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Surface-attached Solid Dispersion

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ABSTRACT – A novel surface-attached solid dispersion is designed to improve the solubility and oral bioavailability of poorly water-soluble drugs without crystalline change. Accordingly, it draws increasing interest because of excellent stability and no pollution for accomplishing enhanced solubility and bioavailability, which have recently been highlighted in connection with a number of higher value-added poorly water-soluble drugs. In addition, excellent stability can be attained when the poorly water-soluble drugs are not dissolved but dispersed in water and provide no crystallinity change. This solid dispersion is given by means of attaching the dissolved carriers such as hydrophilic polymer and surfactant to the surface of dispersed drug particles followed by changing the hydrophobic drug to hydrophilic form. The aim of the present review is to outline the preparation, physicochemical property and bioavailability of novel surface-attached solid dispersion with improved solubility and bioavailability of poorly water-soluble drugs without crystalline change

Key words – poorly water-soluble drug, surface-attached solid dispersion, no changeable crystal, solubility, bioavailability, stability

Generally, poorly water-soluble drugs have low aqueous solubility and high membrane permeability included in class 2 of Biopharmaceutical Classification System (Amidon et al., 1995). Various oral formulations such as solid dispersions (Jung et al., 1999; Kipp, 2004; Overhoff et al., 2007), inclusion complex (Buchanan et al., 2007; Choi et al., 2001; Holvoet et al., 2007), hot-melt extrusion (Miller et al., 2007), dry elixir (Kim et al., 1997), salt formation (Gupta et al., 1997), microemulsion (Park et al, 1999) and micellar formulation (Yi et al., 2007; Yong et al, 2004) have been developed to improve the solubility and bioavailability of poorly water-soluble drugs.

One of the well established methods for increasing the solubility and bioavailability of poorly water-soluble drugs is solid dispersion system (Chiou and Riegelman, 1971). Drugs in solid dispersion systems may exist as an amorphous form in polymeric carriers. This system improved the solubility and dissolution rate of drug compared with crystalline material, since the drugs dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement (Craig, 2002; Taylor and Zografi, 1997). Several conventional methods such as melting, solvent evaporation and solvent wetting method were previously reported to prepare solid dispersions (Leuner and Dressman, 2000). However, the solid dispersion prepared by melting method with high temperature might chemically decompose the drugs (Miller et al., 2007; Newa et al, 2007). In the case of solvent evaporation method and solvent wetting method, the drug in the solid dispersions changed to amorphous form, resulting that the drug might be unstable (Yamashita et al., 2003). Furthermore, the large amounts of hydrophilic carriers against drug in these conventional solid dispersions must be needed to improve the solubility of poorly water-soluble drugs.

To solve these problems of conventional solid dispersions and improve the solubility of poorly water-soluble drugs without crystalline change, a novel solid-dispersion system termed 'surface-attached solid dispersion' has been developed (Joe et al., 2010; Li et al., 2010; Oh et al., 2010; Park et al., 2009a; Park et al., 2009b; Park et al., 2010). 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

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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., 2009b).

Preparation

A novel surface-attached solid dispersion was prepared using spray drying technique with water, hydrophilic polymer and surfactant and without organic solvent. First, to select a hydrophilic polymer and surfactant as carriers suitable for solid dispersions, the solubility of poorly water-soluble drugs in the distilled water containing 1% hydrophilic polymers or 10% surfactants were investigated. The hydrophilic polymer and surfactant selected for solid dispersions were dependent on the solubility nature of poorly water-soluble drugs. The carriers selected for solid dispersions of poorly water-soluble drugs are given in Table I.

In the novel surface-attached solid dispersion, relatively small amounts of carriers as given in Table I were dissolved and a poorly water-soluble drug was dispersed in water. On continuous stirring using magnetic bar, the resulting dispersed solutions were spray-dried, resulting in producing the surface-attached solid dispersion. In this novel solid dispersion, the dissolved carriers such as hydrophilic polymer and surfactant were attached to the surface of dispersed drug particles. This solid dispersion might change the hydrophobic drug to hydrophilic form, resulting in increased solubility and dissolution rate of poorly water-soluble drug (Fig. 1) (Joe et al., 2010; Park et al., 2009a; Park et al., 2009b; Park et al., 2010). This mechanism suggested that this novel solid dispersion might increase the solubility and dissolution rate of poorly water-soluble drug in the gastric-intestinal fluids as well as in distilled water.

Table I. *Carriers selected for Solid Dispersions of Poorly Water-soluble Drugs*

Drug	Carriers
Flurbiprofen	sodium carboxymethyl cellulose (Na-CMC), Tween 80
Tacrolimus	hydroxypropyl-β-cyclodextrin (HP-β-CD), dioctyl sulfosuccinate (DOSS)
Tacrolimus	sodium carboxylmethyl cellulose (Na-CMC), sodium lauryl sulfate (SLS)
Itraconazole	Polyvinylpyrroline (PVP), poloxamer 407
Sibutramine base	hydroxypropylmethyl cellulose (HPMC), poloxamer 407
Ibuprofen	hydroxypropylmethyl cellulose (HPMC), poloxamer 407

Solubility, Dissolution and Pharmacokinetics

To select an optimal formulation of solid dispersion which increased the drug solubility with the minimum amount of carriers, the effect of the amount of polymer and surfactant on aqueous solubility and dissolution rate of poorly water-soluble drug were investigated. All the solid dispersions gave higher drug solubility and dissolution compared to drug powder. However, in the case of liquid surfactant such as Tween 80, the solid dispersions with relatively larger amount of Tween 80 were sticky. Thus, the surfactant amounts must be controlled, because they were the physically unsuitable solid dispersions due to their stickiness. Furthermore, the solid dispersions with relatively lower polymer and higher surfactant could not form the solid dispersion system. Similarly, the solid dispersions with relatively higher polymer and lower surfactant could not enhance the solubility and dissolution rate. Thus, optimal amount or ratio of polymer and surfactant must be needed to form the solid dispersion. The optimal formulations of solid dispersions of poorly water-soluble drugs are shown in Table II. Furthermore, Table III gave the enhanced solubility and dissolution rate against drug powder via solid dispersions. The enhanced solubility and dissolution rate are 5-60 and 2-50 times against poorly water-soluble drugs powder, respectively. In particular, this solid dispersion (specifically, tacrolimus; Fig. 2) colud improve the initial dissolution rate of poorly water-soluble drugs (Chutimaworapan et al., 2000; Oh et al., 2010;

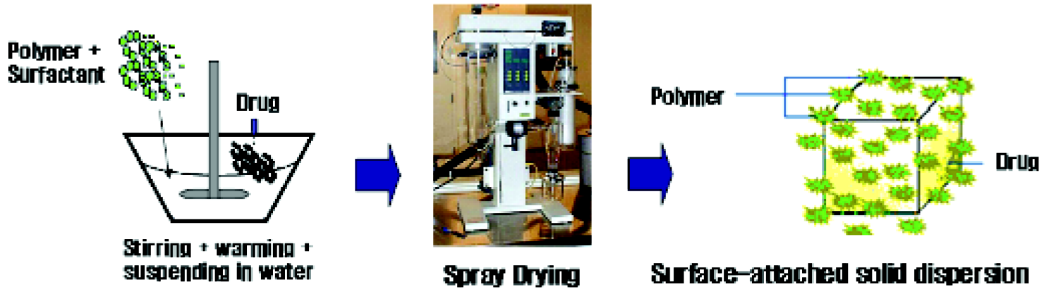

Fig. 1. Principle of surface-attached solid dispersion.

Table II. *Optimal Formulation of Solid Dispersions of Poorly Water-soluble Drugs*

Solid dispersion	Optimal formulation (weight ratio)
Flurbiprofen	flurbiprofen/Na-CMC/Tween 80 (6:2.5:0.5)
Tacrolimus	tacrolimus/HP-β-CD/DOSS (1/8/0.1)
Tacrolimus	tacrolimus/CMC-Na/SLS (3/1.2/0.3)
Itraconazole	itraconazole/PVP/poloxamer (10:2:0.5)
Sibutramine base	sibutramine base/HPMC/poloxamer/citric acid (5/3/3/0.2)
Ibuprofen	ibuprofen/HPMC/poloxamer (10:3:2)

Table III. *Enhanced Solubility, Dissolution Rate and Oral Bioavailability Against Drug Powder Via Solid Dispersions*

Solid dispersion	Solubility (times)	Dissolution rate at 30 min (times)	Oral bioavailability	
			C_{max} (times)	AUC (times)
Flurbiprofen	60	1.5	1.3[1)]	1.5[1)]
Tacrolimus	4	50	-	-
Tacrolimus	10	2		
Itraconazole	40	3.5	1.0[1)]	1.4[1)]
Sibutramine base	50	40	1.1[1)]	1.1[1)]
Ibuprofen	4	1.3	6.9	8.7

Data against drug powder except conventional product[1)]

Park et al., 2010).

The comparison of oral bioavailability of poorly water-soluble drug is determined by evaluating C_{max} and AUC after oral administration of solid dispersion and commercial product/drug powder. Similarly, Table III shows the comparison of oral bioavailability between solid dispersion and commercial product/drug powder. In the case of ibuprofen, the oral bioavailability such as C_{max} and AUC of drug by solid dispersion is about 7 and 9 times compared to drug powder, respectivley. Furthermore, the solid dispersion gave no significant difference in oral bioavailability such as C_{max} and AUC of drug compared to commercial product. However, from the plot on plasma concentration of drug after oral administration, the initial plasma concentrations of drug in most solid dispersion, were significantly higher compared with those in commercial product ($P<0.05$) (data not shown). Thus, the higher initial plasma concentrations of drug were due to the increased dissolution rate of drug in the solid dispersion (Kim et al., 1997; Li et al., 2008). These results suggest that the solid dispersion would be useful to deliver poorly water-soluble drugs in a pattern that allows fast absorption in the initial phase, leading to more complete absorption.

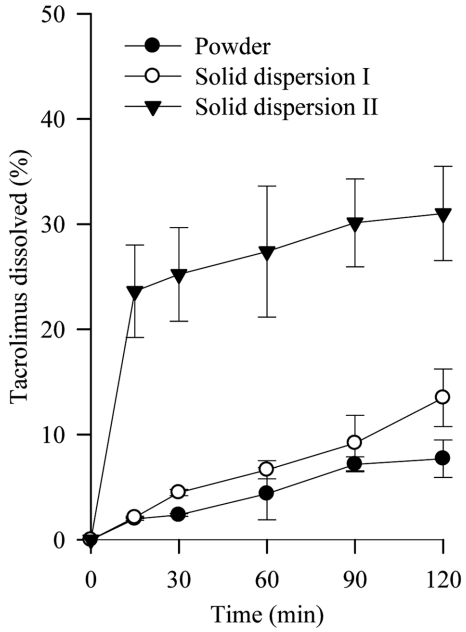

Figure 2. The dissolution of tacrolimus from solid dispersions. The solid dispersion I and II were composed of tacrolimus/CMC-Na/SLS at the weight ratio of 3/1.2/0.3 and 3/24/3, respectively. Each value represents the mean ± S.D. (n=6).

Stability

The stability of drug in the solid dispersion was evaluated by the crystalline observation and content of drug in the solid dispersion for 6 month at two different temperatures (Joe et al., 2010; Park et al., 2009b; Park et al., 2010). Tacrolimus was used as a model drug. There was no noticeable change in the crystalline of drug in the solid dispersion during the period (data not shown). The content of drug was decreased less than 3% even at 45ºC (data not shown). Thus, this solid dispersion was stable for at least 6 month.

Physicochemical property

Scanning electron micrographs of poorly water-soluble drug powder (specifically, tacrolimus) and solid dispersions are given in Fig. 3. Drug powder (Fig. 3A) appeared as smooth-surfaced rectangular crystals in shape (Yamashita et al., 2003). The solid dispersion prepared by the solvent-evaporation method (Fig. 3B) gave an aggregated form with a smooth surface. However, the solid dispersion prepared by the surface-attached method (Fig. 3C) had a relatively rough surface and showed that the soluble carrier might be attached to the surface of the undissolved drug (Joe et al., 2010; Park et al., 2009b; Park et al., 2010).

The thermal behaviour of the drug powder, carriers and solid

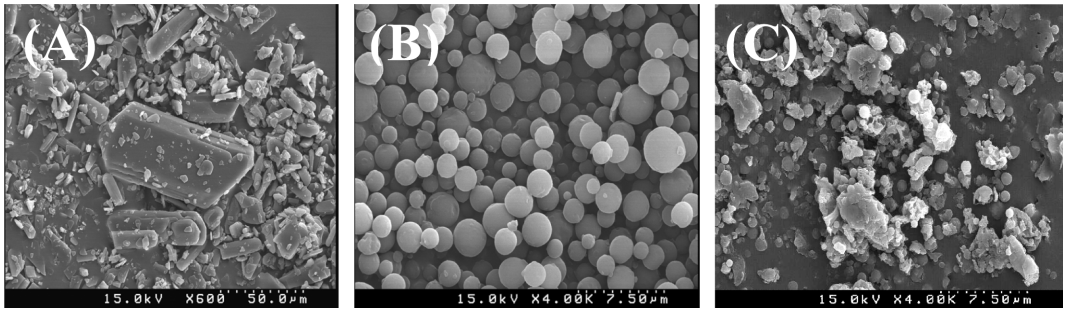

Figure 3. Scanning electron micrographs: (A), tacrolimus powder (X 600); (B), solid dispersion prepared by the solvent-evaporation method (X 4,000); (C), solid dispersion prepared by the surface-attached method (X 4,000).

dispersion are presented in Fig. 4. The DSC curve shows that drug has an endothermic peak at about 130°C corresponding to its melting, indicating its crystalline nature (Fig. 4A). A polymer (HP-β-CD) (Fig. 4B) and a surfactant (DOSS) (Fig. 4C) had no intrinsic peaks. Furthermore, a relatively weak peak corresponding to the drug was also observed in the physical mixture (Fig. 4D). However, a sharp peak corresponding to the drug had disappeared and no peak was observed in the solid dispersion prepared by the solvent-evaporation method (Fig. 4E), 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. 4F), indicating the drug was present in an unchanged crystalline state (Park et al., 2009b).

The powder X-ray diffractometry patterns are shown in Fig. 5. Drug gave sharp peaks at diffraction angles showing a typical crystalline pattern (Fig. 5A) (Yamashita et al., 2003). Polymer had no specific sharp peaks (Fig. 5B) All major characteristic crystalline peaks were observed in the physical mixture (Fig. 5C). However, they were hardly observed in the solid dispersion prepared by the solvent-evaporation method (Fig. 5D). 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. 5E). Similarly, the drug was present in an unchanged crystalline state in this solid dispersion.

In the conventional solid dispersion method, 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

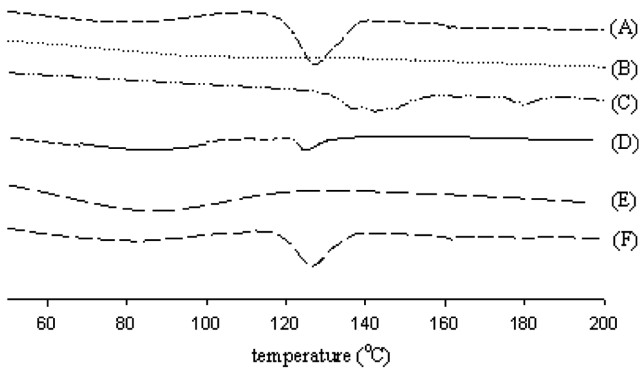

Figure 4. Differential scanning calorimetric thermograms: (A), tacrolimus powder; (B), polymer; (C), surfactant; (D), physical mixture; (E), solid dispersion prepared by the solvent-evaporation method; (F), solid dispersion prepared by the surface-attached method.

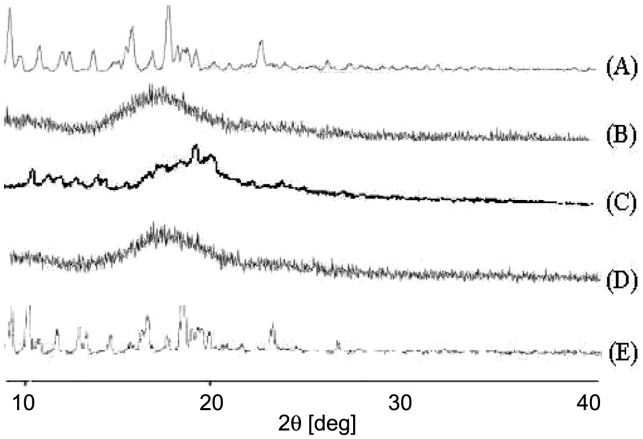

Figure 5. X-ray powder diffraction: (A), tacrolimus powder; (B), polymer; (C), physical mixture; (D), solid dispersion prepared by the solvent-evaporation method; (E), solid dispersion prepared by the surface-attached method.

Dressman, 2000). Generally, polymeric carriers dissolved and re-crystallized together with dissolved drugs in the solvent-evaporation method may give significantly lower solubility and dissolution rate compared to non-dissolved polymeric carriers due to achievement of higher levels of particle size reduc-

tion and surface area enhancement (Taylor and Zografi, 1997; Yamashita et al., 2003).

However, 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 solid dispersion. Unlike the conventional solid dispersion method, 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). The solid dispersion prepared by the surface-attached method improved the drug's solubility, dissolution rate and bioavailability less than the conventional 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).

Conclusion

In the conventional solid dispersion method such as solvent-evaporation, 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. However, even if the solid dispersion prepared by the surface-attached method enhanced the drug's solubility and dissolution rate less than that prepared by conventional solid dispersion method, it had several advantages, because water was used as a solvent unlike the other solid dispersion methods. Thus, the surface-attached solid dispersion would be an excellent candidate with improved the solubility and bioavailability of poorly water-soluble drugs without crystalline change.

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