International Journal of Pharmaceutics 359 (2008) 144–149

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Nimodipine semi-solid capsules containing solid dispersion for improving dissolution

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ARTICLE INFO

Article history:
Received 7 October 2007
Received in revised form 15 March 2008
Accepted 31 March 2008
Available online 7 April 2008

Keywords:
Nimodipine
Semi-solid capsule
Solid dispersion
Hot-melt extrusion
Dissolution
Bioavailability

ABSTRACT

The aim of this study was to improve the dissolution and, therefore, bioavailability of the poorly water-soluble and highly permeable drug nimodipine (NMD). Present research involved the preparation of a solid dispersion (SD) consisting of NMD, Eudragit-E100 and Plasdone-S630 by hot-melt extrusion (HME). Compared with pure drug and physical mixture, the dissolution of NMD was enhanced dramatically (about 80% within 30 min). Adding the nimodipine solid dispersion (NMD-SD) powder to a mixture of Plasdone-S630 and PEG400, and then transferring it to hard HPMC capsules, resulted in nimodipine semi-solid capsules (NMD-SSC). The dissolution from NMD-SSC was increased further (about 95% in 20 min). In addition, the relative bioavailability of the NMD-SSC (test) and Nimotop® (reference) was determined in beagle dogs after a single dose (120 mg NMD) in a randomized crossover, own-control study. The results suggested that there was no significant difference in the areas under the plasma concentration–time curve and the mean peak concentration between NMD-SSC ($AUC_{0-\infty} = 2488 \pm 433$ ng h mL^{-1}, $C_{max} = 321 \pm 78$ ng ml^{-1}) and Nimotop® ($AUC_{0-\infty} = 2272 \pm 398$ ng h mL^{-1}, $C_{max} = 293 \pm 73$ ng mL^{-1}) ($P > 0.05$). However, the apparent rate of absorption of NMD from NMD-SSC ($t_{max} = 1.3$ h) was markedly faster than that from Nimotop® ($t_{max} = 3.1$ h) ($P < 0.05$), which indicates that as a fast release preparation, NMD-SSC is well absorbed.

1. Introduction

Nimodipine (NMD) is a dihydropyridine calcium channel blocker. It has been shown to selectively regulate calcium channels to increase cerebral blood flow. Because of its high permeability, NMD can pass through the blood–brain barrier to protect brain cells by increasing their ability to tolerate hypoxia. The major therapeutic indication of NMD is for the prevention and treatment of delayed ischaemic neurological disorders, which often occur in patients with subarachnoid hemorrhages (Langley and Sorkin, 1989). NMD has also been used in other cerebrovascular disorders, such as ischemic stroke (Mohr et al., 1994) and multi-infarct dementia (Pantoni et al., 2000).

NMD is a poorly water-soluble drug, which is one of the reasons that it has a low bioavailability and limited clinical efficacy. For "low solubility/high permeability" drugs, dissolution plays an important role in their absorption (Amidon et al., 1995). Recently, for the purpose of improving oral bioavailability, a variety of techniques have been used to enhance the solubility in water and in biological fluids at physiological pH values, such as salt formation, solubilization, particle size reduction, solid dispersion (SD), self-dispersing lipid formulations (SDLFs) (Gershanik and Benita, 2000), and the use of inclusion compounds based on cyclodextrin. Among these methods, SD is the most efficient. It is able to produce a local increase in the solubility (within the solid solution), and as the carrier dissolves, the drug comes into close contact with the dissolution medium (Leuner and Dressman, 2000).

There are many techniques for the manufacture of SD, such as embedding by means of spray drying, co-evaporation, co-precipitation and freeze-drying. All these methods require expensive equipment and complex procedures. Even though may be successful in the laboratory, because of safety and reproducibility, they are difficult to produce under bulk manufacturing conditions. Apart from these traditional processing techniques, HME (hot-melt extrusion) has a number of advantages, mainly: (a) it is a non-solvent technology, therefore it is environmentally friendly and cost-effective; and (b) from a commercial point of view, HME can be carried out as a continuous process, thereby allowing the efficient scale-up of production (Chokshi et al., 2005). HME allows the completion of several operations easily with one piece of equipment. Combined with a computer, the equipment can control the technical parameters automatically and precisely, and allow both automation and large-scale manufacturing. The extruder consists of two distinct parts: one is a conveying system, it not only

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0378-5173/$ – see front matter.
doi:10.1016/j.ijpharm.2008.03.040

transports the material, but also helps the materials distributing and mixing; the other part is the die system, it forms the material into required shape. The system involves adding the mixture of drug and adjuvant to a hopper, and then transporting it into the temperature-controlled extrusion channel. During axial movement, the mixture is melted, cut, dispersed, extruded, disposed, and mixed again simultaneously. When the material is sheared between the rotating screws and the wall of the barrel, due to friction, a great deal of heat is generated for melting or fusing; also electric or liquid heaters mounted on the barrel may supply additional heat (Breitenbach, 2002). The results are that each material becomes finer while the mixture becomes more uniform; the collected mixture is converted into a molecular state, molecular level SD is achieved within only a few minutes (Zheng et al., 2006).

Except for SD, research into new techniques is being carried out to enhance drug dissolution. Recently, filling semi-solid or liquid matrices into hard capsules is being used more often because it has several advantages, such as: weight and content uniformity, improvement in the dissolution of poorly water-soluble drugs, and creation of a dust-free manufacturing process (Walker et al., 1980). In addition, excellent bioavailability of semi-solid dispersions has also been reported (Yüksel et al., 2003). However, no such preparation has been reported for the combination of technologies involving SD and semi-solid filling into hard capsules. Thus, for optimum dissolution and bioavailability, apart from the HME technology mentioned above, this study has investigated another approach involving the mixing of a SD powder with other materials, and transferring the mixture to hard HPMC (hydroxypropyl methyl cellulose) capsules, to produce semi-solid capsules (SSC). The semi-solid matrix could produce the highest dissolution of NMD from nimodipine solid dispersion (NMD-SD); also, by controlling the type and amount of carriers, final preparations can be semi-solid at room temperature, consequently, it is easy to store and transport them due to their poor flow properties; alternatively, their excellent flow ability under high temperature makes the filling of hard capsules easy.

The specific objective of the present work was to improve the dissolution and, therefore, the bioavailability of poorly water-soluble drug NMD by a combination of technologies involving SD and semi-solid matrix filling into hard HPMC capsules. Firstly, a SD consisting of NMD, Plasdone-S630 (vinyl pyrrolidone-vinyl acetate copolymer) and Eudragit-E100 (aminoacryl methacrylate copolymer) was prepared by HME. Then, using this SD, a semi-solid system with PEG400 (polyethylene glycol 400) and Plasdone-S630 as vehicles, and PEG6000 (polyethylene glycol 6000) as the suspending agent was employed, and finally, the semi-solid mixture was transferred to hard HPMC capsules. The final preparation was evaluated with regard to its in vitro dissolution, dispersal homogenicity, and bioavailability in beagle dogs compared with the commercially available tablets (Nimotop®).

2. Materials and methods

2.1. Materials

NMD and nitrendipine (internal standard) were obtained from Zhengzhou Ruikang Pharmaceutical Company (Zhengzhou, Henan, China). Plasdone-S630 was purchased from ISP Technologies Inc. (USA). Eudragit-E100 was obtained from Lianyungang Huarui Chemical Engineering Company (Lianyungang, Jiangsu, China). PEG400 and PEG6000 were supplied by Tianjin Bodi Chemicals Co. Ltd. (Tianjin, China). Commercially available tablets Nimotop® (30 mg), used as the reference, were provided by Bayer Healthcare Company Ltd. (H20003010 Beijing, China). All other reagents were either of analytical or chromatographic grade. The HPMC capsules (size 2) were presented by Capsugel® (Pfizer Inc. Shuzhou, China).

Table 1
Formulations of NMD-SD

Formulation no.	NMD (%)	Eudragit-E100 (%)	Plasdone-S630 (%)
SD_0	50	50	0
SD_1	50	40	10
SD_2	50	30	20

2.2. Determination of equilibrium solubility

NMD is light-sensitive. When exposed to UV light (360 nm, 300 lux), the degradation half-life of NMD in aqueous solutions is 16, and 56 h in daylight (Jackobsen et al., 1986). Hence, to prevent the photodecomposition of NMD, the experiments were all performed under low-intensity yellow light.

An excess of NMD was added to 0.1 mol L^{-1} HCl, acetate buffer at pH 4.5, purified water, 0.9% NaCl aq., and phosphate buffers at pH 6.8, 7.2. After shaking for 72 h at 37 °C, samples were withdrawn, passed through 0.45 μm cellulose acetate-type membrane filters, diluted with medium, and assayed by UV spectrophotometry (UV-7504, UV/Vis is spectrophotometer, Xinmao Instrument Company, Shanghai, China) at 356 nm.

2.3. Preparation of NMD-SD

Each physical mixture was extruded using a Coperion KEYA TE-20 (Nanjing, China) twin-screw extruder. The temperature of the extruder barrel zones and die were set as follows using external temperature controllers: Zone 1 = 120 °C, Zone 2 = 130 °C, Zone 3 = 130 °C, Zone 4 = 130 °C and Die = 70 °C. A 5 mm cylindrical die and a screw speed of 36 rpm were employed. About 5 min after filling the hopper with the physical mixture, materials were extruded from the die. The extruded materials were stored in a refrigerator at −20 °C for 4 h, then pulverized and passed through a no. 120 mesh sieve. Physical mixtures were prepared by gentle mixing with a pestle in a porcelain mortar for 5 min. For SD_1, 3 batches of SD powder were prepared, and the R.S.D.% of the contents was 1.91%. The NMD-SD formulations are summarized in Table 1.

2.4. Preparation of nimodipine semi-solid capsules (NMD-SSC)

The calculated amounts of PEG400, Plasdone-S630 and PEG6000 were weighed and mixed together in a beaker, then heated on a water bath at 80 °C with continuous stirring. After the Plasdone-S630 and PEG6000 had melted into the PEG400 completely, NMD-SD_1 (containing NMD 20 mg per capsule) was added slowly. Once the mixture was agitated to a uniform suspended state without air bubbles, it was poured into a plastic injector and trans-

Table 2
Formulations of nimodipine semi-solid dispersion (mg per capsule)

Formulation no.	Nimodipine in SD_1	PEG400	Plasdone-S630	PEG6000
F_1	20	140	40	6
F_2	20	140	60	6
F_3	20	140	80	6
F_4	20	140	100	6
F_5	20	100	80	6
F_6	20	180	80	6
F_7	20	220	80	6
F_8	20	260	80	6

ferred to hard HPMC capsules (size 2) volumetrically. To ensure the efficient flow of the dispersions into capsules, the filling step must be carried out at a temperature above the melting point of PEG6000. Twenty capsules were randomly selected and weighed, and the R.S.D. was 1.87%. Table 2 shows the composition of the semi-solid dispersions consisting of NMD-SD_1, PEG400, Plasdone-S630 and PEG6000.

2.5. Powder X-ray diffraction (PXRD)

PXRD was performed using a D/Max-2400 X-ray Fluorescence Spectrometer (Rigaku, Japan) with a Cu Ka line as the source of radiation. Standard runs using a voltage of 56 KV, a current of 182 mA and a scanning rate of 0.2° min^{-1} over a 2θ range of 3–45° were carried out. Samples were pure NMD, Eudragit-E100, Plasdone-S630, NMD-SD_1 and the physical mixture of NMD-SD_1.

2.6. Differential scanning calorimetry (DSC)

The DSC measurements were carried out using a Thermal Anacyzer-60 WS, Differential Scanning Calorimeter-60 (Shimadzu, Japan). The samples were pure NMD, Eudragit-E100, Plasdone-S630, NMD-SD_1 and the physical mixture of NMD-SD_1. Each sample was heated from 30 to 200 °C, at a rate of 10 °C per minute in an atmosphere of nitrogen.

2.7. Dissolution test

The dissolution medium was 900 mL 0.1 mol L^{-1} HCl. According to USP30-NF25, apparatus 2 was used. Dissolution studies of three NMD-SD formulations, the physical mixture of NMD-SD_1, semi-solid dispersion formulations, the physical mixture of NMD-SD_1 in a semi-solid matrix, pure NMD in hard HPMC capsules (20 mg), and Nimotop® were carried out at 37 °C. Of the total, F_2 was also tested in other media: 900 ml water, acetate buffer at pH 4.5, and phosphate buffers at pH 6.8 and 7.2. The paddle rotation speed was kept at 75 rpm. In all experiments, the absorbance of the carriers at 356 nm was negligible. At 5, 10, 20, 30, 45 and 60 min, 4 mL samples were taken and replaced by fresh medium. Each sample was passed through a 0.45 μm cellulose acetate-type membrane filter, and assayed by UV spectrophotometry at 356 nm. The cumulative percentages of the drug dissolved from the preparations were calculated ($n = 6$).

2.8. Dispersal homogeneity test

NMD semi-solid material were prepared with the amount of F_7, and the final material transferred to tubes, then centrifuged (4000 rpm) for 10 min. The homogeneity of the material was examined by seeing if sediments were present at the bottom of the tubes. Samples were taken from the top and bottom of the tubes and the contents were determined.

2.9. Bioavailability study

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital, China Medical University.

Six beagle dogs were divided into two groups, and a single-dose, randomized, crossover, own control study was applied with a wash-out period of 7 days. The mean weight of the dogs was 8.0 ± 0.5 kg. After fasting overnight, dogs in group 1 received a 120 mg dose of NMD-SSC (F_7) and group 2 received a 120 mg dose of Nimotop® (Bayer, Beijing, China, H20003010) with 200 ml water. Four hours after dosing, the dogs were provided with standard food. On each dosing day, blood samples were taken before and then 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0 and 20.0 h after dosing. Plasma was separated from samples by centrifugation (3000 rpm for 10 min) and stored at −20 °C until required for analysis within 1 month.

For the analysis, 100 μl internal standard (nitrendipine, 1 μg mL^{-1} in mobile phase) was added to 500 μl of each plasma sample. Then 100 μl 0.1 mol L^{-1} NaOH aq. was added. The mixture was vortexed and extracted with 3 ml *n*-hexane-diethyl ether (1:1, v/v) by vortexing for 10 min. After centrifugation at 4000 rpm for 10 min, the organic phase was transferred to another tube and evaporated to dryness at 40 °C using a Centrifugal Concentrator (CentriVap® 78120-03, Labconco, Corp. USA). The residue was reconstituted in 100 μl mobile phase and vortexed for 1 min then 20 μl of the solution was injected into the HPLC system.

A Jasco PU-2080 Intellgent HPLC Pump (Tokyo, Japan) was used. Chromatography was performed on a Diamonsil™ C_{18} column (250 mm × 4.6 mm, 5 μm, Dikma, Technogies), using a mobile phase of methanol–water–acetonitrile (30:30:40, v/v/v). The chromatographic analyses were performed at ambient temperature at a flow-rate of 1.0 mL min^{-1}, with a Jasco UV-2075 Intellgent Detector (Tokyo, Japan) set at 356 nm. The linearity range of this method was 10–1000 ng mL^{-1} with an *r* (correlation coefficient) value of 0.998. The LOD was 2 ng mL^{-1} and the LOQ was 10 ng mL^{-1}. The within-day precision was 6.0% and the between-day precision was 7.6%. The average extraction recovery of NMD was 89.6%.

2.10. Calculation parameters

Using a model independent method, pharmacokinetic parameters were determined from the plasma concentration–time data. The elimination rate constant (K_e) was obtained from the least-squares fitted terminal log-linear portion of the plasma concentration–time profile. The elimination half-life ($t_{1/2}$) was calculated from $0.693/K_e$. The area under the plasma concentration–time curve from time zero to the last measurable plasma concentration point ($t = 20$ h) (AUC_{0-t}) was calculated by the linear trapezoidal method. Extrapolation to time infinity ($AUC_{0-\infty}$) was carried out as follows: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_e$, where C_t is the last measured plasma concentration and K_e is the elimination rate constant.

3. Results and discussion

3.1. Physical characterization of SD

Among the NMD-SD formulations, SD_1 and its physical mixture were studied by PXRD and DSC; also pure NMD, Eudragit-E100 and Plasdone-S630 were tested.

PXRD was used to confirm the loss of drug crystallinity, the results are shown in Fig. 1. Pure NMD has several dominant peaks at 2-theta angles within 30 degrees. In the physical mixture, although

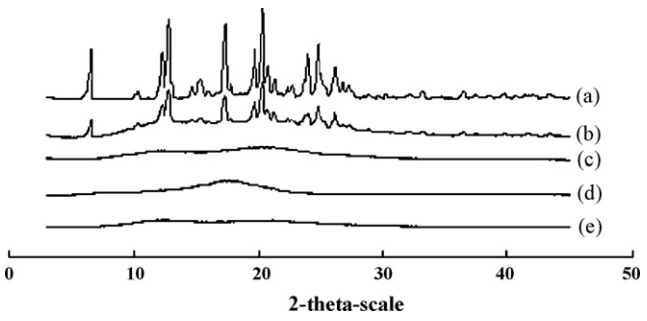

Fig. 1. PXRD patterns: (a) pure NMD; (b) physical mixture of SD_1; (c) SD_1; (d) Eudragit-E100; (e) Plasdone-S630.

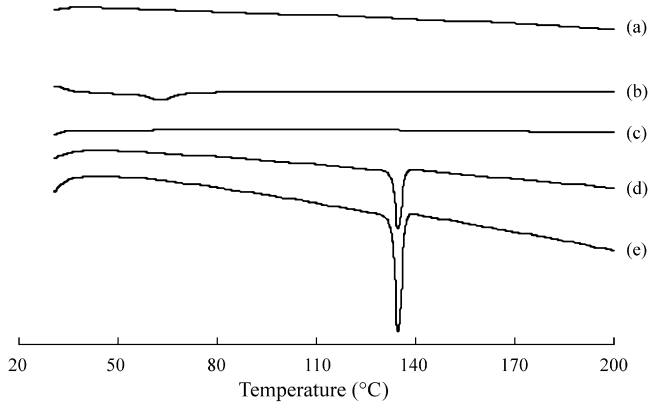

Fig. 2. DSC thermograms: (a) Plasdone-S630; (b) Eudragit-E100; (c) SD_1; (d) physical mixture of SD_1; (e) pure NMD.

these peaks were still present, but became much smaller, indicating that the crystallinity of NMD did not change in the physical mixture. After extrusion, no detectable diffraction peak of NMD was observed, suggesting that NMD was in an amorphous state in SD_1.

Another indication of the crystalline status of NMD in the solid dispersion can be obtained from DSC. Fig. 2 shows the DSC thermograms over the temperature range 30–200 °C. The DSC recording of the pure NMD exhibits a sharp endothermic peak around 127 °C, corresponding to a melting point of 124–128 °C. The physical mixture had a relatively small endothermic peak around 126 °C, however the solid dispersion resulted in a complete suppression of the drug fusion peak. The DSC data show that the solid dispersion technique produced more extensive interactions between NMD and the carriers. The interactions were mainly caused by the high pressure during the extrusion process. The materials were melted, cut, dispersed, disposed, and re-mixed. In the carriers, NMD was completely converted into an amorphous state, which could increase the solubility markedly. It was also found that the mixture of Plasdone-S630 and Eudragit-E100 was an excellent solvent for NMD.

3.2. In vitro dissolution

3.2.1. Dissolution from NMD-SD formulations

NMD is a typical poorly water-soluble drug with an equilibrium solubility of 8.40 μg mL^{-1} in 0.1 mol L^{-1} HCl, 3.14 μg mL^{-1} in acetate buffer at pH 4.5, 3.86 μg mL^{-1} in purified water, 3.07 μg mL^{-1} in 0.9% NaCl aq., 3.19 μg mL^{-1} in phosphate buffer at pH 6.8 and 7.13 μg mL^{-1} in phosphate buffer at pH 7.2 at 37 °C. Fig. 3

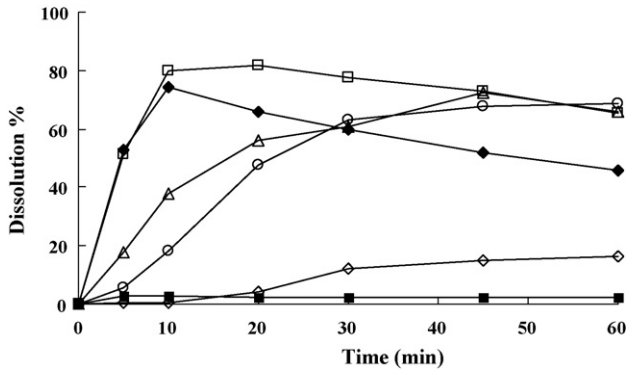

Fig. 3. Drug dissolution profile in 0.1 mol L^{-1} HCl: (♦) SD_0; (□) SD_1; (△) SD_2; (■) pure NMD; (◊) physical mixture of SD_1; (○) Nimotop®.

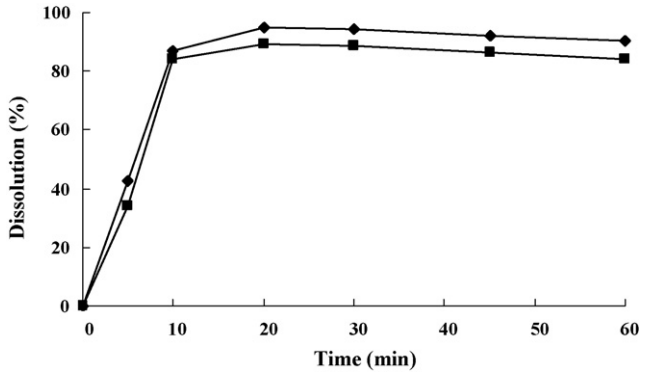

Fig. 4. Dissolution profile (in 0.1 mol L^{-1} HCl). (♦) F_7; (■) physical mixture of F_7.

shows that in 0.1 mol L^{-1} HCl, its dissolution was quite low (nearly zero within 60 min). After mixing NMD with Eudragit-E100 and Plasdone-S630, the dissolution slightly increased (12% in 30 min). However, after being prepared as a SD, substantially was improved (about 80% in 10 min), and became greater than the dissolution of Nimotop® (little more than 60% in 30 min). This is mainly because in the SD, drug was effectively transformed into an amorphous state, as shown in Figs. 1 and 2. However, the improvement was not linear with the increase in Plasdone-S630. As seen in Fig. 3, among the three SD formulations, the best one was formulation SD_1. For the formulation SD_0 (without Plasdone-S630), because of supersaturation, NMD recrystallized quickly (10 min after administration). In contrast, the drug in formulation SD_2 was released relatively slowly, and only 60% had dissolved within 30 min. This shows that the addition of Plasdone-S630, which is a polymer with a molecular weight 58000Dalton (Ghebremeskel et al., 2007), should be maintained at a certain level. If too little is present, NMD does not dissolve completely in the medium and recrystallizes quickly; however, if too much is present, a fairly pycnotic grid structure of the polymer hinders the dissolution of NMD. Therefore, only at a certain ratio of drug/Plasdone-S630 (5:1 in this approach), can Plasdone-S630 fully contribute to the solubilization.

3.2.2. Dissolution from NMD-SSC formulations

Although the SD system consisting of NMD, Eudragit-E100 and Plasdone-S630 significantly enhanced the solubility of NMD, the dissolution rate of the best formulation (SD_1) was only a little more than 80% at 30 min. Therefore, the present study developed a semi-solid system as a post-process to SD. It has been reported that PEG can enhance the solubility of NMD (Guo et al., 2004), so on the basis of the formulation SD_1, a series of NMD-SSC formulations were prepared, with PEG400 and Plasdone-S630 as carriers, and PEG6000 as the suspending agent. In this way, much better solubilization was obtained. To discover which technology was best, the physical mixture of F_7 was also prepared, namely, dispersed the physical mixture of SD_1 in the melt mixture of PEGs and Plasdone-S630, and followed by transferring the uniform material to hard HPMC capsules (containing NMD 20 mg per capsule). Fig. 4 shows that the dissolution of F_7 was better (about 95% at 20 min) compared with its physical mixture (about 90% at 20 min). This means that, to obtain super solubilization, the two technologies, SD and semi-solid filling in hard capsules, must be combined. With regard to which is more important, initial stability studies indicated that after 6 months storage at room temperature with an RH of 25%, the dissolution of SSC containing SD_1 was better than SSC containing the physical mixture of SD_1. The effect of Plasdone-S630 on the dissolution of NMD is clearly apparent from Fig. 5. When the amount of PEG400 was constant (140 mg per capsule), as Plasdone-

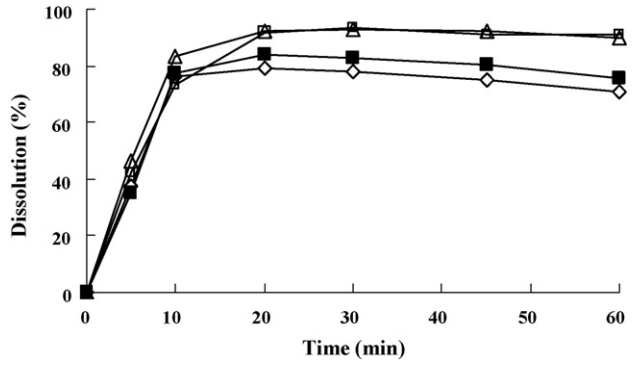

Fig. 5. NMD dissolution of different NMD-SSC formulations (prepared from SD_1) in 0.1 mol L^{-1} HCl. (◊) F_1 (PEG400/Plasdone-S630 140:40); (■) F_2 (PEG400/Plasdone-S630 140:60); (△) F_3 (PEG400/Plasdone-S630 140:80); (□) F_4 (PEG400/Plasdone-S630 140:100).

S630 increased from 40 to 80 mg per capsule, drug dissolution was improved. However, when Plasdone-S630 increased to more than 80 mg, there was no clear improvement. The same phenomenon is also seen in Fig. 6. When the amount of Plasdone-S630 was constant (80 mg per capsule), if PEG400 was more than 140 mg per capsule, no solubilization occurred. F_3, F_4, F_6, F_7 and F_8 exhibited the best drug dissolution among all formulations. Therefore, only the optimum ratio of PEG400 to Plasdone-S630 in NMD-SSC could produce the highest drug dissolution. It is highly likely that, since PEG400 is a polymer with a low molecular weight, several molecules surround one NMD molecule, whereas, as a high molecular weight polymer, Plasdone-S630 may form a grid structure in the dissolution medium. Initially, molecules of the drug (NMD) interact with PEG400 to form small units, and then these units enter the holes which are formed by the grid structure of Plasdone-S630. Finally, the mixed carriers produce a novel solubilization of NMD.

From the dissolution behavior, the final preparation, which is semi-solid under room temperature, melts completely within 10 min in dissolution medium (37 °C). This indicates that after dispersing SD powder in semi-solid matrix, the drug may be absorbed quickly; thereby the oral bioavailability is significantly enhanced.

3.2.3. Dissolution from NMD-SSC in different media

Although the drug dissolved from NMD-SSC completely in 0.1 mol l^{-1} HCl, the pH of the gastrointestinal tract cannot always be maintained at this level. As we know, it is low between meals and high during sleeping. After eating or drinking, the pH of the stomach may increase to 3, sometime even 5. The pH in the small intestine

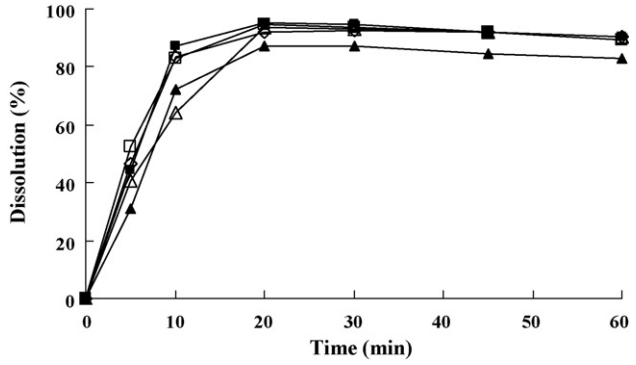

Fig. 6. NMD dissolution of different NMD-SSC formulations (prepared from SD_1) in 0.1 mol L^{-1} HCl. (◊) F_3 (PEG400/Plasdone-S630 140:80); (▲) F_5 (PEG400/Plasdone-S630 100:80); (△) F_6 (PEG400/Plasdone-S630 180:80); (■) F_7 (PEG400/Plasdone-S630 220:80); (□) F_8 (PEG400/Plasdone-S630 260:80).

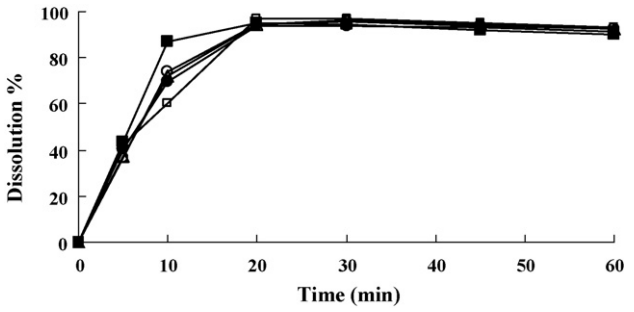

Fig. 7. Dissolution profile of NMD from F_7 of the NMD-SSC formulation (prepared from SD_1) in different dissolution media. (■) in 0.1 mol L^{-1} HCl; (●) acetate buffer at pH 4.5; (△) phosphate buffer at pH 6.8; (□) water; (○) phosphate buffer at pH 7.2.

Table 3
Content determination of centrifuged samples ($n = 3$)

Samples	1 (%)	2 (%)	3 (%)	R.S.D.%
Top of tube	5.62	5.73	5.64	1.04
Bottom of tube	5.59	5.70	5.71	1.18

is between 5 and 7. Usually, 30 min after taking a drug, it enters the small intestine. Eudragit-E100 is only soluble in a highly acidic medium (Vokoboinikova et al., 2005), thus, pH-independence of NMD from SSC is wanted.

As seen in Fig. 7, NMD from SSC shows a rapid, pH-independent dissolution behavior. SSC containing NMD-SD_1 ensures about 95% dissolution of the drug within 20 min in every medium. This indicates that the amount of Eudragit-E100 in the formulation is acceptable; a difference in the pH of the gastrointestinal tract cannot influence the absorption of NMD. There is an additional phenomenon, in Fig. 3, recrystallization is clearly apparent, which cannot be seen in Fig. 7. This suggests that using PEG400 and Plasdone-S630 together, can inhibit the aggregation of consecutive NMD molecules effectively, this prevents the hydrophobic drug from crystallizing in the gastrointestinal tract. Hence, effective absorption is obtained.

3.2.4. Dispersal homogeneity test

After the samples were centrifuged (4000 rpm, 10 min), no precipitation was observed at the bottom of the tube. For farther verification, from the top and bottom of the tube, collected semi-solid samples, and determined their contents. The results are shown in Table 3. It can be seen that there was no difference in the contents between the top and bottom of the tube. In other words, this semi-solid preparation was a uniform and stable system.

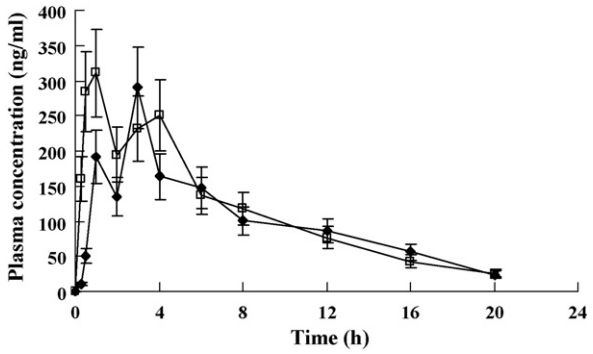

Fig. 8. Mean NMD plasma profiles from a single-dose (120 mg), randomized, crossover bioavailability study comparing two NMD dosage forms ($n = 6$). (♦) Nimotop®; (□) NMD-SSC.

Table 4
Pharmacokinetic parameters of NMD in different dosage forms ($n = 6$)

Simple	C_{max} (ng mL^{-1})	t_{max} (h)	AUC_{0-20} (ng h mL^{-1})	$AUC_{0-\infty}$ (ng h mL^{-1})	$t_{1/2}$ (h)
NMD-SSC	321 ± 78	1.3 ± 0.3	2140 ± 405	2488 ± 433	4.5 ± 0.8
Nimotop®	293 ± 73	3.1 ± 0.4	1986 ± 371	2272 ± 398	4.2 ± 0.5

Each value represents the mean ± S.D.

3.3. Bioavailability study

The bioavailability study of the different dosage forms of NMD was conducted in beagle dogs. In NMD-SSC formulations F_7 was selected for the test, with Nimotop® as a reference. The plasma concentration versus time curves for both test and reference materials are shown in Fig. 8, and the pharmacokinetic parameters are given in Table 4. From the results, it can be seen that there was no statistical difference between the $AUC_{0-\infty}$ values of the two dosage forms (NMD-SSC, 2488 ± 433 ng h mL^{-1}; Nimotop®, 2272 ± 398 ng h mL^{-1}, $P > 0.05$). The mean peak concentration (C_{max}) of NMD-SSC was 321 ± 78 ng mL^{-1}, and Nimotop® was almost identical, with a value of 293 ± 73 ng mL^{-1} ($P > 0.05$). However, the mean time to reach the peak concentration (t_{max}) for the test was 1.3 ± 0.3 h, much earlier than the reference (3.1 ± 0.4 h) ($P < 0.05$). By means of statistical analysis of the $AUC_{0-\infty}$ and C_{max} datum, the two dosage forms were shown to have similar bioavailability.

In this study, the $t_{1/2}$ of both test and reference determined in beagle dogs was more than 4 h. In addition, a double peak was found both in two plasma concentration–time curves. These can be explained by the fact that a large amount of NMD (120 mg) was administered. Usually, a preparation can stay in the stomach for about 30 min, but for beagle dogs, it is impossible to absorb 120 mg NMD within such a short time. About 30 min after taking the drug, the preparation begins to enter the intestinal tract, but there is still undissolved drug in the preparation. On coming into contact with bile, the lipophilic NMD might be taken up by specific proteins, and then reabsorbed by the small intestine, so a second peak appears. However, the C_{max} of the reference was on the second peak, while the C_{max} of test was on the first one. This is probably because of the difference between drug release behaviors. Nimotop® releases gradually, and completely disappears within 20 min in 900 ml 0.1 mol L^{-1} HCl, as observed in the dissolution test. Because of the slower dissolution in stomach of the tablets, a lot of the drug enters the small intestine. Due to reabsorption, the C_{max} was on the latter peak. In contrast, as a semi-solid preparation, NMD-SSC is semi-solid at room temperature, and it becomes liquid within about 10 min after being administered. Mainly in the stomach, the carriers are leaking and extending while the capsule is breaking down. Because there is a little hydrophobic excipient (Eudragit-E100) in hydrophilic carriers (PEG400 and Plasdone-S630), the preparation cannot build up into bolus. So the carriers are dispersed uniformly, and the drug is able to come into contact with biomembranes quickly. In addition, besides passive transport, NMD may also be absorbed with the help of PEG400. It has been reported that low concentration of PEG400 can increase the permeability of the gastrointestinal epithelium (Schulze et al., 2003). So, SSC could contribute NMD to an early C_{max} (1.3 h post-dosing). Hence, there is a possibility that at a lower dosage, the bioavailability of NMD-SSC may be higher than that of Nimotop®.

4. Conclusions

The present study shows that it is possible to improve the dissolution of the hydrophobic drug NMD by using SD and transferring SD powder to semi-solid capsules (SSC). Using X-ray diffraction and DSC analysis, both Eudragit-E100 and Plasdone-S630 were found to be compatible with NMD in the SD system. HME was applied to disperse drugs to a molecular level in a given matrix. Using the semi-solid system, not only a rapid, pH-independent dissolution of NMD was obtained, but recrystallization was also prevented. The bioavailability study in beagle dogs suggests that NMD-SSC and Nimotop® exhibit identical bioavailabilities, while NMD-SSC has a faster absorption. It can bee seen that combination of the techniques of SD and the semi-solid filling into hard HPMC capsules is an excellent way to enhance the dissolution and bioavailability of poorly water-soluble drugs.

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