International Journal of Pharmaceutics 395 (2010) 161–166

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Effect of the solid-dispersion method on the solubility and crystalline property of tacrolimus

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ARTICLE INFO

Article history:
Received 19 January 2010
Received in revised form 13 May 2010
Accepted 18 May 2010
Available online 24 May 2010

Keywords:
Solid-dispersion method
Tacrolimus
Hydroxypropyl-β-cyclodextrin
Dioctyl sulfosuccinate
Solubility

ABSTRACT

Three solid dispersions containing poorly water-soluble tacrolimus were prepared with hydroxypropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulfosuccinate (DOSS) using a spray-drying technique via the solvent-evaporation method with a methylene chloride/ethanol mixture, the solvent-wetting method with ethanol and the surface-attached method with water, respectively. The solubility and dissolution of the drug in the three solid dispersions were evaluated compared to drug powder. Furthermore, their physicochemical properties were investigated using SEM, DSC and powder X-ray diffraction. The solubility and dissolution of the drug were significantly improved in the order of the tacrolimus-loaded solid dispersion prepared by: solvent-evaporation method > solvent-wetting method > surface-attached method. The solid dispersions prepared by solvent evaporation appeared as an aggregated form with the amorphous form. In particular, the solid dispersion prepared by the solvent-evaporation method improved solubility about 900-fold and dissolution of tacrolimus 15-fold because of its reduced particle size, increased surface area and close contact between the hydrophilic carrier and the drug. In the solvent-wetting method, the drug, which was changed to an amorphous form, was attached onto the surface of undissolved carriers. However, the solid dispersion prepared by the surface-attached method gave an unchanged crystalline form. In this solid dispersion, the carriers were attached to the surface of the undissolved drug, resulting in changing the drug from being hydrophobic to hydrophilic. As the crystal form of drug in this solid dispersion was not converted to the amorphous form unlike other solid dispersions, it gave relatively less solubility and dissolution of the drug than did the others. Thus, in the development of a solid-dispersion system containing poorly water-soluble drugs, the method of preparation plays an important role in the solubility and crystallinity of the drugs.

1. Introduction

Tacrolimus with potent immunosuppressive activity is poorly water-soluble (Honbo et al., 1987; Kino et al., 1987; Tamura et al., 2002). In order to improve the solubility of tacrolimus, various oral formulations of tacrolimus such as an inclusion complex (Arima et al., 2001), nanoparticles (Nassar et al., 2008; Sinswat et al., 2008), a prodrug with poly(ethylene glycol) esters (Chung and Cho, 2004), liposome (Lee et al., 1995), microemulsion (Borhade et al., 2008a,b) and solid dispersion with sodium carboxylmethyl cellulose (Park et al., 2009; Yamashita et al., 2003) have been studied.

The solid-dispersion system is a well-established method for increasing the solubility of poorly water-soluble drugs. Several solid-dispersion methods such as the melting method, the solvent-evaporation method and the solvent-wetting method were previously reported to prepare the solid dispersions (Miller et al., 2007; Leuner and Dressman, 2000; Yamashita et al., 2003). Moreover, a novel solid-dispersion system termed 'surface-attached solid dispersion' has been developed (Li et al., 2010; Park et al., 2009). Unlike other solid dispersions, surface-attached solid dispersion is prepared with water and carriers without an organic solvent for enhancing the solubility and stability of poorly water-soluble drugs. This solid-dispersion method has several advantages over other methods on an industrial scale, such as there being no necessity to remove an organic solvent, less potential toxicity and no danger of explosion of organic solvents. Furthermore, this solid dispersion could enhance the solubility and bioavailability of poorly water-soluble drugs without changing their crystalline state (Li et al., 2010; Park et al., 2009).

In this study, to evaluate the effect of the solid-dispersion method on the solubility and crystallinity of poorly water-

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0378-5173/$ – see front matter.
doi:10.1016/j.ijpharm.2010.05.023

soluble tacrolimus, three solid dispersions containing poorly water-soluble tacrolimus were prepared with hydroxypropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulfosuccinate (DOSS) using a spray-drying technique via the solvent-evaporation method with methylene chloride/ethanol mixture, the solvent-wetting method with ethanol and the surface-attached method with water, respectively. The solubility and dissolution of the drug in the three solid dispersions were evaluated compared to drug powder. Furthermore, their physicochemical properties were investigated using SEM, DSC and X-ray diffraction.

2. Materials and methods

2.1. Materials

Tacrolimus was purchased from Shanghai Qiao Chemical Science Co. (Shanghai, China). Hydropropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulfosuccinate (DOSS) were supplied from Hanmi Pharm. Co. (Suwon, South Korea). Sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and polyethylene glycol 6000 were purchased from Duksan Chemical Co. (Ansan, Korea). Poloxamer 188 was purchased from BASF (Ludwigshafen, Germany). All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of three tacrolimus-loaded solid dispersions

A Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland) was used for the preparation of the tacrolimus-loaded solid dispersions. Three tacrolimus-loaded solid dispersions were prepared with 1 g tacrolimus, 8 g HP-β-CD and 0.1 g DOSS. Tacrolimus was used after pre-sieving through 60 mesh screen. In the solvent-evaporation method, they were dissolved in 300 ml methylene chloride/ethanol mixture (1:2, v/v). In the solvent-wetting method, tacrolimus and DOSS were dissolved in 300 ml ethanol, and HP-β-CD was dispersed. Conversely, in the surface-attached method, HP-β-CD and DOSS were dissolved in 300 ml water, and tacrolimus was dispersed. They were then delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump and spray-dried at 125 °C inlet temperature and 65–70 °C outlet temperature. The pressure of the sprayed air was 4 kg/cm^2 and the flow rate of the drying air was maintained at the aspirator setting of 10 which indicated the pressure of the aspirator filter vessel as −25 mbar. The direction of air flow was the same as that of sprayed products.

2.3. Aqueous solubility

Excess of tacrolimus powder (about 10 mg) were added to 10 ml of 1% carriers shown in Table 1. Furthermore, excessive amount of solid dispersions (about 20 mg) were added to 10 ml of water. They were shaken in a water bath for 3 days, centrifuged at 3000 × *g* for 10 min (Eppendorf, USA) and filtered through a membrane filter (0.45 μm). The concentration of tacrolimus in the resulting solution was then analyzed by HPLC as described below.

2.4. Dissolution

Three solid dispersions equivalent to 1 mg of tacrolimus were inserted into a sinker and placed in the dissolution tester (Shinseang Instrument Co., South Korea) (Choi et al., 1998). A dissolution test was performed at 37 ± 0.5 °C using the paddle method at 50 rpm with 500 ml 0.005% hydroxypropyl cellulose solution adjusted to pH 4.5 with phosphoric acid. At predetermined intervals, 3 ml of the medium was sampled and filtered through a membrane filter (0.45 μm). Then, the concentration of tacrolimus in the supernatant layer was analyzed by HPLC. The resulting solution (2 ml) was mixed with 0.5 ml of acetonitrile solution, vortexed for 2 min and centrifuged at 10,000 × *g* for 10 min. Then, 100 μl of the supernatant layer was analyzed by HPLC (Hitachi, Tokyo, Japan) equipped with a Supecosil LC-CN column (SUPELCO^{TM}, 3 μm, 7.5 cm × 4.6 mm i.d.) and UV detector (Model L-2420). The mobile phase consisted of water, acetonitrile and isopropanol (7/2/1, v/v/v). The eluent was monitored at 210 nm with a flow rate of 0.4 ml/min (Moyano et al., 2006).

Table 1
Aqueous solubility of tacrolimus.

Carriers	Aqueous solubility (μg/ml)
Water	0.67 ± 0.19
Polymeric carrier	
Sodium carboxymethyl cellulose	7.51 ± 1.29
Hydroxypropylmethyl cellulose	1.95 ± 0.14
Hydroxypropyl-β-cyclodextrin	14.25 ± 1.35
Surfactants	
Polyethylene glycol 6000	1.00 ± 0.15
Poloxamer 188	2.02 ± 0.20
Dioctyl sulfosuccinate	190.64 ± 21.27

Each value means the solubility of tacrolimus in the distilled water containing 1% polymeric carrier or surfactant.
Each value represents the mean ± SE (n = 5).

2.5. Shape and surface morphology

The shape and surface morphology of the three tacrolimus-loaded solid dispersions were examined using a scanning electron microscope (S-4100, Hitachi, Japan). The powders were fixed on a brass specimen club using double-side adhesive tape and made electrically conductive by coating in a vacuum (6 Pa) with platinum (6 nm/min) using a Hitachi Iron Sputter (E−1030) for 300 s at 15 mA (Newa et al., 2007).

2.6. Thermal characteristics and crystallinity

The thermal characteristics of tacrolimus powder, carriers and solid dispersions were investigated using a differential scanning calorimeter (DSC-2010, TA Instruments, USA). Samples of about 2 mg were placed in sealed aluminium pans, before heating under a nitrogen flow (25 ml/min) at a heating rate of 10 °C/min from 30 to 215 °C. Furthermore, the crystallinity of the powder, carriers and solid dispersions were assessed by X-ray powder diffraction (D/MAX-2500, Rigacu, Japan) conducted at 25 °C using monochromatic Cu Kα-radiation (λ = 1.54178 Å) at 40 mA and 40 kV in the region of $2.5^\circ \leq 2\theta \leq 40^\circ$ with an angular increment of 0.02°/s.

3. Results

To select a polymer and surfactant as carriers suitable for tacrolimus-loaded solid dispersion, the solubility of tacrolimus in the distilled water containing 1% carriers (Table 1). The aqueous solubility of tacrolimus was about 0.7 μg/ml, which indicated that this drug was poorly water-soluble (Tamura et al., 2002; Watts et al., 2009). Among the polymers tested, HP-β-CD showed maximum solubility of drug. Furthermore, among the surfactants tested, the solubility of tacrolimus at DOSS was highest as about 190 μg/ml. Thus, HP-β-CD and DOSS were selected as carriers in the preparation of tacrolimus-loaded solid dispersions.

The tacrolimus-loaded solid dispersions were prepared with 1 g tacrolimus, 1–8 g HP-β-CD and 0.01 g DOSS using solvent-evaporation method. The effect of HP-β-CD on the aqueous solubility of tacrolimus in the solid dispersions was then investigated (Fig. 1). In the preparation of solid dispersion, DOSS was

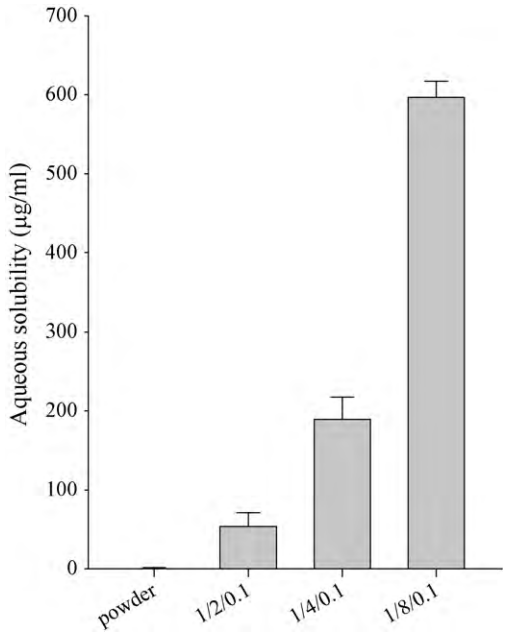

Fig. 1. Effect of HP-β-CD on the aqueous solubility of tacrolimus. All solid dispersions were composed of tacrolimus, HP-β-CD and DOSS. Each value represents the mean ± SD ($n = 5$).

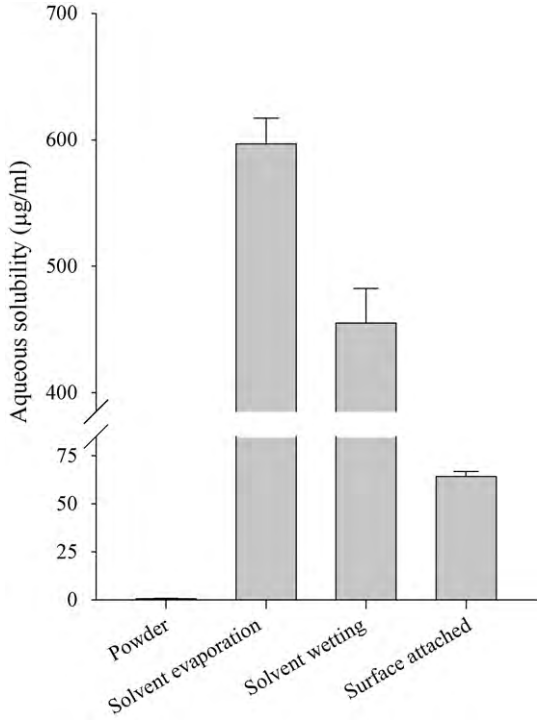

Fig. 2. Effect of the solid-dispersion method on the aqueous solubility of tacrolimus. All solid dispersions were composed of tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1. Each value represents the mean ± SD ($n = 5$).

used to avoid attaching solid-dispersions to the inner wall of spray-drying chamber (Li et al., 2008). Furthermore, this material could improve the solubility of poorly water-soluble drugs in the development of solid dispersion (Park et al., 2009). The aqueous solubility of tacrolimus in the solid dispersion was significantly increased with increased amount of HP-β-CD. Thus, the tacrolimus-loaded solid dispersion composed of tacrolimus, HP-β-CD and DOSS with a weight ratio of 1/8/0.1 was selected for further study.

In the solvent-evaporation method, they were dissolved in methylene chloride/ethanol mixture (Leuner and Dressman, 2000). In the solvent-wetting method, tacrolimus and DOSS were dissolved in ethanol, and HP-β-CD was dispersed (Yamashita et al., 2003). Conversely, in the surface-attached method, HP-β-CD and DOSS were dissolved in water, and tacrolimus was dispersed (Choi et al., 2001; Li et al., 2008; Yong et al., 2004). All the resulting productions were spray-dried under the same conditions, leading to the production of three different tacrolimus-loaded solid dispersions.

The aqueous solubility of tacrolimus in these solid dispersions is given in Fig. 2. All the solid dispersions increased the drug solubility over that of the drug powder. Furthermore, the aqueous solubility of the drug was significantly improved in the order of the tacrolimus-loaded solid dispersion prepared by: solvent-evaporation method > solvent-wetting method > surface-attached method. In particular, the solid dispersion prepared by the solvent-evaporation method improved about 900-fold the solubility of the drug compared to drug powder.

To evaluate the dissolution of the drug from the solid dispersions, the dissolution test on three tacrolimus-loaded solid dispersions was carried out (Fig. 3). Similarly, all the solid dispersions gave higher dissolution rates compared to the drug powder. Among the solid dispersions tested, the solid dispersion prepared by the solvent-evaporation method with the highest drug solubility gave the significantly highest dissolution rate of the drug (Craig, 2002). The dissolution amount of drug from it at 60 min was about 15-fold higher compared to the drug powder (69.80 ± 4.69% vs. 4.38 ± 0.48%).

Scanning electron micrographs of tacrolimus powder and solid dispersions are shown in Fig. 4. Tacrolimus powder (Fig. 4A) appeared as smooth-surfaced rectangular crystals in shape (Yamashita et al., 2003). The solid dispersion prepared by the solvent-evaporation method (Fig. 4B) gave an aggregated form with a smooth surface. However, the solid dispersion prepared by the

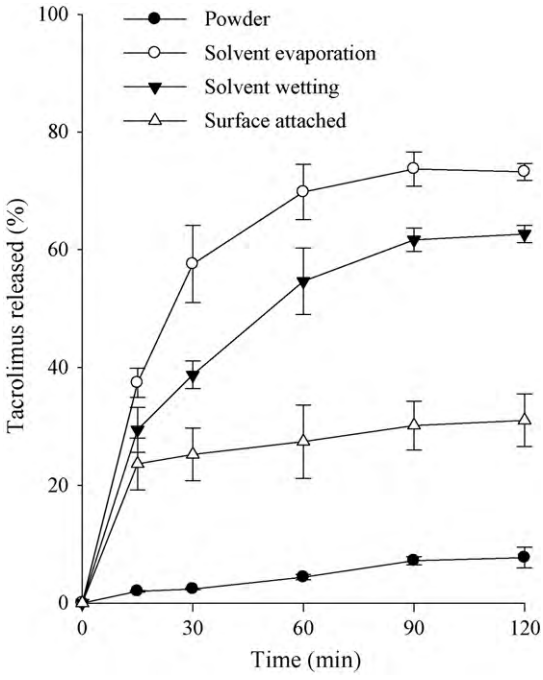

Fig. 3. Effect of the solid-dispersion method on the dissolution of tacrolimus. All solid dispersions were composed of tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1. Each value represents the mean ± SD ($n = 6$).

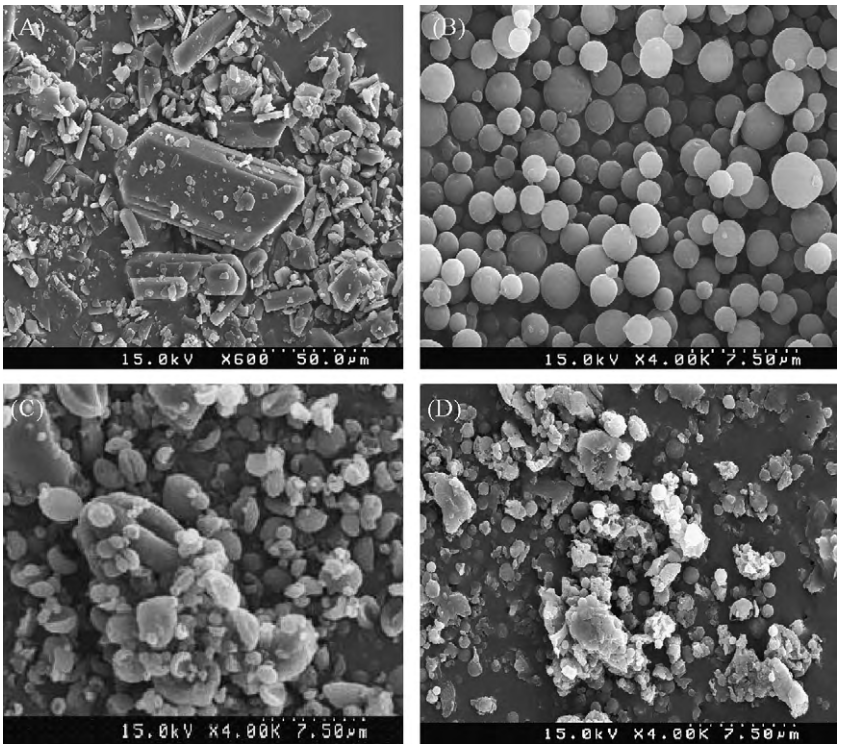

Fig. 4. Scanning electron micrographs: (A) tacrolimus powder (600×), (B) solid dispersion prepared by the solvent-evaporation method (4000×), (C) solid dispersion prepared by the solvent-wetting method (4000×) and (D) solid dispersion prepared by the surface-attached method (4000×). All solid dispersions were composed of tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1.

solvent-wetting method (Fig. 4C) gave a relatively rough surface and showed that the soluble drug might be attached onto the surface of the undissolved carrier. Similarly, the solid dispersion prepared by the surface-attached method (Fig. 4D) has a relatively rough surface and showed that the soluble carrier might be attached to the surface of the undissolved drug.

The thermal behaviour of the drug powder, carriers and solid dispersion are presented in Fig. 5. The DSC curve shows that tacrolimus has an endothermic peak at about 130 °C corresponding to its melting, indicating its crystalline nature (Fig. 5A) (Sinswat et al., 2008). HP-β-CD (Fig. 5B) and DOSS (Fig. 5C) had no intrinsic peaks. Furthermore, a relatively weak peak corresponding to the drug was also observed in the physical mixture (Fig. 5D). The physical mixture was prepared by simply mixing tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1. However, a sharp peak corresponding to the drug has disappeared and no peak was observed in the solid dispersion prepared by the solvent-evaporation method (Fig. 5E) and the solvent-wetting method (Fig. 5F), suggesting that the drug was present in an amorphous state (Walser et al., 1997). The solid dispersion prepared by the surface-attached method gave a characteristic peak corresponding to the drug (Fig. 5G), indicating the drug was present in an unchanged crystalline state (Park et al., 2009).

The powder X-ray diffractometry patterns are shown in Fig. 6. Tacrolimus gave sharp peaks at diffraction angles showing a typical crystalline pattern (Fig. 6A) (Yamashita et al., 2003). All major char-

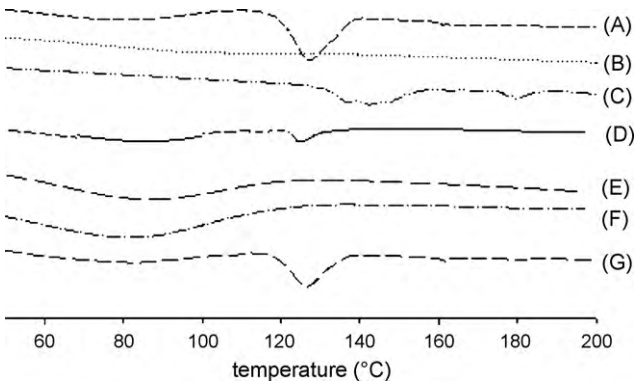

Fig. 5. Differential scanning calorimetric thermograms: (A) tacrolimus powder, (B) HP-β-CD, (C) DOSS, (D) physical mixture, (E) solid dispersion prepared by the solvent-evaporation method, (F) solid dispersion prepared by the solvent-wetting method and (G) solid dispersion prepared by the surface-attached method. The physical mixture was prepared by simply mixing tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1.

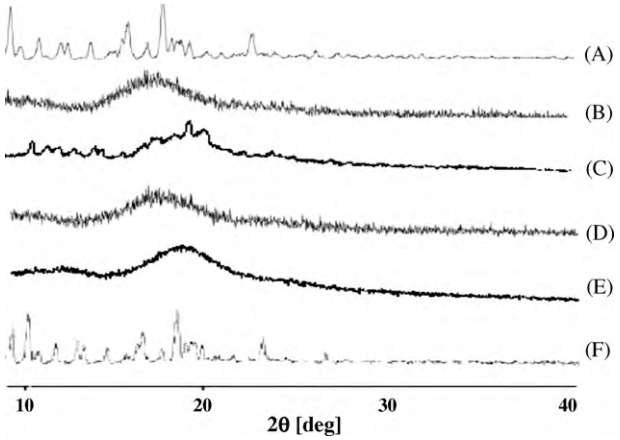

Fig. 6. X-ray powder diffraction: (A) tacrolimus powder, (B) HP-β-CD, (C) physical mixture, (D) solid dispersion prepared by the solvent-evaporation method, (E) solid dispersion prepared by the solvent-wetting method and (F) solid dispersion prepared by the surface-attached method. The physical mixture was prepared by simply mixing tacrolimus, HP-β-CD and DOSS in the weight ratio of 1/8/0.1.

acteristic crystalline peaks were observed in the physical mixture (Fig. 6C). However, they were hardly observed in the solid dispersion prepared by the solvent-evaporation method (Fig. 6D) and the solvent-wetting method (Fig. 6E). Thus, like the DSC results, the drug was present in an amorphous state (Doherty and York, 1987; Okimoto et al., 1997). Like the drug and the physical mixture, the characteristic crystalline peaks appeared in the solid dispersion prepared by the surface-attached method (Fig. 6F). Similarly, the drug was present in an unchanged crystalline state in this solid dispersion.

4. Discussion

The tacrolimus-loaded preparations composed of tacrolimus, HP-β-CD and DOSS with a weight ratio of 1/8/0.1 were prepared using three different solid-dispersion methods. In this study, solid state characterization such as SEM, DSC and powder X-ray diffractometry did not prove that tacrolimus formed inclusion complexes with HP-β-CD (Arima et al., 2001; Choi et al., 2001). Thus, our results suggested that these preparations were not inclusion compounds but simple solid-dispersion systems.

In the solvent-evaporation method, the drug and carriers were dissolved in organic solvents and spray-dried, leading to production of a tacrolimus-loaded solid dispersion. This solid dispersion appeared as an irregular aggregate form with smooth surfaces. It changed the drug crystallinity to an amorphous form, since the drug was soluble in the organic solvent followed by re-crystallizing through the elimination of solvents (Leuner and Dressman, 2000).

In the solvent-wetting method, the drug was dissolved and the carrier was dispersed in the solvent, and spray-dried, resulting in another tacrolimus-loaded solid dispersion. In this solid dispersion, the dissolved drug was attached to the surface of dispersed carriers. Like the solvent-evaporation method, the drug was transferred in an amorphous state, as it was soluble in the organic solvent followed by re-crystallizing onto the carrier surface by the elimination of solvents (Yamashita et al., 2003). However, the solid dispersion prepared by this method gave significantly lower solubility and dissolution of tacrolimus than did that prepared by the solvent-evaporation method. In the solvent-evaporation method, the drugs were dissolved together with polymeric carriers in the organic solvent followed by re-crystallizing together with the carrier by the elimination of solvents. Thus, in the preparation of solid dispersion, polymeric carriers dissolved and re-crystallized together with dissolved drugs in the solvent-evaporation method may give significantly lower solubility and dissolution compared to non-dissolved polymeric carriers due to achievement of higher levels of particle size reduction and surface area enhancement (Taylor and Zografi, 1997; Yamashita et al., 2003).

In the surface-attached method, the carrier was dissolved and the drug was dispersed in water (Chutimaworapan et al., 2000). The resulting dispersion was spray-dried, resulting in the production of the other solid dispersion. Unlike the other solid-dispersion methods, it did not change the crystallinity of drug. Simply, it changed the drug from being hydrophobic to hydrophilic, because the dissolved carrier was attached to the surface of dispersed drug particles (Li et al., 2010).

Among the solid dispersions tested, the solid dispersion prepared by the solvent-evaporation method gave the highest solubility and dissolution. Thus, the most enhanced solubility of poorly water-soluble tacrolimus was due to the transformation of drug crystallinity into the amorphous state and its reduced particle size, increased surface area and close contact between the hydrophilic carrier and drug resulting from dissolving and re-crystallizing of the drug in the organic solvents (Leuner and Dressman, 2000; Yamashita et al., 2003). The solid dispersion prepared by the surface-attached method improved the drug's solubility and dissolution less than the other methods did. However, as water was used as a solvent unlike the other solid-dispersion methods, this solid-dispersion method had several advantages over other methods on an industrial scale, such as there is no necessity to remove an organic solvent and the ease of meeting strict legally required air-quality controls, less potential toxicity and no danger of explosion of organic solvents (Kachrimanis et al., 2000; Khan and Jiabi, 1998).

5. Conclusion

In the solvent-evaporation and solvent-wetting methods, the drug in the solid dispersions was converted to an amorphous form. However, in the surface-attached method, the drug was not changed. It only changed the drug from being hydrophobic to hydrophilic, because the dissolved carrier was attached to the surface of the dispersed drugs. The solid dispersion prepared by the solvent-evaporation method gave the highest solubility and dissolution. However, even if the solid dispersion prepared by the surface-attached method enhanced the drug's solubility and dissolution less than the other methods, it had several advantages, because water was used as a solvent unlike the other solid-dispersion methods. Thus, in the development of a solid-dispersion system containing poorly water-soluble drugs, the preparation method plays an important role in the solubility and crystallinity of the drugs.

Acknowledgements

This work was supported by Mid-career Researcher Program through 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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