International Journal of Pharmaceutics 420 (2011) 412–418

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Comparison of solid self-microemulsifying drug delivery system (solid SMEDDS) prepared with hydrophilic and hydrophobic solid carrier

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ARTICLE INFO

Article history:
Received 15 July 2011
Received in revised form 30 August 2011
Accepted 11 September 2011
Available online 16 September 2011

Keywords:
Solid self-emulsifying drug delivery system
Dextran
Colloidal silica
Crystalline property
Dissolution
Oral bioavailability

ABSTRACT

In order to compare the effects of hydrophilic and hydrophobic solid carrier on the formation of solid self-microemulsifying drug delivery system (SMEDDS), two solid SMEDDS formulations were prepared by spray-drying the solutions containing liquid SMEDDS and solid carriers. Colloidal silica and dextran were used as a hydrophobic and a hydrophilic carrier, respectively. The liquid SMEDDS, composed of Labrafil M 1944 CS/Labrasol/Trasncutol HP (12.5/80/7.5%) with 2% w/v flurbiprofen, gave a *z*-average diameter of about 100 nm. Colloidal silica produced an excellent conventional solid SMEDDS in which the liquid SMEDDS was absorbed onto its surfaces. It gave a microemulsion droplet size similar to that of the liquid SMEDDS (about 100 nm) which was smaller than the other solid SMEDDS formulation. In the solid SMEDDS prepared with dextran, liquid SMEDDS was not absorbed onto the surfaces of carrier but formed a kind of nano-sized microcapsule with carrier. However, the drug was in an amorphous state in two solid SMEDDS formulations. Similarly, they greatly improved the dissolution rate and oral bioavailability of flurbiprofen in rats due to the fast spontaneous emulsion formation and the decreased droplet size. Thus, except appearance, hydrophilic carrier (dextran) and hydrophobic carrier (colloidal silica) hardly affected the formation of solid SMEDDS such as crystalline properties, dissolution and oral bioavailability.

1. Introduction

Over recent years, much attention has been focused on lipid-microemulsion formulations, with particular emphasis on liquid self-microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs (Balakrishnan et al., 2009b; Cui et al., 2009; Woo et al., 2008). However, these delivery systems had a few limitations, such as stability, the manufacturing methods, the interaction between the filling and the capsule shell, and the storage temperature (Nazzal et al., 2002). When the product is kept at lower temperatures, there may be some precipitation of the active ingredient and/or the excipients. Therefore, the precipitated materials should be dissolved again when warmed to room temperature or the drug will not be present in solution or as a fine emulsion droplet (Woo et al., 2008). Moreover, its efficiency is dependent upon a moist environment (Chen et al., 2008). Thus, solid SMEDDS should be carefully explored as a means of overcoming these problems.

Solid SMEDDS, one of the lipid-based drug delivery systems prepared by the incorporation of liquid excipients into powders by solidification, is a promising drug delivery system for poorly water-soluble compounds as it combines the advantages of liquid SMEDDS (solubility and bioavailability enhancement) with those of solid dosage forms (high stability with various dosage forms options) (Nazzal and Khan, 2006; Wang et al., 2009). Solid SMEDDS produce oil-in-water microemulsions with droplet sizes of less than 200 nm upon mild agitation in aqueous media (such as gastrointestinal fluids) (Tang et al., 2008; Wang et al., 2009). These fine microemulsion droplets have the advantage of presenting the drug in a dissolved form with a large interfacial surface area for drug absorption, which results in an enhanced and more uniform and reproducible bioavailability (Rao and Shao, 2008). The spray-drying technique using colloidal silica as a solid carrier has generally been employed to prepare solid SMEDDS (Balakrishnan et al., 2009a; Yi et al., 2008). Furthermore, most of the previous studies only focused on solid SMEDDS prepared with colloidal silica. Thus, there is a lack of knowledge on the effects of different types of solid carriers on

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doi:10.1016/j.ijpharm.2011.09.007

the formation of solid SMEDDS, although carriers are essential in the development of a desirable solid SMEDDS.

Therefore, in this study, in order to compare the effects of hydrophilic and hydrophobic solid carrier on the formation of solid self-microemulsifying drug delivery system (SMEDDS), two solid SMEDDS formulations were prepared by spray-drying the solutions containing liquid SMEDDS and solid carriers. Colloidal silica and dextran were used as a hydrophobic and a hydrophilic carrier, respectively. The poorly water-soluble flurbiprofen was selected here as the model drug. Their crystalline properties were investigated using scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). Furthermore, the dissolution rate and oral bioavailability of flurbiprofen in rats were evaluated compared to a flurbiprofen powder.

Colloidal silica (Aerosil® 200), a nonporous hydrophilic form of silica, is one of the most important carriers that enables fast drug dissolution by improving the wettability of the drug particles, and it was confirmed that drugs become molecularly dispersed within the matrix formed with silica particles (Balakrishnan et al., 2009a; Takeuchi et al., 2005). Dextran, glucose polymer has been used as plasma volume expansion, and potential macromolecular carriers and conjugates for delivery of drugs and proteins, primarily to increase the longevity of therapeutic agents in the circulation (Mehvar, 2000; Thoren, 1980). Furthermore, it has been utilized good stabilizers for nanoparticles owing to its excellent biocompatibility and water-solubility (Gupta and Gupta, 2005).

2. Materials and methods

2.1. Materials

Flurbiprofen was supplied from Kolon Life Science Co. (Kwacheon, Korea). Polyglycolyzed glycerides (Capryol 90, Labrafac CC, Labrasol, Labrafil M 1944 CS, Labrafil M 2125 CS, Lauroglycol FCC and Transcutol HP) were obtained from Gattefosse (Saint-Priest Cedextran, France). Castor oil, corn oil, cotton seed oil, mineral oil, sesame oil, sunflower oil, peanut oil, and dextran (typical average Mw = 60,000–90,000) were supplied by Sigma–Aldrich Co. (St. Louis, MO, USA). Polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), sorbitan monolaurate 20 (Span 20) and sorbitan monooleate 80 (Span 80) were purchased from DC Chemical Co. (Seoul, South Korea). Colloidal silica (Aerosil® 200) was supplied from Hanmi Pharm. Co. (Hwassung, South Korea).

2.2. Animals

Male Sprague-Dawley rats (7–9 weeks old, weighing 250–310 g) were purchased from the Charles River Company Korea (Orient, Seoul, Korea). The rats were fasted for 24–36 h prior to the experiments but were allowed free access to water and were kept at a temperature of 20–23 °C and a relative humidity of 50 ± 5%. All animal care and experimental procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989, revised in 1999, and amended in 2008 by the Society of Toxicology (SOT, 2008). The protocols for the animal studies were also approved by the Institute of Laboratory Animal Resources of Yeungnam University.

2.3. Solubility studies

An excess of flurbiprofen powder (about 500 mg) was added to 1 ml of vehicles, as shown in Table 1, shaken in a water bath at 25 °C for 7 days, and centrifuged at 3000 × *g* for 15 min (Eppendorf; Hauppauge, NY, USA) (Choi et al., 2001). The supernatant was diluted with ethanol for the quantification of flurbiprofen and analysed by HPLC as described below.

Table 1
Solubility of flurbiprofen in various vehicles.

Vehicle	Solubility of flurbiprofen (mg/ml)
Water	5.1 ± 0.2 ($\times 10^{-3}$)
Oil	
Sunflower oil	21.15 ± 3.34
Castor oil	25.84 ± 11.18
Labrafil M 1944 CS	84.75 ± 6.00
Labrafil M 2125 CS	77.72 ± 9.17
Labrafac CC	46.43 ± 1.37
Mineral oil	0.582 ± 0.11
Peanut oil	15.60 ± 1.37
Corn oil	19.00 ± 1.33
Sesame oil	17.22 ± 2.95
Cotton seed oil	20.70 ± 1.12
Surfactant	
Tween 20	173.32 ± 12.07
Tween 80	189.56 ± 9.24
Span 20	51.22 ± 2.82
Span 80	37.51 ± 0.86
Labrasol	214.84 ± 46.88
Lauroglycol FCC	126.24 ± 48.35
Cremophor EL	111.19 ± 21.44
Capryol 90	140.92 ± 5.01
Transcutol HP	424.15 ± 33.48

Each value represents the mean ± S.E. (n = 3).

2.4. Construction of the ternary phase diagram

The existence of self-emulsifying oil formulation fields that could self-emulsify under dilution and gentle agitation were identified from ternary phase diagrams of systems containing an oil-surfactant-co-surfactant. A series of self-emulsifying systems were prepared in the formula with varying concentrations of 200 mg/ml of flurbiprofen (2% w/v), Labrafil M 1944 CS (oil phase; 5–45% v/v), Labrasol (surfactant; 50–95% v/v) and Transcutol HP (co-surfactant; 0–50% v/v). The formulation (0.3 ml) was introduced into 300 ml of water in a glass beaker at 37 °C and the contents were gently mixed using a magnetic bar. The tendency to spontaneously emulsify and also the progress of the emulsion droplets were observed. The tendency to form an emulsion was judged as 'good' when the droplets easily spread out in water and formed a fine milky emulsion, and it was judged 'bad' when there was poor or no emulsion formation with the immediate coalescence of oil droplets, especially when stirring was stopped. Phase diagrams were constructed to identify the good self-emulsifying region. All studies were repeated three times, with similar observations being made between repeats. The self-emulsifying performance was visually assessed after infinite dilution using purified water.

2.5. Preparation of liquid SMEDDS

Flurbiprofen (200 mg) was dissolved in 1 ml of the mixture of 12.5% Labrafil M 1944 CS, 80% Labrasol and 7.5% Transcutol HP. The final mixture was vortexed until a clear solution was obtained. The final drug content of the liquid SMEDDS was 18.6% w/w ratio. The formulation was examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies. The particle size of the emulsion was then measured by Zetasizer Nano ZS, as described below.

2.6. Preparation of solid SMEDDS

A Büchi 190 nozzle-type mini-spray dryer (Flawil, Switzerland) was used for the preparation of solid SMEDDS. Colloidal silica (1 g)

was suspended in 100 ml ethanol. Furthermore, dextran (1 g) was dissolved in 100 ml water. The liquid SMEDDS (1 ml) was added to these solutions with constant stirring, and the solution was continuously stirred at room temperature for 15 min to obtain good suspensions or emulsions. Each ethanolic and aqueous solution was delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump and spray dried at inlet temperatures of 100 and 60 °C and outlet temperatures of 80 and 40 °C, respectively. The air pressure of the spray was 4 kg/cm^2. The flow rate of the drying air was maintained at an aspirator setting of 10, which indicated that the pressure of the aspirator filter vessel was −25 mbar. The direction of air flow was the same as that of the sprayed product. The particle size of the solid SMEDDS was then measured by Zetasizer Nano ZS, as described below.

2.7. Characterization of the solid SMEDDS

2.7.1. Morphological analysis of solid SMEDDS

The outer macroscopic structures of flurbiprofen powder and solid SMEDDS formulations were examined using a scanning electron microscope (S-4100, Hitachi, Japan) with an image analysis system (ImageInside Ver 2.32). The powders were fixed to a brass specimen club using double-sided adhesive tape made electrically conductive by coating in a vacuum (6 Pa) with platinum (6 nm/min) using a Hitachi Ion Sputter (E-1030) for 300 s at 15 mA.

2.7.2. Solid state characterization of solid SMEDDS

The thermal characteristics of flurbiprofen powder and the carriers, physical mixtures and solid SMEDDS formulations were investigated using a differential scanning calorimeter (DSC Q200 v24.2 build 107, TA Instruments, USA). About 2 mg of the samples were placed in sealed aluminium pans before heating under a nitrogen flow (25 ml/min) at a heating rate of 10 °C/min from 50 °C to 2000 °C. Furthermore, the powder crystallinity of the solid SMEDDS formulations was assessed by powder X-ray diffraction (MPD for bulk, PAN Analytical, Netherlands), conducted at room temperature using monochromatic Cu Kα-radiation (λ = 1.5406 Å) at 30 mA and 40 kV in the region of $10^\circ \leq 2\theta \leq 50^\circ$ with an angular increment of 0.02° per second.

2.8. Emulsion particle size measurement

The particle size of the emulsion was determined using a Zetasizer Nano ZS (Malvern Instruments, UK) dynamic light scattering particle size analyser at a wavelength of 635 nm and a scattering angle of 90° at 25 °C. Liquid SMEDDS or solid SMEDDS (equivalent to 10 mg flurbiprofen) was added to 25 ml of distilled water and shaken gently to form a fine emulsion and kept for 12 h at room temperature. All studies were repeated three times and the values of *z*-average diameters were used. The *z*-average diameter, also referred to as the harmonic intensity-weighted average hydrodynamic diameter, of each emulsion was derived from cumulated analysis by Automeasure software (Malvern Instruments, Malvern, UK). In contrast, plain diameter was a straight line passing through the center of a figure, especially of a circle or sphere, whose endpoints were on the periphery.

2.9. Dissolution

The flurbiprofen-loaded solid SMEDDS formulations (equivalent to 50 mg of flurbiprofen) and 50 mg of flurbiprofen powder were each placed in a dissolution tester (Shinseang Instrument Co., South Korea). This dissolution tester was equipped with an outer water-bath in order to maintain constant temperature and sink conditions. The dissolution test was performed at 36.5 °C using the basket method at 100 rpm with 900 ml water as the dissolution medium. At predetermined intervals, an aliquot (2 ml) of the sample was collected and filtered through a membrane filter (0.45 μm; nylon syringe filter). The concentration of flurbiprofen in the resulting solution (50 μl) was analysed using the HPLC method described below. An equivalent volume (2 ml) of fresh dissolution medium was added to compensate for any loss due to sampling.

2.10. In vivo study

2.10.1. Oral administration and blood collection

The rats were divided into three groups and administered with two flurbiprofen-loaded solid SMEDDS formulations and flurbiprofen powder (control) at a drug dose of 10 mg/kg. Each rat, anaesthetized in an ether-saturated chamber, was secured to a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat. The solid SMEDDS formulations and flurbiprofen powder were placed in small hard gelatin capsules (#9, Suheung capsule Co., Seoul, Korea), respectively. They were orally administered to the rats in each group. Then, 0.15 ml of blood was collected from the right femoral artery at predetermined time intervals and centrifuged at 3000 × *g* for 15 min using a 5415C centrifuge (Eppendorf; Hauppauge, NY, USA).

2.10.2. Blood sample analysis

To 50 μl of plasma, 0.6 ml of acetonitrile and 50 μl of internal standard (acetonitrile solution containing 10 (g/ml of valsartan) was added and shaked vigorously for 5 min. After centrifuging at 8000 × *g* for 2 min, the supernatant was transferred to a microtube and evaporated. The residue was reconstituted with 150 μl of the mobile phase, vortexed for 1 min, and centrifuged at 10,000 × *g* for 5 min. Then, 50 μl of the supernatant layer was analysed by HPLC (Hitachi, Tokyo, Japan), equipped with an Inertsil ODS-3 C_{18} column (GL Science, 0.5 μm, 15 cm × 0.46 cm i.d.) and a UV detector (Model L-7450). The mobile phase was composed of acetonitrile, water and phosphoric acid (600/400/5, volume ratio). The eluent was monitored at 254 nm with a flow rate of 1.5 ml/min (Kim et al., 1995; Li et al., 2010; Oh et al., 2011a).

3. Results and discussion

3.1. Solubility

The self-emulsifying formulations consisted of oil, surfactants, co-surfactants and the drug, and should be a clear and monophasic liquid at room temperature when introduced to the aqueous phase with good solvent properties to allow presentation of the drug in solution. The solubility of flurbiprofen in various vehicles is given in Table 1. The aqueous solubility of flurbiprofen was about 5 μg/ml, indicating that it was poorly water-soluble (Oh et al., 2011b; Li et al., 2010). The drug was more soluble in all of the vehicles compared to its aqueous solubility. The Labrafil M series showed higher drug solubility compared to the other oils. Furthermore, Labrafil M 1944 CS (oleoyl macrogol glyceride) showed better solubility for flurbiprofen than Labrafil M 2125 CS (linoleoyl macrogol glyceride). Thus, Labrafil M 1944 CS was selected as the oily vehicle due to its good solubility. Among the surfactants tested in this study, Transcutol HP showed the highest drug solubility. This surfactant gave good solubility and gave an optimal SMEDDS formulation resulting in improved drug loading and spontaneous fine emulsion formation (Kang et al., 2004). Labrasol, a medium length alkyl chain surfactant with HLB 14, showed a higher drug solubility compared to the other surfactants. Moreover, Labrasol was reported to enhance the intestinal absorption of drugs (Prasad et al., 2003). Therefore, Labrasol and Transcutol HP were selected as the surfactant and co-surfactant, respectively. Labrafil M 1944 CS, selected as the oily

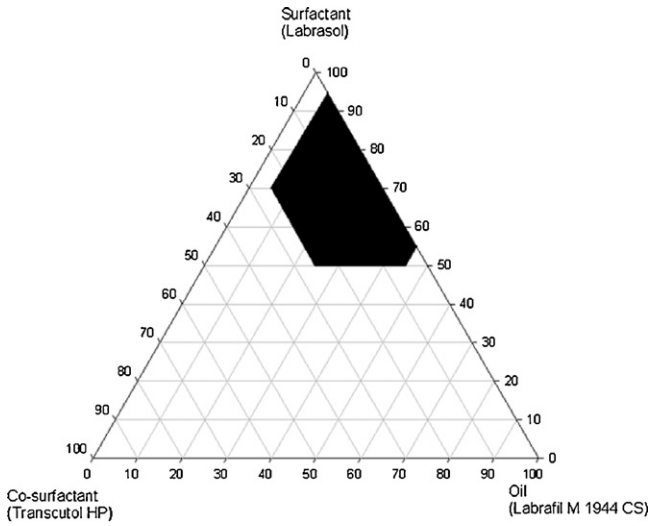

Fig. 1. Pseudo ternary phase diagram.

vehicle in this study, was well miscible, formed a clear solution with Labrasol and spontaneously formed an emulsion with a small *z*-average droplet diameter (Balakrishnan et al., 2009a).

3.2. Liquid SMEDDS

A series of SMEDDS were prepared and their self-emulsifying properties were visually observed. Pseudo-ternary phase diagrams were constructed in the absence of flurbiprofen to identify the self-emulsifying regions and to optimize the concentrations of oil, surfactant and co-surfactant in the SMEDDS formulations. The phase diagram of the system containing Labrafil M 1944 CS, Labrasol and Transcutol HP as the oil, surfactant and co-surfactant, respectively, is shown in Fig. 1. It was observed that incorporation of the co-surfactant, Transcutol HP, within the self-emulsifying region increased the spontaneity of the self-emulsification process. The efficiency of emulsification was good when the surfactant/co-surfactant concentration was more than 75% v/v of the SMEDDS formulation. It was observed that spontaneous emulsion formation was not efficient with less than 50% v/v of the surfactant in the SMEDDS. In this system, the formulations surrounding the good self-emulsifying region in the phase diagram exhibited a poor emulsion-forming ability. It has been reported that the drug incorporated in the SMEDDS may have some effect on the self-emulsifying performance (Balakrishnan et al., 2009a). However, in our study, no significant differences were found in the self-emulsifying performance when compared to the corresponding formulations containing 2% w/v drug loads.

In SMEDDS systems, the primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification can be estimated by determining the rate of emulsification and droplet size distribution. The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as absorption (Constantinides et al., 1994). It was observed that increasing the surfactant concentration (from 50% to 75% v/v) in the SMEDDS formula decreased the *z*-average diameter of the emulsion formed, but above 80% with Labrafil M 1944 CS the *z*-average diameter slightly increased (Fig. 2). There was no significant difference between the *z*-average diameter of the emulsion in the SMEDDS formula with 75% and 80% surfactant. As shown in Fig. 3, the co-surfactant (Transcutol HP) decreased the *z*-average diameter in SMEDDS to 7.5% at 80% surfactant and 12.5% at 75% surfactant, followed by an increasing the *z*-average

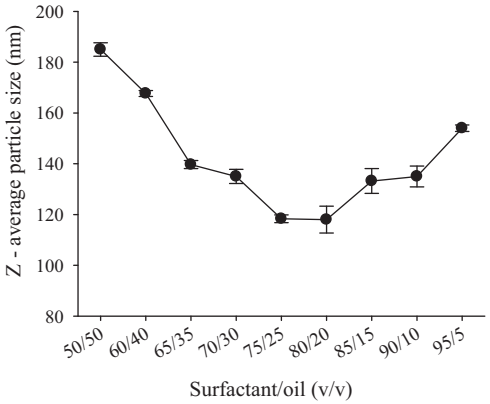

Fig. 2. Effect of surfactant/oil ratio on the droplet size of emulsions. These emulsions were composed of 0.1 ml mixture of surfactant/oil and 100 ml water.

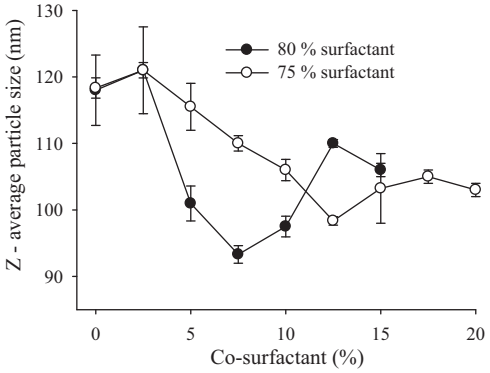

Fig. 3. Effect of co-surfactant on the mean emulsion droplet diameter of emulsions. These emulsions contained 75 or 80% of constant surfactant.

diameter. Moreover, the SMEDDS prepared with 7.5% co-surfactant (at 80% surfactant) gave significant smaller *z*-average diameters than that prepared with 12.5% co-surfactant (at 75% surfactant). Thus, Labrafil M 1944 CS/Labrasol/Trasncutol HP (12.5/80/7.5%) was chosen as the optimized liquid SMEDDS formulation for further study.

3.3. Solid SMEDDS

The solid SMEDDS formulations were prepared by spray-drying aqueous solution containing liquid SMEDDS and carriers. Colloidal silica and dextran were used as a hydrophobic and hydrophilic solid carrier, respectively. The *z*-average diameters of the liquid SMEDDS and solid SMEDDS formulations are presented in Fig. 4. The polydispersity index (PDI) of liquid SEDDS, solid SEDDS prepared with colloidal silica and dextran were 0.156 ± 0.004, 0.276 ± 0.001 and 0.194 ± 0.007, respectively. The liquid SMEDDS with 2% w/v flurbiprofen gave a *z*-average diameter of about 100 nm. The average droplet sizes of solid SMEDDS formulations were dependent upon the solid carriers. The solid SMEDDS prepared with colloidal silica gave a microemulsion droplet size similar to that of liquid SMEDDS (98 ± 2 nm vs. 101 ± 4 nm). Dextran, hydrophilic carrier, produced the solid SMEDDS with significantly larger emulsion droplet size compared to liquid SMEDDS. However, like the solid SMEDDS prepared with colloidal silica, this solid SMEDDS produced micro-sized emulsion droplet (about 150 nm).

The scanning electron micrographs of flurbiprofen powder and the solid SMEDDS formulations are shown in Fig. 5. Flurbiprofen powder (Fig. 5a) appeared as smooth-surfaced rectangular crystals in shape (Oh et al., 2011b). The SMEDDS prepared with colloidal

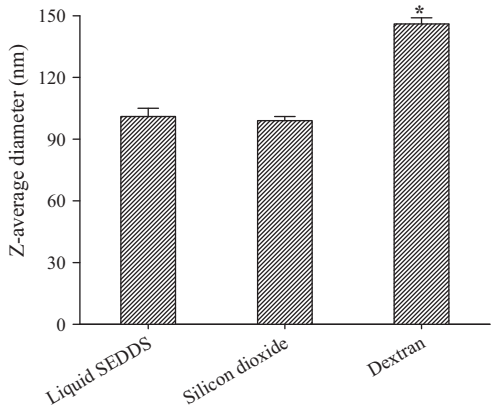

Fig. 4. Mean emulsion droplet size and polydispersity index of liquid and solid SMEDDS formulations. Each value represents the mean ± S.E. ($n = 3$).

silica (Fig. 5b) appeared as rough-surfaced particles, indicating that the liquid SMEDDS was absorbed or coated inside the pores of colloidal silica. Unlike the former solid SMEDDS formulation, the SMEDDS formulation prepared with dextran (Fig. 5c) gave spherical particles with irregular and crushed shapes. Our results suggested that the liquid SMEDDS was not absorbed onto the surfaces of carriers but formed a kind of micro-sized microcapsule with dextran, hydrophilic carrier.

The DSC curves of pure flurbiprofen and the solid carriers, physical mixtures and solid SMEDDS formulations are shown in Fig. 6. The physical mixtures were prepared by simply mixing the carriers and drug. Pure flurbiprofen showed a sharp endothermic peak at about 115 °C (Fig. 6a), corresponding to its melting point and indicating its crystalline nature. Colloidal silica (Fig. 6b) and dextran (Fig. 6e) showed no peaks over the entire range of temperatures tested. The melting point, which appeared in the drug peak, was shown with a reduced intensity in these physical mixtures (Fig. 6c and f). However, the endothermic peaks of the drug were absent in the SMEDDS formulation prepared with colloidal silica (Fig. 6d) and dextran (Fig. 6g). Our results indicate that flurbiprofen might have been in an amorphous state in the SMEDDS formulations prepared with the carriers.

The powder X-ray diffractometry patterns are presented in Fig. 7. Flurbiprofen had sharp peaks at the diffraction angles, showing a typical crystalline pattern (Fig. 7a). Colloidal silica (Fig. 7b) and dextran (Fig. 7e) showed no intrinsic peaks. All of the major characteristic crystalline peaks for the drug and each carrier were observed in these physical mixtures (Fig. 7c and f). Two SMEDDS formulations showed peaks at diffraction angles, showing an amorphous pattern (Fig. 7d and g). Thus, like the DSC results, flurbiprofen was present in a changed amorphous state in the SMEDDS formulations prepared with colloidal silica and dextran.

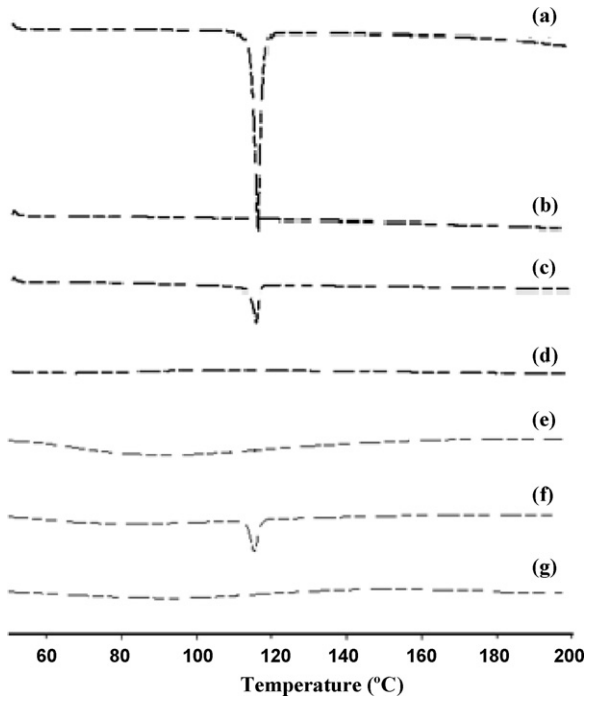

Fig. 6. Differential scanning calorimetric thermogram: (a), flurbiprofen; (b), colloidal silica; (c), physical mixture of flurbiprofen and colloidal silica; (d), SMEDDS prepared with colloidal silica; (e), dextran; (f) physical mixture of flurbiprofen and dextran; (g), SMEDDS prepared with dextran.

The dissolution rate of the drug from the solid SMEDDS formulations was compared with that of flurbiprofen powder (Fig. 8). After 5 min, the solid SMEDDS formulations prepared with colloidal silica and dextran showed higher dissolution rates than the powder. However, there were no significant differences in dissolution rates of drug between the solid SMEDDS formulations prepared with colloidal silica and dextran. In particular, these solid SMEDDS formulations gave a dissolution rate of about 70% within 5 min as a result of the fast spontaneous emulsion formation and the smallest droplet size.

3.4. In vivo study

Fig. 9 shows the change in the mean plasma concentration of flurbiprofen after the oral administration of flurbiprofen powder or each of the solid SMEDDS to rats. The total plasma concentrations of the drug in these solid SMEDDS formulations were significantly higher than in flurbiprofen powder. Furthermore, the solid SMEDDS formulation prepared with colloidal silica gave higher plasma concentrations of the drug compared to that with dextran, but there were no significant differences.

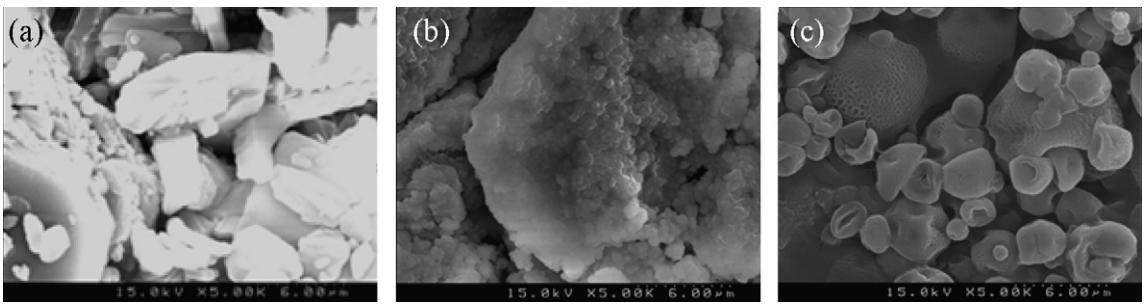

Fig. 5. Scanning electron micrographs (×1000): (a) flurbiprofen powder; (b) SMEDDS prepared with colloidal silica and (c) SMEDDS prepared with dextran.

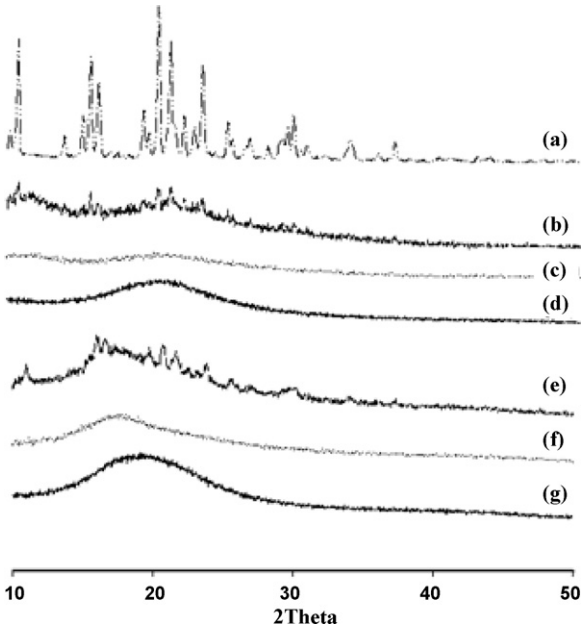

Fig. 7. X-ray powder diffraction: (a), flurbiprofen; (b), colloidal silica; (c), physical mixture of flurbiprofen and colloidal silica; (d), SMEDDS prepared with colloidal silica; (e), dextran; (f), physical mixture of flurbiprofen and dextran; (g), SMEDDS prepared with dextran.

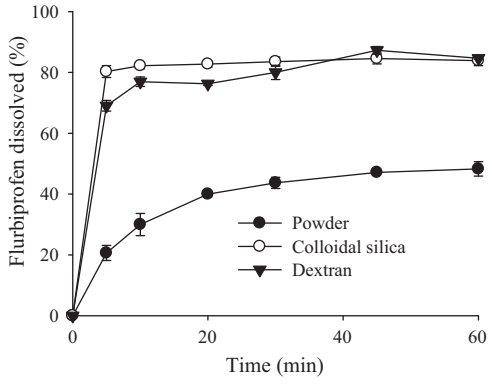

Fig. 8. Dissolution profile of flurbiprofen powder and solid SMEDDS formulations in water. Each value represents the mean ± S.D. ($n = 6$).

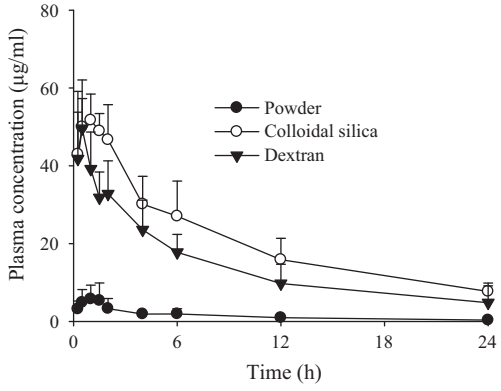

Fig. 9. Plasma concentration-time profiles of flurbiprofen after oral administration of powder and solid SMEDDS formulations in rats. Each value represents the mean ± S.D. ($n = 6$). *$P < 0.05$ compared with powder.

Table 2
Pharmacokinetic parameters.

Parameter	Powder	Colloidal silica	Dextran
T_{max} (h)	0.87 ± 0.29	0.84 ± 0.36	0.47 ± 0.08
C_{max} (μg/ml)	5.58 ± 3.83	53.38 ± 6.70*	48.06 ± 13.23*
AUC (h μg/ml)	40.78 ± 7.78	609.10 ± 151.99*	360.57 ± 49.12*
$t_{1/2}$ (h)	2.11 ± 1.99	6.50 ± 2.89	2.51 ± 1.69
K_{el} (h^{-1})	0.33 ± 0.41	0.11 ± 0.05	0.28 ± 0.16

Each value represents the mean ± S.D. ($n = 6$).
* $P < 0.05$ compared with powder.

The pharmacokinetic parameters are shown in Table 2. The solid SMEDDS formulations gave significantly higher AUC and C_{max} of drug than the flurbiprofen powder ($P < 0.05$). The AUC value of solid SMEDDS formulation prepared with colloidal silica was higher than that with dextran, but they were not significantly different. In particular, the AUC values of solid SMEDDS formulation prepared with colloidal silica and dextran were 15- and 8-fold greater than that of the powder, respectively, indicating that all of the formulations greatly improved the oral bioavailability of drug. The enhanced oral bioavailability of drug from these solid SMEDDS formulations might have contributed to the marked increase in the absorption rate of flurbiprofen due to the increased rate of dissolution of the drug from the solid SMEDDS formulations (Kim et al., 1995; Mura et al., 1995). On the other hands, the T_{max}, K_{el} and $t_{1/2}$ values of the solid SMEDDS formulations were not significantly different from those of the powder.

In this study, colloidal silica, a hydrophobic solid carrier, produced an excellent conventional solid SMEDDS that liquid SMEDDS was absorbed onto its surfaces. This solid SMEDDS gave a microemulsion droplet size similar to that of the liquid SMEDDS (about 100 nm) which was smaller than the other solid SMEDDS formulation. In the solid SMEDDS prepared with dextran, liquid SMEDDS was not absorbed onto the surfaces of carriers but formed a kind of micro-sized microcapsule with hydrophilic carrier unlike colloidal silica. As the drug dissolved in the liquid SMEDDS was spray-dried in the preparation of solid SMEDDS, the drug was kept in an amorphous state in these solid SMEDDS formulations. When they were dissolved in the water, it immediately became dispersed within the medium and swelled up. Subsequently, the drug could easily and swiftly diffuse out to the medium. These SMEDDS formulations allowed the spontaneous formation of an interface between the oil droplets and the water and decreasing the size of the droplets (Balakrishnan et al., 2009a). In conventional self-emulsifying systems, the amount of free energy required to form an emulsion is very low, thereby allowing the spontaneous formation of an interface between oil droplets and the water (Balakrishnan et al., 2009b). This suggests that the oil/surfactant/co-surfactant and water phases effectively swell, decreasing the size of the oil droplets and eventually increasing the drug release rate. Furthermore, these SMEDDS formulations greatly improved the oral bioavailability of the drug in rats, even if the SMEDDS formulation prepared with colloidal silica insignificantly improved the oral bioavailability of the drug than did that with dextran. Thus, except appearance, dextran and colloidal silica hardly affected the formation of solid SMEDDS such as crystalline properties, dissolution and oral bioavailability, even though the selection of carrier is an important factor in the development of solid SMEDDS.

4. Conclusion

Like colloidal silica, dextran produced a solid SMEDDS with microemulsion droplet sizes, and improved the dissolution rate and the oral bioavailability of flurbiprofen due to the fast spontaneous emulsion formation and the decreased droplet size. Thus, in this study, these two carriers had no significant effects on the

formation of solid SMEDDS such as crystalline properties, dissolution and oral bioavailability of flurbiprofen.

Acknowledgements

This research was supported by the Midcareer Researcher Program through a NRF grant funded by the MEST (No. 2010-0000363) and a grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A092018).

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