLC system consisted of an L-7100 HPLC pump, an L-7200 autosampler equipped with a 100 μL loop, an L-7420 UV detector set at 237 nm and a D-7000 interface (Hitachi, Japan). 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.

Animal Experiments and Drug Administration

The male beagle dogs were purchased from General Hospital of Shenyang Military Region (China) and were given a normal standard chow diet and free access to water. Animals were housed in laminar flow house maintained at 22 ± 2°C, 50–60% relative humidity under a 12 hr light:12 hr dark cycles throughout the experiment. Additionally, the animals were kept in these facilities for at least 1 week prior to these experiments, and the studies were performed in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology in July 1989 and revised in March 1999.

The study design was fasting, single dose with eight treatments and eight periods. Each dog was administered eight preparations with a one-week washout period between each preparation. Six dogs were used for each treatment group. The dogs were fasted for 24 hr prior to experiments, and the preparations (solid dispersion, physical mixture, pure NMD or Nimotop® tablets) containing 60 mg of drug were administered in the morning and a standard lunch was given 4 hr after dosing. Blood was withdrawn via canulated needle from front legs. 3 mL of blood were collected in heparinized tubes immediately prior to dosing (time zero) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, and 12 hr after dosing. Blood was centrifuged for 10 min within 20 min of sampling, and plasma was stored at ≤ –20°C until analyzed by HPLC.

Extraction Procedure and HPLC Assay

0.5 mL of plasma was spiked with 100 μL of internal standard solution (nitrendipine, 1000 ng/mL dissolved in methanol) and 100 μL of methanol. The sample was subsequently alkalinized with 200 μL of 1 M NaOH and extracted with 3 mL of extraction solvent (*n*-hexane/diethylether/ isopropyl alcohol = 20:10:1) by vortexing for 10 min. After centrifugation at 4000 rpm for 10 min, the supernatant was transferred to a conical tube. The separated organic phases were then evaporated to dryness under a gentle stream of nitrogen at 50°C. The residue was reconstituted in 50 μL of mobile phase and then 20 μL was injected into an HPLC system consisting of a PU-2080 plus intelligent HPLC pump, a 2075 plus intelligent UV/VIS detector

(Jasco, Japan) and a Ckchrom chromatographic integrator (Japan).

Chromatography was performed on a C_{18} column (Diamonsil, 5 μm, 4.6 mm × 250 mm, Dikma, China) guarded with a precolumn (C_{18}, 2.0 mm × 20 mm, Alltech) and using a flow rate of 1.0 mL/min and a detection wavelength of 358 nm. The mobile phase, consisting of 40% water and 60% methanol (v/v), was filtered through a membrane filter (0.45 μm) and degassed by ultrasonication before use. These conditions resulted in a typical elution time for 10.22 min for NMD and 11.29 min for nitrendipine. A typical chromatogram is shown in Fig. 2.

Drug plasma concentrations were obtained from NMD standard curves that were linear between 10 and 1000 ng/mL ($R^2 > 0.99$). The limit of quantification for the drug was 10 ng/ml in plasma. The accuracy was 96.4% at this concentration, while the precision was 10.7%. Within-batch accuracy ranged from 94.7% during the validation to 103.3%, and within-batch precision remained below 9%. The between-batch accuracy ranged between 95.2% and 104.8%, and precision remained below 10%. The extraction recovery of NMD from plasma was more than 80%.

As NMD is sensitive to light-induced degradation, all operations were carried out under thorough light shelter (Muck and Bode, 1994).

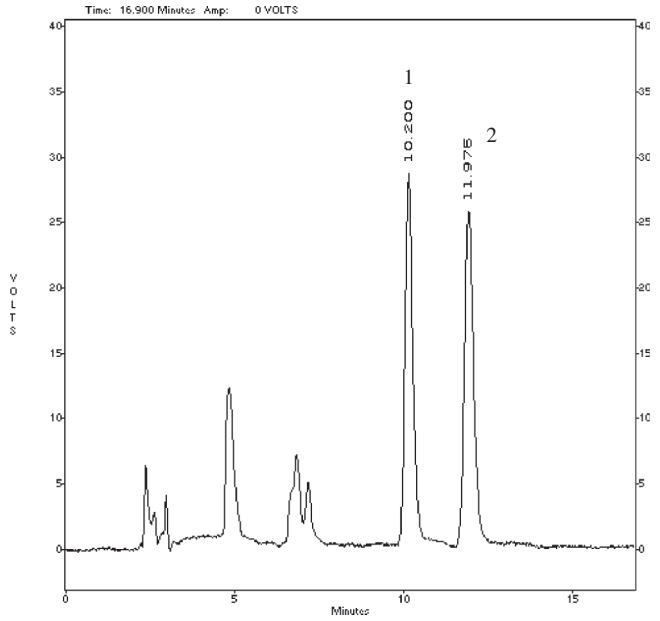

FIGURE 2 Representative chromatogram showing the internal standard, nitrendipine (1, 10.200 min), and NMD (2,11.975 min).

Data Analysis

Non-compartmental pharmacokinetic analysis was conducted to calculate the area under the curve from 0 to 12 hr (AUC_{0-12}). The peak plasma concentration (C_{max}) and the time to reach peak plasma concentration (T_{max}) of the different dosage forms were determined by a visual inspection of the experimental data. The threshold for differences to be considered significant was set at $p \leq 0.05$. The relative bioavailability was calculated as follows:

$$\text{Relative bioavailability (F\%)} = \frac{AUC_{0-12}\text{test}}{AUC_{0-12}\text{control}} \times 100$$

RESULTS AND DISCUSSION

In Vitro Dissolution Study

The in vitro dissolution profiles of the three solid dispersion-containing preparations are shown in Fig. 3 together with the dissolution data of their physical mixtures and Nimotop® tablets. A dissolution medium containing 0.05% (w/v) of SDS was used since it has been reported to have sufficient discriminating power to evaluate the relationship between in vitro dissolution and in vivo absorption of NMD products (He et al., 2004). Nimotop® tablets and the capsules containing PVP/VA extrudate exhibited rapid drug dissolutions, with more than 70% drug released

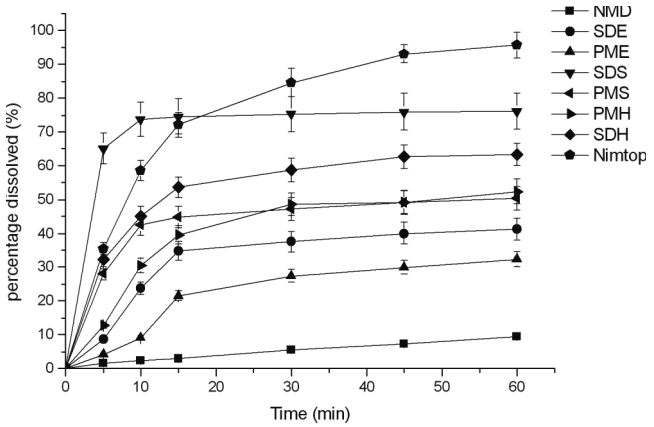

FIGURE 3 Dissolution profiles of different preparations including Nimotop®; solid dispersions of HPMC (SDH), Eudragit® EPO (SDE) and PVP/VA (SDS); physical mixtures of HPMC (PMH), Eudragit® EPO (PME) and PVP/VA (PMS); and raw nimodipine powder (NMD). The dissolution (paddle method) was carried out in 900 ml pH 4.5 acetate buffer containing 0.05% (w/v) sodium dodecyl sulfate, at 37°C, 75 rpm.

within 15 min. The HPMC-containing extrudates showed an intermediate drug release rate, while the Eudragit® EPO-containing extrudates only released 40% of the drug after 1 hr. Physical mixtures exhibited a small improvement in dissolution rate over pure drug powder, which may have been due to increased wettability of the drug and the inhibition of drug particle aggregation by the carrier. However, all solid dispersions showed a faster dissolution rate than their physical mixtures. The enhancement of NMD dissolution rate by the solid dispersion technique can be attributed to the solubilization effect of the carrier and improved wettability/dispersibility of the drug upon administration. NMD is molecularly dispersed in the Eudragit® EPO and PVP/VA solid dispersions soft. So the extrusion process made drug PVP/VA and EPO systems homogenous in contrast to HPMC as two phases with two T_g as determined by DSC and XRPD. This finding explains the slower dissolution rate from HPMC dispersions as compared to Eudragit® EPO and PVP/VA dispersions.

In Vivo Evaluation

The preparations (solid dispersions, physical mixtures, pure NMD powder, and Nimotop® tablets) were orally administered to beagle dogs. The pharmacokinetic parameters are listed in Table 1, while Fig. 4 and 5 show the plasma drug concentrations as a function of time after oral administration.

The mean T_{max} values ranged from 1.58 ± 0.80 hr for Nimotop® and 2.25 ± 1.51 hr for the HPMC physical mixture. The results revealed that the Nimotop® gave the highest C_{max} value, followed by Eudragit® EPO solid dispersion. However, there was no significant difference between C_{max} values of Eudragit® EPO solid dispersion and Nimotop®. The C_{max} of all solid dispersions manufactured by hot-melt extrusion, were significantly higher than those of the physical mixtures with the same polymer carrier, and pure NMD powder resulted in the lowest C_{max}.

The mean $AUC_{0-12\ hr}$ after administration of Nimotop® and the Eudragit® EPO solid dispersion formulation were comparable while the other preparations exhibited lower values. The order of preparations according to their relative oral bioavailability was Nimotop ≈ Eudragit® EPO SD > PVP/VA SD > HPMC SD ≈ Eudragit® EPO PM > PVP/VA PM > HPMC PM ≈ pure NMD. The same trend was observed in the C_{max} values. These values clearly indicate the improvement in drug bioavailability from the studied solid dispersions when compared to pure drug powder. Bioavailability of the three physical mixtures was significantly less than solid dispersions of the same carriers. Large intersubject variability in the pharmacokinetic behavior of NMD was observed, which is partially due to extensive first-pass metabolism. Moreover, the dog-drinking behaviors were different, which may have impacted drug dissolution from the dosage forms and thereby causing variable bioavailability.

Although in vitro dissolution studies showed that the rank order of drug dissolution rate was PVP/VA > Eudragit® EPO > HPMC solid dispersion, in vivo investigations found that HPMC and PVP/VA resulted in lower mean $AUC_{0-12\ hr}$ and C_{max} values than Eudragit® EPO. Thus, in vitro dissolution in a medium of pH 4.5 acetate buffer containing 0.05% (w/v) SDS did not accurately represent in vivo behavior. It was speculated that the contradiction between in vivo and in vitro data may have resulted from the pH-dependence of Eudragit® EPO. The dissolution rate of the EPO-containing solid dispersion should be

TABLE 1 **Pharmacokinetic parameters (±*S.D.*) of NMD after oral administration of eight different formulations in beagle dogs, including solid dispersion (SD), physical mixture (PM), Nimotop and raw NMD powder**

Parameters	C_{max} (ng/mL*hr)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC(0–12) (ng/mL*hr)	*F* (%)
HPMC SD	213.18 ± 74.45	1.62 ± 0.74	4.40 ± 1.12	615.22 ± 202.92	71.92 ± 8.97
HPMC PM	91.479 ± 15.40	2.25 ± 1.51	3.27 ± 0.96	358.16 ± 107.77	41.97 ± 3.01
Eudragit® EPO SD	236.27 ± 87.78	1.67 ± 0.41	2.81 ± 0.80	872.98 ± 224.37	103.44 ± 10.91
Eudragit® EPO PM	133.33 ± 20.18	1.75 ± 0.69	4.2 ± 1.26	622.03 ± 56.14	77.12 ± 19.97
PVP/VA SD	228.99 ± 87.24	1.63 ± 0.97	2.58 ± 1.19	712.03 ± 279.89	82.32 ± 14.69
PVP/VA PM	108.03 ± 22.80	1.92 ± 0.49	3.32 ± 1.10	404.86 ± 71.22	48.84 ± 7.02
Nimotop	259.38 ± 96.18	1.58 ± 0.80	2.51 ± 0.53	858.17 ± 260.79	100.00 ± 0.00
Raw NMD powder	87.45 ± 13.06	1.75 ± 0.52	3.95 ± 2.31	298.22 ± 67.13	35.55 ± 3.73

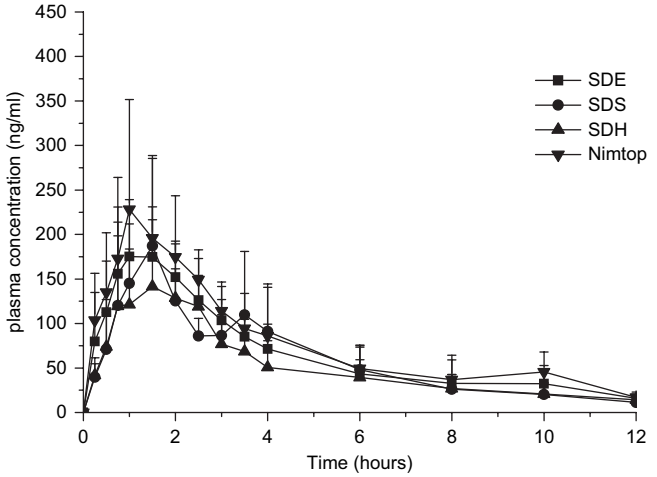

FIGURE 4 **Average plasma concentration vs. time profiles of NMD after oral administration (60 mg NMD doses) of Nimotop®; solid dispersions of HPMC (SDH), Eudragit® EPO (SDE) and PVP/VA (SDS) in beagle dogs (*n* = 6). Error bars indicate the standard error of the mean.**

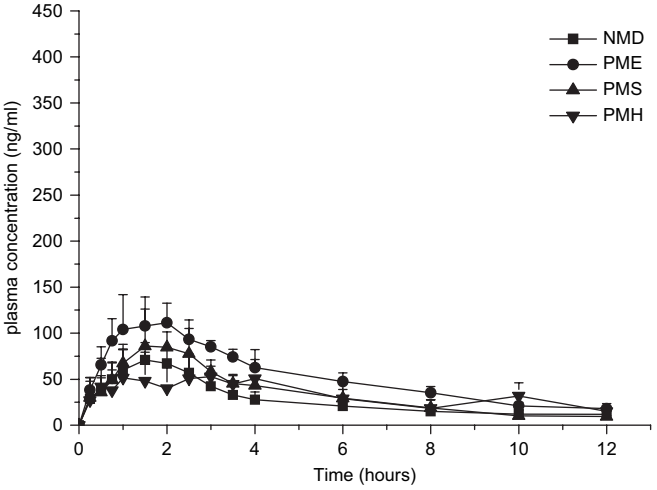

FIGURE 5 **Average plasma concentration vs. time profiles of NMD after oral administration (60 mg NMD doses) of physical mixtures of HPMC (PMH), Eudragit® EPO (PME) and PVP/VA (PMS); and raw nimodipine powder (NMD) in beagle dogs (*n* = 6). Error bars indicate the standard error of the mean.**

faster in gastric fluid than in pH 4.5 dissolution media, whereas the other polymers do not exhibit pH-dependent solubility. Thus, the poor predictability of oral bioavailability was likely due to unsuitable dissolution conditions. To confirm this hypothesis, another dissolution test was performed in which the preparations were dissolved in 900 mL 0.1 N hydrochloric acid containing 0.05% (w/v) SDS at 37°C with a paddle rotation speed of 75 rpm. The dissolution profiles are showed in Fig. 6. The results revealed that

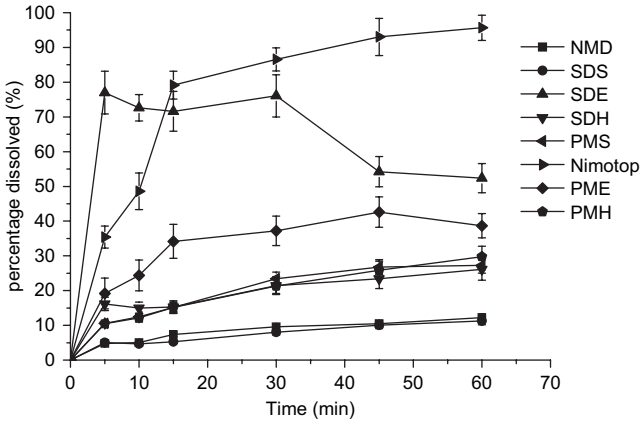

FIGURE 6 **Dissolution profiles of different preparations including Nimotop®; solid dispersions of HPMC (SDH), Eudragit® EPO (SDE) and PVP/VA (SDS); physical mixtures of HPMC (PMH), Eudragit® EPO (PME) and PVP/VA (PMS); and raw nimodipine powder (NMD). The dissolution (paddle method) was carried out in 900 mL 0.1 N hydrochloric acid containing 0.05% (w/v) sodium dodecyl sulfate, at 37°C, 75 rpm.**

the NMD solid dispersion with Eudragit® EPO dissolved significantly faster than all formulations except Nimotop®, supporting the high bioavailability observed with the Eudragit® EPO solid dispersion.

Another possible explanation of the bioavailability difference between Eudragit® EPO and the other two polymers may be the instability of the NMD in intestinal tract. It was reported that NMD is metabolized by cytochrome P-450 (CYP3A) both in the liver and small intestine (Guengerich et al., 1991; Ramsch et al., 1985; Scherling et al., 1991) and that the absorption of NMD in the intestinal mucosa is inhibited by a P-glycoprotein efflux pump (Saeki et al., 1993). P-glycoprotein and CYP3A4 are believed to act synergistically in first-pass metabolism. The increased $AUC_{0-12\ hr}$ and C_{max} of the NMD-Eudragit® EPO solid dispersion as compare to other preparation might have resulted from rapid dissolution in the stomach that saturated the efflux pump and CYP3A4 in the intestinal mucosa, thus increasing drug bioavailability.

Drug solubility in the polymer, pH-dependence of the polymer, and metabolic pathways of the drug can also explain the difference in bioavailability results between NMD in this paper and itraconazole in previous research (Six et al., 2005) that used the same polymeric carriers. With itraconazole, the mean AUC values after oral administration of the HPMC formulation were significantly higher than those of the Eudragit® E100 and Eudragit® E100-PVP/VA formulations.

Although it was difficult to draw definite conclusions from this limited in vivo study, some interesting points can be made. The mean relative bioavailability of the Eudragit® EPO solid dispersion is similar to that of Nimotop® tablets. This finding suggests that solid dispersions prepared by melt extrusion can improve dissolution rate and oral bioavailability of poorly water-soluble drugs.

CONCLUSION

This study showed that the $AUC_{0-12\ hr}$ after oral administration of Nimotop® tablets and a Eudragit® EPO solid dispersion were comparable while that of HPMC and PVP/VA dispersions was lower. However, all solid dispersions exhibited significantly higher exposure than their corresponding physical mixtures and pure nimodipine powder. Despite a limited number of animals involved in this study and the high variability in nimodipine pharmacokinetics, it can be concluded that hot-melt extrusion is a viable alternative for manufacturing of nimodipine solid dispersions. Although six dogs belonged to each treatment group, the statistical significance of the results is not very high as the inter-subject variability was very high. So another test including more subjects is necessary to evaluate the present results and in further investigations and clinical trials will be needed to determine if the results obtained in this study can be extrapolated to humans.

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