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Research paper

Effects of solid carriers on the crystalline properties, dissolution and bioavailability of flurbiprofen in solid self-nanoemulsifying drug delivery system (solid SNEDDS)

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ABSTRACT

In order to investigate the effects of solid carriers on the crystalline properties, dissolution and bioavailability of flurbiprofen in a solid self-nanoemulsifying drug delivery system (solid SNEDDS), different solid SNEDDS formulations were prepared by spray-drying the solutions containing liquid SNEDDS and various carriers. The liquid SNEDDS, 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. Silicon dioxide, a hydrophobic solid carrier, produced an excellent conventional solid SNEDDS with a nanoemulsion droplet size of less than 100 nm, similar to the liquid SNEDDS and smaller than the other solid SNEDDS formulations. The drug was in an amorphous state in this solid SNEDDS. Furthermore, it greatly improved the dissolution rate and oral bioavailability of flurbiprofen in rats because it allowed the spontaneous formation of an interface between the oil droplets and the water. Magnesium stearate, a hydrophobic carrier, produced a solid SNEDDS with the largest diameter. However, it greatly enhanced the dissolution rate and oral bioavailability due to the formation of a simple eutectic mixture. The hydrophilic carriers such as polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (Na-CMC) and hydroxypropyl-β-cyclodextrantrin (HP-β-CD) did not form a solid SNEDDS but rather a solid dispersion (or microcapsule). HP-β-CD improved the dissolution rate but did not improve the oral bioavailability as much as the hydrophobic polymers. PVA and Na-CMC hardly improved the dissolution rate but maintained constantly high plasma levels in rats for a long period. Thus, the selection of carrier is an important factor in the development of solid SNEDDS, since the carriers had significant effects on the crystalline properties, dissolution and oral bioavailability of flurbiprofen and on the formation of solid SNEDDS.

1. Introduction

Over recent years, much attention has been focused on lipid-microemulsion formulations, with particular emphasis on liquid self-nanoemulsifying (SNEDDS), self-microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs [1–3]. 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 [4]. When the product is stored 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 [3]. Moreover, its efficiency is dependent upon a moist environment [5]. Thus, solid SNEDDS should be carefully explored as a means of overcoming these problems.

Solid SNEDDS, 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 SNEDDS (solubility and bioavailability enhancement) with those of solid dosage forms (high stability with various dosage form options) [6,7]. Solid SNEDDS produce oil-in-water nanoemulsions with droplet sizes of less than 200 nm upon mild agitation in aqueous media (such as gastrointestinal fluids) [7,8]. These fine nanoemulsion 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 [9]. The spray-drying technique using

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silicon dioxide as a solid carrier has generally been employed to prepare solid SNEDDS [10,11]. Furthermore, most of the previous studies only focused on solid SNEDDS prepared with silicon dioxide. Thus, there is a lack of knowledge on the effects of different types of solid carriers on the crystalline properties, dissolution and bioavailability of drugs in solid SNEDDS, although carriers are essential in the development of a desirable solid SNEDDS.

Therefore, in this study, in order to investigate the effects of solid carriers on the crystalline properties, dissolution rate and bioavailability of a drug in solid SNEDDS, solid SNEDDS formulations were prepared by spray-drying an aqueous solution containing liquid SNEDDS and various carriers. The poorly water-soluble flurbiprofen was selected here as the model drug. The hydrophobic solid carriers, silicon dioxide and magnesium stearate, and the hydrophilic solid carriers, polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (Na-CMC) and hydroxypropyl-β-cyclodextrantrin (HP-β-CD), were used. 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 bioavailability of flurbiprofen in rats were evaluated compared to a flurbiprofen powder.

Silicon dioxide (Aerosil® 200), a nonporous hydrophilic form of silica, is one of the most important carriers that can improve the dissolution by improving the wettability of the drug particles [10]. Moreover, drugs become molecularly dispersed within the matrix formed with silica particles [10,12]. Magnesium stearate has been used as an adhesion modifier to improve the flow properties of powders in pharmaceutical solid dosage forms [13]. Polyvinyl alcohol (PVA) has been used as a stabilizer originally in emulsion polymerization and as an additive for the spray-drying of dispersions [14]. Sodium carboxymethyl cellulose (Na-CMC), a water-soluble cellulose polymer, has been used as a stabilizer of emulsion systems [15–17]. Hydroxypropyl-β-cyclodextrantrin (HP-β-CD) has been found to improve drug solubility and dissolution due to the formation of inclusion complex [18,19].

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, hydroxypropyl-β-cyclodextrantrin (HP-β-CD) and polyvinyl alcohol (PVA) 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). Silicon dioxide (Aerosil® 200), magnesium stearate and sodium carboxymethyl cellulose (Na-CMC) were 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 [20]. 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) [21]. The supernatant was diluted with ethanol for the quantification of flurbiprofen and analyzed by HPLC method mentioned below in Section 2.10.3.

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 was 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; 0–45%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 SNEDDS

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.

Table 1
Solubility of flurbiprofen in various vehicles (each value represents the mean ± SD, $n = 3$).

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

The final mixture was vortexed until a clear solution was obtained. The final drug content of the liquid SNEDDS was 16.7%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 in Section 2.8.

2.6. Preparation of solid SNEDDS

A Büchi 190 nozzle-type mini-spray dryer (Flawil, Switzerland) was used for the preparation of solid SNEDDS. The hydrophobic solid carriers (1 g) such as silicon dioxide and magnesium stearate were each suspended in 100 ml ethanol. Furthermore, the hydrophilic solid carriers (1 g) such as PVA, Na-CMC and HP-β-CD were each dissolved in 100 ml water. The liquid SNEDDS (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 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 SNEDDS was then measured by Zetasizer Nano ZS, as described below in Section 2.8.

2.7. Characterization of the solid SNEDDS

2.7.1. Morphological analysis of solid SNEDDS

The outer macroscopic structures of flurbiprofen powder and solid SNEDDS 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 SNEDDS

The thermal characteristics of flurbiprofen powder and the carriers, physical mixtures and solid SNEDDS formulations were investigated using a differential scanning calorimeter (DSC Q200 v24.2 build 107, TA Instruments, USA). Each physical mixture was prepared by physically mixing flurbiprofen, each carrier, Labrafil M 1944 CS, Labrasol and Trasncutol HP at the weight ratio of 2/10/1.25/8/0.75. About 2 mg of the samples was placed in sealed aluminum pans before heating under a nitrogen flow (25 ml/min) at a heating rate of 10 °C/min from 50 °C to 200 °C. Furthermore, the powder crystallinity of the solid SNEDDS 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 $10^\circ \leqslant 2\theta \leqslant 50^\circ$ 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 analyzer at a wavelength of 635 nm and a scattering angle of 90° at 25 °C. Liquid SNEDDS or solid SNEDDS (equivalent to 10 mg flurbiprofen) were 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).

2.9. Dissolution

The flurbiprofen-loaded solid SNEDDS 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. 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 analyzed using the HPLC method described below in Section 2.10.3. 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 six groups and administered with five flurbiprofen-loaded solid SNEDDS formulations and flurbiprofen powder (control) at a flurbiprofen 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 SNEDDS 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 with capsule injector (HEBU medical, Tuttlingen, Germany) 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 μg/ml of valsartan) were 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 analyzed by HPLC method described below in Section 2.10.3.

2.10.3. HPLC condition

HPLC (Hitachi, Tokyo, Japan) equipped with an Inertsil ODS-3 C_{18} column (GL science, 5 μm, 15 cm × 0.46 cm i.d.) and a UV detector (Model L-7450) was used in this analysis. 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 [22–24]. The retention times were as follows: valsartan (internal standard), 4.2 min and flurbiprofen (drug), 5.9 min. The calibration curve was constructed over a range of 0.25–50 μg/ml in plasma (R^2 = 0.9998) and with a lower limit of quantification (LLOQ) of 250 ng/ml for drug. For the validation, inter- and intra-day differences were conducted, and the differences were found to be within an acceptable range.

2.10.4. Pharmacokinetic data analysis and statistical analysis

The area under the drug concentration–time curve from zero to infinity (AUC) and the half-life ($t_{1/2}$) were calculated using

noncompartmental analysis (WinNonlin; professional edition, version 2.1; Pharsight Co., Mountain View, CA, USA). The maximum plasma concentration of the drug (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were directly obtained from the plasma data. Levels of statistical significance ($p < 0.05$) were assessed using the Student's t-test between two means for unpaired data. All data are expressed as mean ± standard deviation (SD) or as the median (ranges) for T_{max}.

3. Results

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. This result indicates that the drug was poorly water-soluble [14,23]. 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), even if there was no significant difference. Thus, Labrafil M 1944 CS was selected as the oily vehicle due to its good solubility. Labrafil M 1944 CS was reported to be well miscible, formed a clear solution with Labrasol, a surfactant, and spontaneously formed an emulsion with a small z-average droplet diameter [10]. Among the surfactants tested in this study, Transcutol HP showed the highest drug solubility. This surfactant gave good solubility and gave an optimal SNEDDS formulation resulting in improved drug loading and spontaneous fine emulsion formation [25]. 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 [26]. Therefore, Labrasol and Transcutol HP were selected as the surfactant and co-surfactant, respectively.

3.2. Liquid SNEDDS

A series of SNEDDS 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 SNEDDS 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 SNEDDS formulation. It was observed that spontaneous emulsion formation was not efficient with less than 50%v/v of the surfactant in the SNEDDS. In this system, the formulations surrounding the good self-emulsifying region in the phase diagram could not form an emulsion (Fig. 1). It has been reported that the drug incorporated in the SNEDDS may occasionally have some effect on the self-emulsifying performance [10]. 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 SNEDDS 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 [27]. It was observed that increasing the surfactant concentration (from 50% to 75%v/v) in the SNEDDS 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 SNEDDS formula with 75% and 80% surfactant. As shown in Fig. 3, the co-surfactant (Transcutol HP) decreased the z-average diameter in SNEDDS to 7.5% at 80% surfactant and 12.5% at 75% surfactant, followed by an increasing the z-average diameter. Moreover, the SNEDDS 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 SNEDDS formulation for further study.

3.3. Solid SNEDDS

The solid SNEDDS formulations were prepared by spray-drying aqueous solution containing liquid SNEDDS and carriers. The hydrophobic solid carriers, silicon dioxide and magnesium

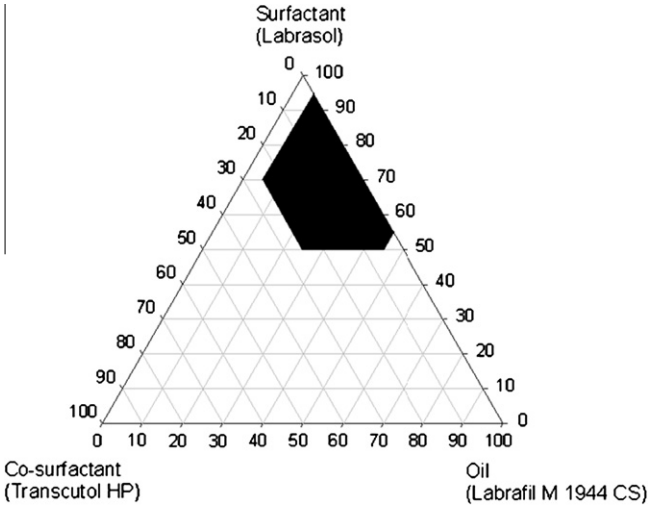

Fig. 1. Pseudo-ternary phase diagram.

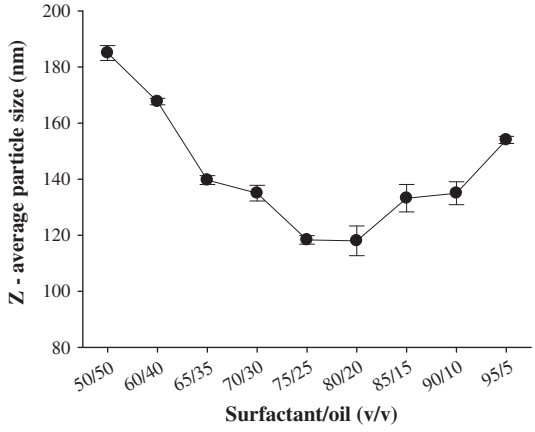

Fig. 2. Effect of surfactant/oil ratio on the droplet size of the emulsions. The emulsions were composed of 0.1 ml of a mixture of surfactant/oil and 100 ml water.

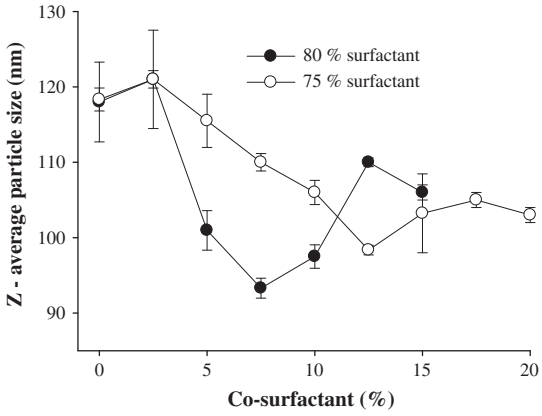

Fig. 3. Effect of the co-surfactant on the mean droplet diameter of the emulsions. The emulsions contained 75% or 80% of constant surfactant.

Table 2
Mean emulsion droplet size and polydispersity index of the liquid and solid SNEDDS formulations (each value represents the mean ± SE, $n = 3$).

Carrier	z-Average diameter (nm)	Polydispersity index (PDI)
Liquid SNEDDS	101 ± 4	0.156 ± 0.004
Solid SNEDDS		
Silicon dioxide	98 ± 2	0.276 ± 0.001
Magnesium stearate	1940 ± 140	0.368 ± 0.120
PVA	173 ± 1	0.340 ± 0.040
Na-CMC	910 ± 20	0.359 ± 0.048
HP-β-CD	796 ± 4	0.239 ± 0.020

stearate, and the hydrophilic solid carriers PVA, Na-CMC and HP-β-CD, were used. The *z*-average diameters and polydispersity indices (PDI) of the solid SNEDDS and liquid SNEDDS formulations are presented in Table 2. The liquid SNEDDS with 2% w/v flurbiprofen gave a *z*-average diameter of about 100 nm. The average droplet sizes of all of the systems were greatly dependent upon the solid carriers. The *z*-average diameters of the emulsions in the solid SNEDDS formulations were in the order of silicon dioxide < PVA < Na-CMC < HP-β-CD < magnesium stearate. Only the solid SNEDDS prepared with silicon dioxide gave an emulsion droplet size similar to that of liquid SNEDDS (98 ± 2 nm vs. 101 ± 4 nm). Furthermore, the other hydrophobic carrier, magnesium stearate, produced the solid SNEDDS with largest emulsion droplet size.

The scanning electron micrographs of flurbiprofen powder and the solid SNEDDS formulations are shown in Fig. 4. Flurbiprofen powder (Fig. 4A) appeared as smooth-surfaced rectangular crystals in shape [14]. The SNEDDS prepared with silicon dioxide (Fig. 4B) appeared as rough-surfaced particles, indicating that the liquid SNEDDS was absorbed or coated inside the pores of silicon dioxide. The SNEDDS prepared with magnesium stearate contained so-called excipient bridges randomly linked with the liquid SNEDDS (Fig. 4C), indicating that it produced an agglomerated solid SNEDDS. Moreover, the other SNEDDS formulations prepared with the hydrophilic carriers PVA (Fig. 4D), Na-CMC (Fig. 4E) and HP-β-CD (Fig. 4F) gave spherical particles with irregular and crushed shapes. Our results suggested that the liquid SNEDDS was not absorbed onto the surfaces of carriers but formed a kind of microcapsule or solid dispersion with the hydrophilic carriers instead.

The DSC curves of pure flurbiprofen and the solid carriers, physical mixtures and solid SNEDDS formulations are shown in Fig. 5. The physical mixtures were prepared by simply mixing the carriers and drug. Pure flurbiprofen showed a sharp endothermic peak at

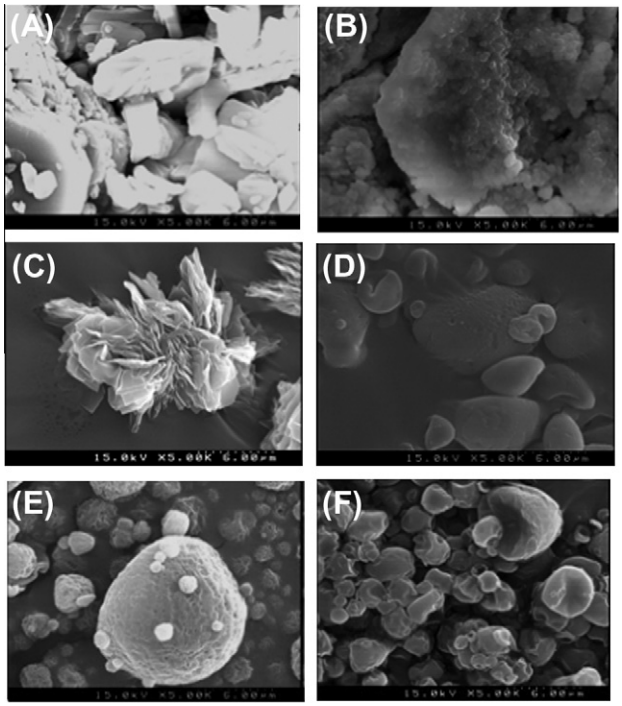

Fig. 4. Scanning electron micrographs (5000×): (A) flurbiprofen powder; (B) SNEDDS prepared with silicon dioxide; (C) SNEDDS prepared with magnesium stearate; (D) SNEDDS prepared with PVA; (E) SNEDDS prepared with Na-CMC; (F) SNEDDS prepared with HP-β-CD.

about 115 °C (Fig. 5A-a), corresponding to its melting point and indicating its crystalline nature. Except for magnesium stearate, none of the solid carriers showed any peaks over the entire range of temperatures tested (Fig. 5A-b, C-b, D-b and E-b). The melting point, which appeared in the drug peak, was shown with a reduced intensity in these physical mixtures (Fig. 5A-c, C-c, D-c and E-c). However, the endothermic peaks of the drug were absent in the SNEDDS formulations prepared with carriers, except for magnesium stearate (Fig. 5A-d, C-d, D-d and E-d). Our results indicate that flurbiprofen might have been in an amorphous state in the SNEDDS formulations prepared with the carriers, except for magnesium stearate.

On the other hand, magnesium stearate gave a broad endothermic peak at around 110 °C (Fig. 5B-b). However, the physical mixture exhibited not only an endothermic peak in the drug and carrier but also a new endothermic peak at a much lower temperature of about 70 °C (Fig. 5B-c). Moreover, the SNEDDS formulations prepared with magnesium stearate showed no peaks in the physical mixture but a new peak at 100 °C in the DSC diagram (Fig. 5B-d), resulting from water bound in the molecules. The bound nature of the moisture was indicated by the sharpness of the respective DSC endothermic peak (Fig. 5B-c).

The powder X-ray diffractometry patterns are presented in Fig. 6. Flurbiprofen had sharp peaks at the diffraction angles, showing a typical crystalline pattern (Fig. 6A-a). Silicon dioxide showed no intrinsic peaks (Fig. 6A-c). Magnesium stearate (Fig. 6C-c), PVA (Fig. 6C-c), Na-CMC (Fig. 6D-c) and HP-β-CD (Fig. 6E-c) showed intrinsic peaks. All of the major characteristic crystalline peaks for the drug and each carrier were observed in these physical mixtures (Fig. 6A-b, C-b, D-b and E-b). Except for magnesium stearate, the SNEDDS formulations showed no peaks at diffraction angles, showing an amorphous pattern (Fig. 6A-d, C-d, D-d and E-d). Thus, like the DSC results, flurbiprofen was present in a changed amorphous state in the SNEDDS formulations prepared with carriers except for magnesium stearate. However, a new large peak appeared

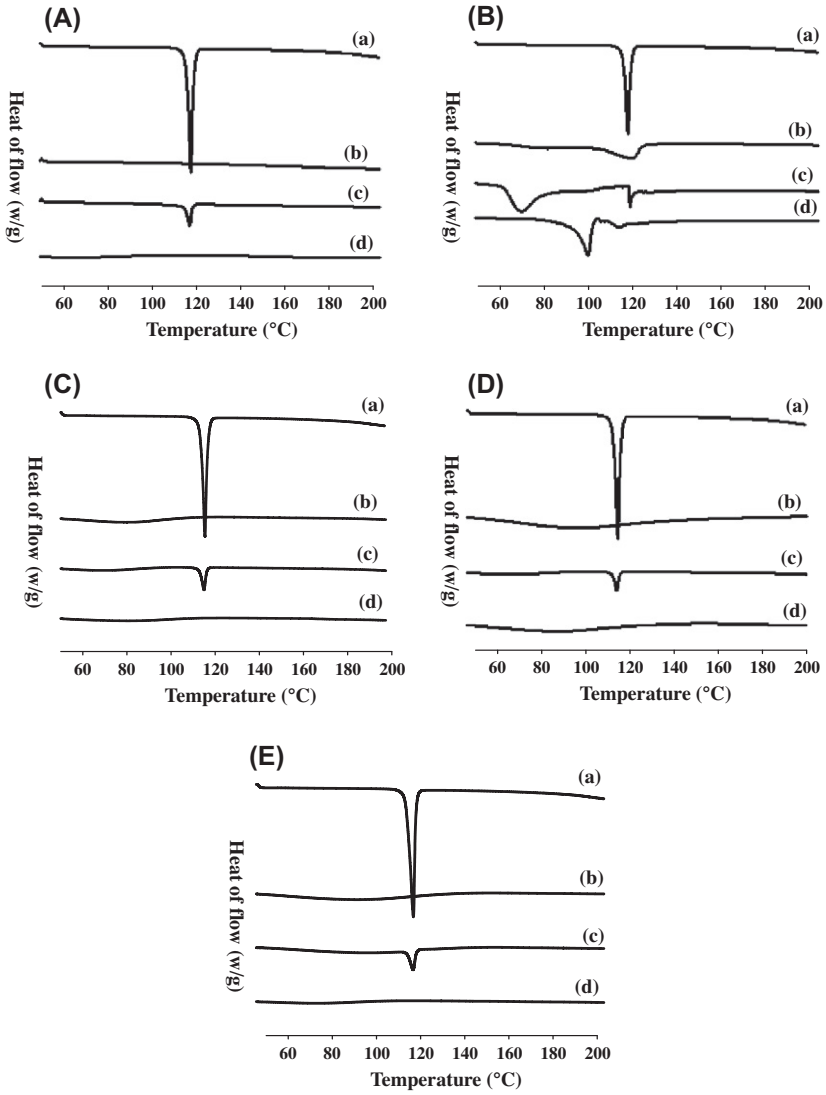

Fig. 5. Differential scanning calorimetric thermogram: (A) silicon dioxide; (B) magnesium stearate; (C) PVA; (D) Na-CMC; (E) HP-β-CD: (a) flurbiprofen; (b) carrier; (c) physical mixture; (d) SNEDDS.

in the SNEDDS formulation prepared with magnesium stearate, suggesting that there might be an interaction between the drug and the carrier during spray-drying. Thus, the crystalline property of the drug in this SNEDDS was not proven, and further study on this is needed.

3.4. Dissolution

The dissolution rate of the drug from the solid SNEDDS formulations was compared with that of flurbiprofen powder (Fig. 7). After 5 min, the solid SNEDDS formulations prepared with silicon dioxide, magnesium stearate and HP-β-CD showed higher dissolution rates than the powder. In particular, the solid SNEDDS formulations prepared with silicon dioxide gave a dissolution rate of about 80% within 5 min as a result of the fast spontaneous emulsion formation and the smallest droplet size. Among the solid SNEDDS formulations tested, the solid SNEDDS formulation prepared with magnesium stearate showed the highest dissolution rate of 100% within 20 min. About 90% of the drug was dissolved from the solid SNEDDS formulation prepared with HP-β-CD within 5 min. On the other hand, the hydrophilic carriers PVA and Na-CMC hardly improved the dissolution rate of flurbiprofen from the solid SNEDDS formulations. These solid SNEDDS formulations showed sustained release of the drug.

3.5. Pharmacokinetics

Fig. 8 shows the change in the mean plasma concentration of flurbiprofen after the oral administration of flurbiprofen powder or each of the solid SNEDDS to rats. The total plasma concentrations of the drug in all of the solid SNEDDS formulations were higher than in flurbiprofen powder. In particular, the initial plasma concentrations of drug in all of the solid SNEDDS formulations were significantly higher than in flurbiprofen powder [28]. Moreover, the solid SNEDDS formulations prepared with magnesium stearate and silicon dioxide gave higher plasma concentrations of flurbiprofen than the other formulations. In particular, from 1.5 to 4 h, the plasma concentrations of drug in these solid SNEDDS formulations were significantly higher than in the others. Furthermore, the solid SNEDDS formulation prepared with Na-CMC maintained high levels of flurbiprofen: 13–16 μg/ml until 6 h.

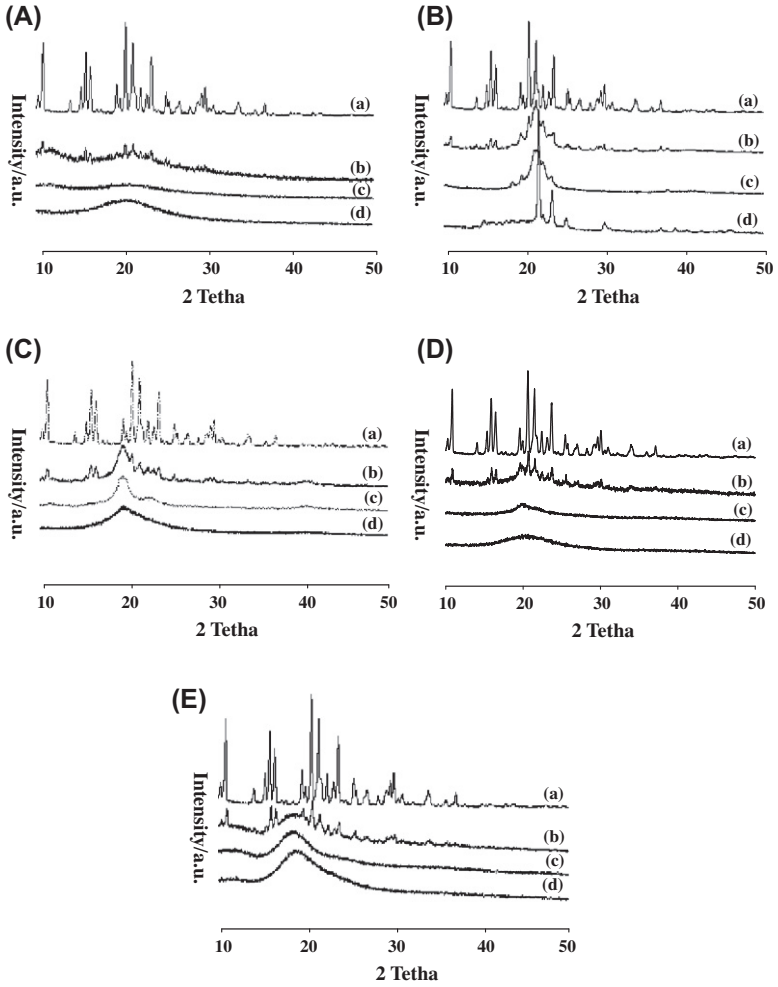

Fig. 6. X-ray powder diffraction: (A) silicon dioxide; (B) magnesium stearate; (C) PVA; (D) Na-CMC; (E) HP-β-CD; (a) flurbiprofen; (b) physical mixture; (c) carrier; (d) SNEDDS.

The pharmacokinetic parameters are shown in Table 3. The solid SNEDDS formulations gave a significantly higher AUC and C_{max} of flurbiprofen than the flurbiprofen powder ($p < 0.05$). The AUC values of all of the formulations were 3–15-fold greater than that of the powder, indicating that all of the formulations improved the oral bioavailability of flurbiprofen. The AUC values of flurbiprofen in the solid SNEDDS formulations were in the order of silicon dioxide > magnesium stearate > Na-CMC > HP-β-CD > PVA. However, the solid SNEDDS formulations prepared with silicon dioxide, magnesium stearate and Na-CMC showed no significant differences in the AUC values. Similarly, there was no significant difference in the AUC value between HP-β-CD and PVA. The enhanced oral bioavailability of flurbiprofen from the solid SNEDDS formulations prepared with silicon dioxide and magnesium stearate 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 SNEDDS formulations. In particular, the improved oral bioavailability of flurbiprofen by Na-CMC, even though it showed a relatively low dissolution rate of the drug, was partly due to the sustained release of the drug. Moreover, magnesium stearate and silicon dioxide showed significantly higher C_{max} values of flurbiprofen than the others ($p < 0.05$) due to the increased solubility induced by the formation of the eutectic mixture [22,29]. Nevertheless, the T_{max} value of the solid SNEDDS formulations was not significantly different from that of the flurbiprofen powder. Moreover, except for Na-CMC, the $t_{1/2}$ values of the solid SNEDDS formulations were not significantly different from those of the powder. The solid SNEDDS formulation prepared with Na-CMC had an 8-fold higher $t_{1/2}$ compared to the powder, suggesting that it showed a controlled release pattern due to the postponed release by Na-CMC.

4. Discussion

In this study, the solid SNEDDS formulations were prepared by spray-drying an aqueous solution containing liquid SNEDDS and various carriers. The liquid SNEDDS was composed of Labrafil M 1944 CS/Labrasol/Trasncutol HP (12.5/80/7.5%) with 2% w/v flurbiprofen loading. Furthermore, the hydrophobic solid carriers, silicon dioxide and magnesium stearate, and the hydrophilic solid carriers, PVA, Na-CMC and HP-β-CD, were used.

Silicon dioxide, a hydrophobic solid carrier, produced an excellent conventional solid SNEDDS with a nanoemulsion droplet size similar to that of the liquid SNEDDS (about 100 nm) and which was smaller than the other solid SNEDDS formulations. Its DSC and X-ray results indicate that the drug was in an amorphous state in this SNEDDS. Furthermore, this formulation greatly improved the dissolution rate and oral bioavailability of the drug in rats because it allowed the spontaneous formation of an interface

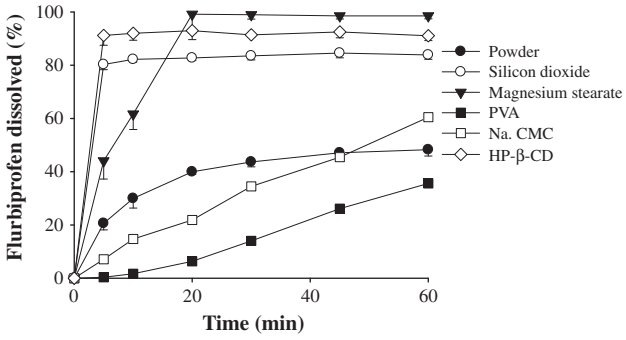

Fig. 7. Dissolution profile of flurbiprofen powder and solid SNEDDS formulations in water. Each value represents the mean ± SD (n = 6).

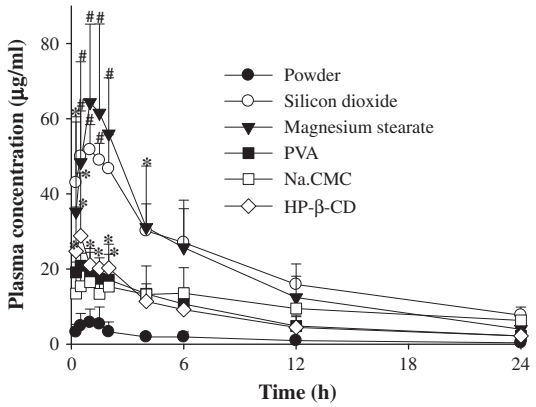

Fig. 8. Plasma concentration–time profiles of flurbiprofen after the oral administration of powder and solid SNEDDS formulations in rats. Each value represents the mean ± SD (n = 6). $^{*}p < 0.05$ compared with powder. $^{\#}p < 0.05$ compared with PVA, Na-CMC and HP-β-CD.

Table 3
Pharmacokinetic parameters (each value represents the mean ± SD, n = 6).

Parameters	T_{max} (h)	C_{max} (μg/ml)	AUC (h μg/ml)	$t_{1/2}$ (h)
Powder	0.87 ± 0.29	5.58 ± 3.83	40.78 ± 7.78	2.11 ± 1.99
Silicon dioxide	0.84 ± 0.36	53.38 ± 6.70[a,b,c]	609.10 ± 151.99[a,b]	6.50 ± 2.89
Magnesium stearate	1.12 ± 0.37	64.12 ± 17.36[a,b,c]	483.36 ± 41.27[a,b]	2.31 ± 2.39
PVA	0.50 ± 0.19	20.87 ± 3.43[a]	178.33 ± 66.74[a]	7.13 ± 2.46
Na-CMC	0.72 ± 0.95	16.46 ± 10.12[a]	451.48 ± 131.28[a,b]	17.48 ± 5.96[a]
HP-β-CD	0.46 ± 0.29	29.43 ± 6.08[a]	186.86 ± 82.77[a]	4.28 ± 1.56

[a] $p < 0.05$ compared with powder.
[b] $p < 0.05$ compared with PVA and HP-β-CD.
[c] $p < 0.05$ compared with Na-CMC.

between the oil droplets and the water and decreasing the size of the droplets [10]. 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 [1]. 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.

Magnesium stearate, a hydrophobic solid carrier, produced an agglomerated solid SNEDDS with the largest diameter of all of the solid SNEDDS. Our DSC and X-ray results indicated that it interacted with the drug. This interaction was due to the formation of a simple eutectic mixture between magnesium stearate and flurbiprofen [29]. Like silicon dioxide, it greatly enhanced the dissolution rate and oral bioavailability of the drug in rats. In a preliminary study, there was no significant change in the drug contents in this solid SNEDDS formulation (data no shown). Our results suggested that the highest dissolution rate was due to the formation of a eutectic mixture [30]. However, the solid SNEDDS prepared with magnesium stearate could be unstable over time because of its interaction with the drug.

The hydrophilic carriers PVA, Na-CMC and HP-β-CD did not form a solid SNEDDS but rather a solid dispersion (or microcapsule), even though the drug showed an amorphous state in this formulation. Among the hydrophilic carriers, only HP-β-CD improved the dissolution rate of the drug due to its solubilizing capacity [18,19], even though it had a relatively large droplet size (see Table 2). However, it did not improve the oral bioavailability of the drug as much as the other hydrophobic polymers. Polyvinyl alcohol and Na-CMC hardly improved the dissolution rate of flurbiprofen from the solid SNEDDS formulations. These solid SNEDDS formulations showed sustained release of the drug [14,15]. The SNEDDS must be immediately dispersed in a medium and become swollen when dissolved in water. Subsequently, the drug can easily and swiftly diffuse out to the medium [10,31]. Thus, hydrophilic polymers such as PVA and Na-CMC could not play a role as carriers in the preparation of solid SNEDDS formulations. Instead, they formed a microcapsule or solid dispersion. However, PVA and Na-CMC maintained constantly high plasma levels for a long period. In particular, Na-CMC showed a relatively high AUC value and long half-life due to the maintenance of high plasma drug levels for 6 h, due to the sustained release of flurbiprofen.

5. Conclusion

In conclusion, the formation of solid SNEDDS was found to be dependent upon the carrier. A hydrophobic carrier such as silicon dioxide must be chosen for the preparation of excellent solid SNEDDS with nanoemulsion droplet sizes. However, magnesium stearate, a hydrophobic carrier, formed a poor solid SNEDDS due to its interaction with the drug. Furthermore, all of the carriers had significant and positive effects on the crystalline properties, dissolution rate and oral bioavailability of flurbiprofen in the solid SNEDDS. As the drug dissolved in the liquid SNEDDS was spray-dried in the preparation of solid SNEDDS, the drug was kept in an amorphous state in the solid SNEDDS formulations. When the SNEDDS was 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. Thus, the SNEDDS prepared with hydrophobic carriers improved the dissolution rate and the oral bioavailability of flurbiprofen due to the fast spontaneous emulsion formation and the decreased droplet size. However, the hydrophilic carriers PVA, Na-CMC and HP-β-CD could enhance these properties via other mechanisms, such as their solubilizing capacity and sustained release property, even though the hydrophilic carriers could form not solid SNEDDS, but solid dispersions instead. Thus, in the development of solid SNEDDS, the selection of carrier plays an important role in the crystalline properties, dissolution and oral bioavailability of flurbiprofen and in the formation of solid SNEDDS. For more detailed comparison of these solid SNEDDS systems with various carriers, further study on its stability will be performed.

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