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Research paper

A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs

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ABSTRACT

The objectives of the present work were, first, to develop a new solid self-microemulsifying drug delivery system (SMEDDS) for oral poorly water-soluble drugs such as nimodipine; and second, to evaluate its oral bioavailability in healthy rabbits. The liquid SMEDDS consisted of ethyl oleate, Labrasol®, Cremophor® RH 40 and nimodipine. The solid SMEDDS was prepared by spray-drying the liquid SMEDDS in a laboratory spray dryer, using dextran as solid carrier. The imaging of TEM and photo correlation spectroscopy revealed no difference in the droplet size of reconstituted microemulsion between both SMEDDS. Solid state characterization of the solid SMEDDS was performed by SEM, DSC, and X-ray powder diffraction. The same dose of nimodipine in the solid SMEDDS and in the liquid SMEDDS resulted in similar AUC and C_{max} values, but the maximum absorption was retarded by the solid SMEDDS. AUC and C_{max} after oral administration of the solid SMEDDS were 2.6- and 6.6-fold higher, respectively, compared with those of the conventional tablet. These results demonstrate that the solid SMEDDS may preserve an improved bioavailability with releasing microemulsion lipid droplets from the formulation in vivo. Thus, this solid self-microemulsifying system may provide a useful solid dosage form for oral poorly water-soluble drugs.

1. Introduction

Nowadays, the use of high throughput screening in drug discovery has led to large proportions of new drug candidates having poor water solubility and hence poor and highly variable oral bioavailability. To overcome this barrier many formulation strategies, such as micronization, complexation with cyclodextrin [1], solid dispersions [2] and nanosuspensions [3] were developed.

In recent years, self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) [4–10] have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs [6,7]. SEDDS and SMEDDS are normally prepared either as liquids or encapsulated in soft gelatin capsules, which have some shortcomings especially in the manufacturing process, leading to high production costs [11]. Moreover, these dosage forms may be inconvenient to use and incompatibility problems with the shells of the soft gelatin are usual [12]. Incorporation of a liquid self-emulsifying formulation into a solid dosage form may combine the advantages of SEDDS with those of a solid dosage form and overcome the disadvantages of liquid formulations described above [13].

Recently, increasing research has focused on this area. A solid-state microemulsion for the delivery of cyclosporine was prepared by coating a pre-microemulsion with enteric coating materials [14]. A eutectic-based self-nanoemulsified drug delivery system of ubiquinone was incorporated into a tablet dosage form, using blends of maltodextrin, modified povidone and microcrystalline cellulose (MCC) [15]. The release of lipid formulations from this tablet dosage form could be controlled by the addition of MCC of finer particle size and colloidal silicates [13]. Pellets containing self-emulsifying mixtures were prepared by extrusion/spheronization [12,16–18] or wet granulation in high-shear mixer [11], with inclusion of MCC and lactose. The in vitro release of the drug from such pellets could be controlled by coating with a polymer film [19]. However, these solid SEDDS were almost prepared by extrusion/spheronization, containing water-insoluble materials as solid carriers. There are a limited number of publications reporting the oral bioavailability of solid SEDDS [11,12,14]. Additionally, few investigations on reconstitution properties of solid SEDDS have been performed.

Spray drying has been employed to prepare dry emulsions by removing water from an ordinary emulsion containing a water-soluble solid carrier [20–22]. The initial emulsion mostly consisted of oil, water and an ordinary emulsifying agent, and the droplet size of reconstituted emulsions from dry emulsions was usually more than 1 μm. Nimodipine, a second-generation dihydropyridine calcium antagonist with therapeutic indications for cerebrovascular spasm, stroke and migraine is poorly water-

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soluble, and has low bioavailability for oral administration [23,24].

The objectives of the present study were therefore: (1) to develop a new solid SMEDDS of nimodipine by spray drying, using dextran 40 as water-soluble solid carrier. Reconstitution properties of the spray dried powders were investigated and correlated to solid state characterization of the powders performed by Scanning Electron Microscope (SEM), Differential Scanning Calorimetry (DSC) and X-ray powder diffraction; (2) to determine whether the solid SMEDDS maintained the absorption characteristics of the liquid SMEDDS. A comparative bioavailability study was performed in fasted rabbits with the solid SMEDDS, the liquid SMEDDS and a conventional tablet of nimodipine.

2. Materials and methods

2.1. Materials

Nimodipine and nimodipine tablet were purchased from Kaifeng Pharmaceutical Corp. (Henan, China). Ethyl oleate was purchased from Shanghai Chemical Reagent Corporation (Shanghai, China). Labrasol® (saturated polyglycolysed C_6–C_{14} glycerides, where C_8 is 58.1% and C_{10} is 39.8%) was obtained from Gattefossé Corp. (France). Polyoxyl 40 hydrogenated castor oil 40 (Cremophor® RH 40) was obtained from BASF Corp. (Ludwigshafen, Germany). Dextran 40 (average molecular weight 40,000) was purchased from Shanghai Huamao Pharmaceutical Company (Shanghai, China). Other chemicals were of HPLC or analytical grade.

2.2. Methods

2.2.1. Preparation of liquid SMEDDS

Based on previous researches [25], it was established that the liquid SMEDDS consisted of ethyl oleate, Cremophor® RH 40, Labrasol®, and nimodipine (60:28:7:5, w/w). Briefly, nimodipine was dispersed into the mixture of oil and surfactants. Then, the components were mixed by gentle stirring and vortex mixing at 37 °C until nimodipine was completely dissolved. The mixture was stored at room temperature until used.

2.2.2. Preparation of solid SMEDDS

Dextran 40 (10.0 g) was dissolved in 100 ml distilled water by magnetic stirring. The liquid SMEDDS (10.0 g) was then added with constant stirring, and the solution was kept at 50 °C for 10 min to obtain a good o/w emulsion. The emulsion was spray dried with a Büchi mini spray dryer B-191 apparatus (Büchi, Switzerland) under the following conditions: inlet temperature, 120 °C; outlet temperature, 70 °C; aspiration, 85%; drying air flow, 500 NL/h; feeding rate of the emulsion, 5 ml/min.

2.2.3. Reconstitution properties of solid SMEDDS

2.2.3.1. Reconstitution. Liquid SMEDDS (50 μl) and solid SMEDDS (100 mg) prepared as described above were dispersed with 10 ml distilled water, respectively, by vortex mixing (30 s), and then incubated for 30 min at 25 °C.

2.2.3.2. Droplet size of reconstituted microemulsions. The average droplet size, size distribution and polydispersity index of microemulsions from liquid SMEDDS and from solid SMEDDS were assessed by photo correlation spectroscopy (Nano ZS90, Malvern Instruments, U.K.) at a wavelength of 635.0 nm and a scattering angle of 90° at 25 °C. All studies were repeated three times and the average values were used.

2.2.3.3. Morphology of reconstituted microemulsions. The microstructure of microemulsions from liquid SMEDDS and from solid SMEDDS was investigated by the transmission electron microscope (TEM, Tecnai G2 20, FEI, the Netherlands). TEM was conducted with negative staining of phosphotungstic acid (PTA) solution (1%, w/v) and dried in air at room temperature before loading in the microscope.

2.2.4. Morphological analysis of solid SMEDDS

The outer macroscopic structure of the solid SMEDDS was investigated by SEM with a FEI Sirion-200 scanning electron microscope (FEI, the Netherlands), operating at 10 kV. The sample was fixed on a SEM-stub using double-sided adhesive tape and then coated with a thin layer of gold.

2.2.5. Solid state characterization of solid SMEDDS

2.2.5.1. DSC. The physical state of nimodipine in solid SMEDDS was characterized by the differential scanning calorimetry thermogram analysis (Diamond DSC, PerkinElmer, USA). The samples (about 3.00 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature ramp speed of 5 °C/min and the heat flow from 0 to 180 °C.

2.2.5.2. X-ray powder diffraction. To verify the physical state of nimodipine in solid SMEDDS, X-ray powder scattering measurements were carried out with an X'Pert PRO diffractometer (PANalytical, the Netherlands). A voltage of 40 kV and a current of 40 mA for the generator were applied with Cu as the tube anode material. The solids were exposed to a Cu–K radiation, over a range of 2θ angles from 10°–40°, at an angular speed of 2° (2θ)/min, a sampling interval of 0.02°.

2.2.6. In vitro dissolution test

The dissolution test was undertaken with paddle method in 900 ml of pH 4.5 acetate buffer containing various concentrations of sodium dodecyl sulfate (SDS) at 37 °C with a paddle speed of 75 rpm [26]. The solid SMEDDS containing 20 mg of nimodipine were filled into hard gelatin capsules (capsule No. 00). Samples for analysis were collected at appropriate time intervals through filters and the concentration of nimodipine was determined by reversed phase HPLC (Agilent 1100 series, Agilent, USA). The column was a Lichrospher C_{18} column (5 μm, 4.6 mm ID × 25 cm). A mobile phase consisted of acetonitrile and 0.05 mol/l ammonium acetate (65:35 v/v). The flow rate was 1 ml/min, and the effluents were monitored at 360 nm.

2.2.7. In vivo absorption study

The study was approved by the Ethical Committee of Huazhong University of Science and Technology. Eighteen New Zealand male rabbits, weighting 2.5–3.0 kg, were obtained from the Laboratory Animal Center, Hubei Academy of Preventive Medicine (Wuhan, China). All animals were housed individually in standard cages on a 12 h light-dark cycles and were fed with standard animal chow daily and had free access to drinking water [21].

The rabbits were fasted for 12 h before drug administration but were allowed free access to water. The animals were divided at random into three groups (six animals each), and each animal received one of the following dosage forms: the solid SMEDDS, the liquid SMEDDS and the nimodipine conventional tablet, corresponding to a dose of 20 mg. The formulations were administrated by the oral route with a gastric catheter which was subsequently flushed with 10 ml water [21].

About 2 ml of blood sample was collected through peripheral ear vein into heparinized tubes at designated time intervals after dosing. Plasma was separated by centrifugation (4 °C, 2500 rpm,

15 min) and kept frozen (−70 °C) until analysis. The concentration of nimodipine in rabbit plasma was determined by HPLC as follows: 40 μl of nitrendipine solution as an internal standard (5 μg/ml in methanol) was added into 400 μl of plasma and mixed for 30 s. Then, the plasma samples were extracted with 800 μl acetonitrile ether by vortex-mixing for 10 min and centrifuging at 12,000 rpm for 10 min. The organic layer was transferred to a new tube and evaporated by nitrogen purging and the residue was reconstituted in 100 μl of mobile phase. After vortex-mixing for 10 min, 50 μl of the sample was used for HPLC as described above.

Pharmacokinetic analysis was performed by means of a model-independent method using DAS2.0 computer program (issued by the State Food and Drug Administration of China for pharmacokinetic study). The area under the plasma concentration versus time curve from zero to 12 h ($AUC_{0\rightarrow 12h}$) was calculated using the trapezoidal rule. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were directly obtained from plasma data.

2.2.8. Statistical analysis

All results were expressed as mean ± SD. The data from different formulations were compared for statistical significance by one-way analysis of variance (ANOVA).

3. Results and discussion

3.1. Reconstitution properties of solid SMEDDS

The mean droplet size and polydispersity index of the reconstituted microemulsions are presented in Table 1. As shown in the table, the average droplet sizes of both microemulsions were less than 50 nm. The droplet size of the microemulsion from the solid SMEDDS was slightly increased, but with lack of statistically significant difference, compared to the liquid SMEDDS. At the same time, a broader size distribution (larger polydispersity index) was observed. The similar results are shown in TEM images of the reconstituted microemulsions (Fig. 1). Fig. 1b shows that the spherical droplets from solid SMEDDS were slightly larger than those from liquid SMEDDS (Fig. 1a). From these results, encapsulating the liquid SMEDDS in dextran 40 by spray-drying did not seem to have a remarkable effect on droplet size. The solid SMEDDS preserved the self-emulsification performance of the liquid SMEDDS.

Table 1
Droplet size with polydispersity index of the reconstituted microemulsions (mean ± SD, n = 3)

Formulation	Size (nm)	Polydispersity index
Liquid SMEDDS	41.3 ± 3.1	0.130 ± 0.012
Solid SMEDDS	44.1 ± 4.5	0.247 ± 0.028[a]

[a] $P < 0.05$, when compared with those of liquid SMEDDS by the ANOVA test.

3.2. Morphological analysis of solid SMEDDS

In previous studies on spray drying, some water-soluble materials were used as solid carrier, such as amorphous sucrose, maltodextrine and hydroxypropylmethylcellulose [20–22]. Among these carriers, maltodextrine has the ability to diminish the degree of spray-dried particle agglomeration [21]. In this study, dextran 40 was applied as a solid carrier. According to the SEM images (Fig. 2), the solid SMEDDS consisted of well-separated particles. Moreover, the particle showed a satisfactory regular spherical shape with shallow dents. It is suggested that dextran 40 has the same ability to diminish agglomeration as maltodextrine.

3.3. Solid state characterization of solid SMEDDS

The physical state of nimodipine in the solid SMEDDS was investigated since it would have an important influence on the in vitro and in vivo release characteristics. DSC curves of pure nimodipine, the physical mixture of nimodipine and dextran 40 (2.5: 97.5, w/w), the liquid SMEDDS of nimodipine, and the solid SMEDDS of nimodipine are shown in Fig. 3. Pure nimodipine showed three sharp endothermic peaks at temperatures between 110 and 130 °C (curve a) [24]. Due to the dilution by dextran 40, the physical mixture exhibited up to two small endothermic peaks for nimodipine (curve b). The liquid SMEDDS of nimodipine showed one peak, representing the melting of lipid near 20 °C (curve c). No obvious peaks for nimodipine and lipid were found in the solid SMEDDS of nimodipine (curve d). It might be explained that the melting behavior of the lipid was changed by dextran and the crystallization of nimodipine was inhibited by dextran and surfactants.

From X-ray powder diffractograms shown in Fig. 4, the internal physical state of nimodipine in the solid SMEDDS was further verified. Due to the dilution by dextran, a few peaks appeared in the physical mixture of nimodipine and dextran (curve b). No obvious peaks representing crystals of nimodipine were seen for the solid SMEDDS (curve c).

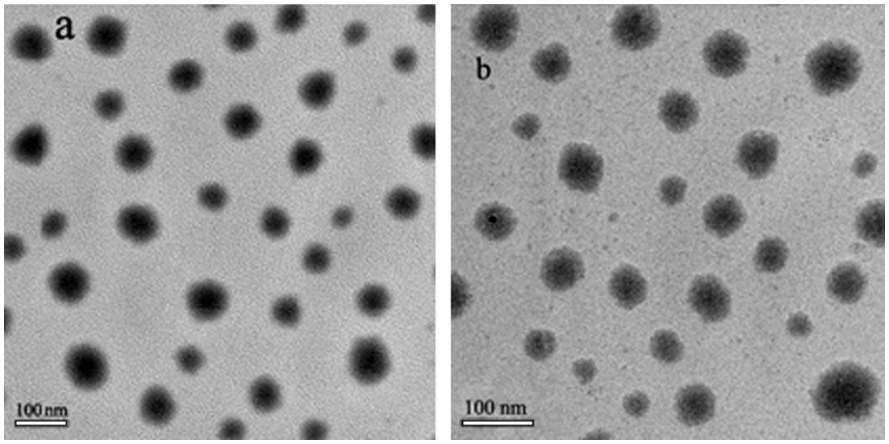

Fig. 1. TEM images of the reconstituted microemulsions from (a) the liquid SMEDDS and (b) the solid SMEDDS, with negative staining of phosphotungstic acid. Bar = 100 nm.

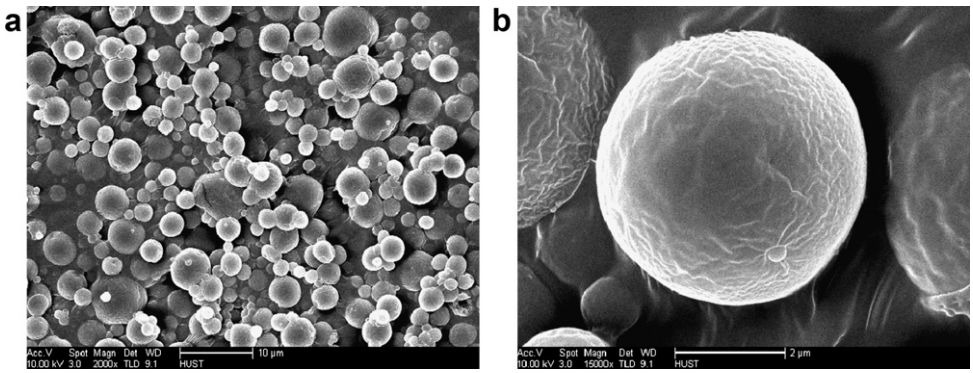

Fig. 2. SEM images of the solid SMEDDS (a: 2000×, bar = 10 μm; b: 15,000×, bar = 2 μm).

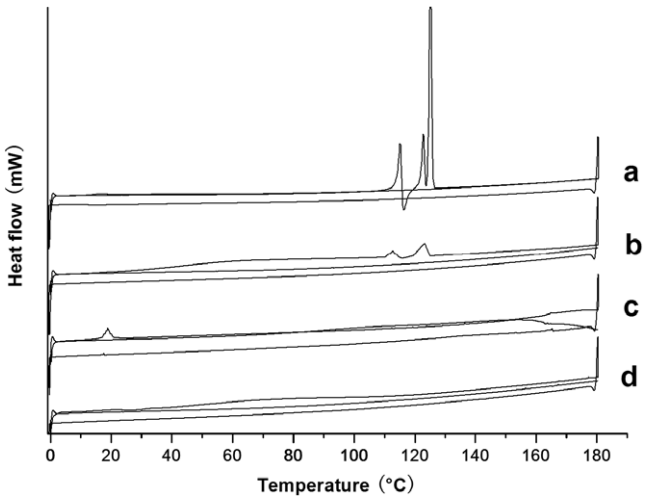

Fig. 3. DSC curves of (a) pure nimodipine powder, (b) physical mixture, (c) the liquid SMEDDS of nimodipine and (d) the solid SMEDDS of nimodipine.

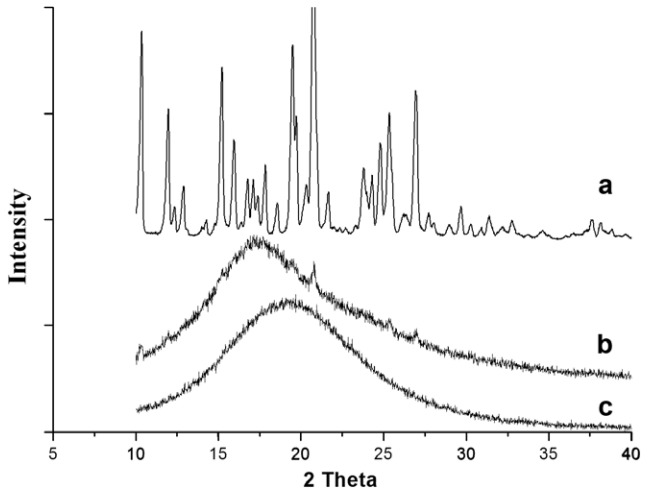

Fig. 4. X-ray powder diffractometry of (a) pure nimodipine powder, (b) physical mixture and (c) the solid SMEDDS of nimodipine.

Therefore, it could be concluded that nimodipine in the solid SMEDDS was in the amorphous or disordered crystalline phase of a molecular dispersion state in the polymer matrix after the fabrication.

3.4. In vitro dissolution test

British Pharmacopoeia (BP) 2000 prescribes pH 4.5 acetate buffer containing 0.3% (w/v) of SDS as the dissolution medium for nimodipine tablets. In this medium, the release of nimodipine from the solid SMEDDS was faster than from the conventional tablet (Fig. 5). When the concentration of SDS in dissolution medium was reduced to 0.05% (w/v), the difference in the release of nimodipine was more obvious ($p < 0.05$). Dissolution from the conventional tablet was improved with increasing amount of SDS in medium ($p < 0.05$). On the other hand, the dissolution of nimodipine from the solid SMEDDS was not influenced by SDS added ($p > 0.05$). Nimodipine from the solid SMEDDS was completely and rapidly dissolved in both medium. Thus, it seemed that the solid SMEDDS might preserve the improvement of in vitro dissolution of SMEDDS. It was also suggested that, a high concentration of SDS in dissolution medium may reduce the discriminative power between the different formulations of poorly water-soluble drug [27].

3.5. In vivo absorption study

The solid SMEDDS administered orally to rabbits were tested versus the same dose of nimodipine (20 mg) in the liquid SMEDDS or the conventional tablet. The mean plasma nimodipine concentrations versus time profiles of the three formulations are shown in Fig. 6. The conventional tablet of nimodipine showed the lowest average nimodipine plasma concentration. Referring to Table 2, it can be observed that the $AUC_{0\rightarrow 12h}$ was approximately two times greater when nimodipine was administered as SMEDDS (solid or liquid) compared to the tablet, and that the areas under the curves for solid SMEDDS and liquid SMEDDS were not statistically different ($p > 0.05$). The mean values of C_{max} for solid SMEDDS and liquid SMEDDS (103.68 and 78.93 ng/ml) were 6.6 and 5.0 times, respectively, greater than that of nimodipine administered as the conventional tablet (15.82 ng/ml). However, the initial rate of absorption from solid formulations (solid SMEDDS and tablet) tended to be slightly lower than from liquid SMEDDS. In part, this was due to the retardation of the dissolution by solid excipients. These results showed that it was possible to improve the bioavailability of a poorly soluble drug (like nimodipine) if given in the solid SMEDDS, and that presenting nimodipine in the form of solid SMEDDS kept the absorption enhancement as high as with liquid SMEDDS.

A previous study showed that the AUC of cyclosporine A given in enteric-coated solid SEDDS was much lower than in the liquid SEDDS and depended on the nature of enteric-coating polymers [14]. It was probably due to the decrease of drug release by enteric coating polymers. On the contrary, a self-emulsifying pellet of progesterone containing MCC as a carrier showed a good in vitro release profile and maintained the improved bioavailability of the

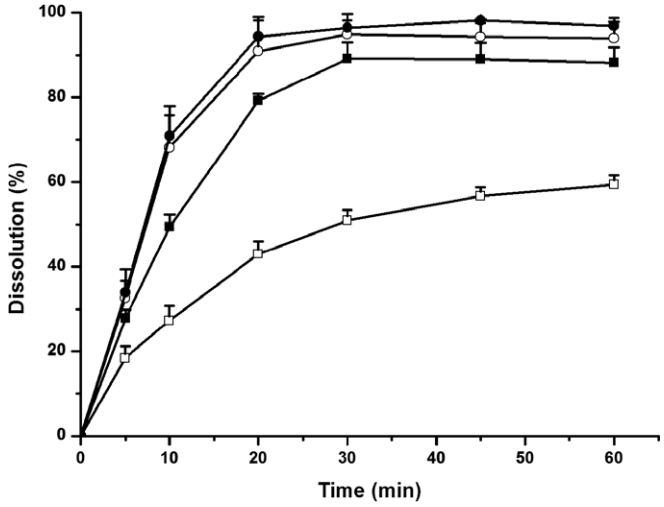

Fig. 5. Dissolution profile of nimodipine from formulations in pH 4.5 acetate buffer containing (a) 0.3% of sodium dodecyl sulfate or (b) 0.05% of sodium dodecyl sulfate. The solid SMEDDS in dissolution medium (a) ● or in dissolution medium (b) ○; the conventional tablet in dissolution medium (a) ■ or in dissolution medium (b) □. Data are expressed as mean ± SD (n = 3).

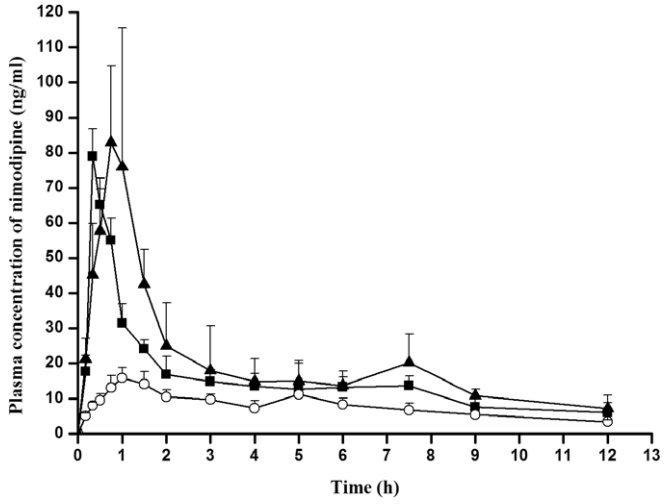

Fig. 6. Plasma concentration-time profile of nimodipine in fasted rabbits after oral administration in self-microemulsifying formulation of 20 mg nimodipine as solid form (solid SMEDDS ▲) and liquid form (liquid SMEDDS ■) and as the conventional tablet (○).

Table 2
Pharmacokinetic parameters after oral administration of nimodipine formulations to rabbits (mean ± SD, n = 6)

Formulation	$AUC_{0\rightarrow 12h}$ (ng h/ml)	C_{max} (ng/ml)	T_{max} (h)
Tablet	94.74 ± 15.15	15.82 ± 2.86	1.00 ± 0.00[c]
Liquid SMEDDS	184.40 ± 13.61[a]	78.93 ± 7.92[b]	0.33 ± 0.00
Solid SMEDDS	242.79 ± 51.81[a]	103.68 ± 15.65[b]	0.83 ± 0.14[c]

[a] $P < 0.05$, when compared with the parameters of tablet by the ANOVA test.
[b] $P < 0.001$, when compared with the parameters of tablet by the ANOVA test.
[c] $P < 0.05$, when compared with the parameters of liquid SMEDDS by the ANOVA test.

liquid SEDDS [12]. In the present study, the solid SMEDDS containing dextran 40 as a carrier has a faster in vitro release rate and a higher in vivo absorption compared to the conventional tablet. From these results, it was suggested that the absorption characteristics of solid SEDDS might be influenced by the solid carrier used. In addition, our preliminary investigation showed different carriers that resulted in different rates of drug in vitro release. The rate-limiting process of absorption of BCS class II drug like nimodipine is the drug dissolution step [28] and biorelevant dissolution tests can be used to predict differences in bioavailability among different formulations [29]. It would be useful to choose an appropriate solid carrier through the in vitro dissolution test.

SMEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug, which form fine oil-in-water (O/W) microemulsions under gentle agitation followed by dilution in aqueous media [8]. In such a system, the lipophilic drug is present in solution or in small droplets of oil, leading to the elimination of the dissolution step and the maintenance of drug in a dissolved state during transport to the unstirred water layer of the intestinal membrane [10]. The presence of surfactant (Labrasol®) [30] may affect the bioavailability of the drug in SMEDDS. Furthermore, the liquid SMEDDS is likely to be a type III lipid formulation in the lipid formulation classification system [8]. In fact, the main advantage of lipid formulation is maintaining the drug in solution throughout its period in the GI tract [31]. In this study, the solid SMEDDS was equally bioequivalent in rabbits to the same drug self-microemulsifying system administered as a liquid dosage form. It was probably due to the fact that the solid SMEDDS containing dextran 40 as a solid carrier preserved the self-emulsification performance of the liquid SMEDDS and formed fine O/W microemulsion in the GI tract, where the drug was presented in small droplets of oil.

4. Conclusion

In the present investigation, the solid SMEDDS of nimodipine was prepared by spray drying, using water-soluble dextran 40 as solid carrier. The solid SMEDDS consisted of well-separated spherical particles with shallow dents and preserved the self-emulsification performance of the liquid SMEDDS. Both DSC measurements and X-ray diffraction analysis suggested that nimodipine in the solid SMEDDS was in the amorphous or molecular dispersion state. In vitro dissolution test showed that the solid SMEDDS had a faster in vitro release rate than the conventional tablet. In vivo absorption study showed that presenting nimodipine in the form of solid SMEDDS kept the absorption enhancement as high as with liquid SMEDDS. Thus, this solid self-microemulsifying system may provide a useful solid dosage form for oral poorly water-soluble drugs.

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