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Effect of Solubilizing and Microemulsifying Excipients in Polyethylene Glycol 6000 Solid Dispersion on Enhanced Dissolution and Bioavailability of Ketoconazole

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Polyethylene glycol (PEG) 6000-based solid dispersions (SDs), by incorporating various pharmaceutical excipients or microemulsion systems, were prepared using a fusion method, to compare the dissolution rates and bioavailabilities in rats. The amorphous structure of the drug in SDs was also characterized by powder X-ray diffractometry (XRD) and differential scanning calorimetry (DSC). The ketoconazole (KT), as an antifungal agent, was selected as a model drug. The dissolution rate of KT increased when solubilizing excipients were incorporated into the PEG-based SDs. When hydrophilic and lipophilic excipients were combined and incorporated into PEG-based SDs, a remarkable enhancement of the dissolution rate was observed. The PEG-based SDs, incorporating a self microemulsifying drug delivery system (SMEDDS) or microemulsion (ME), were also useful at improving the dissolution rate by forming a microemulsion or dispersible particles within the aqueous medium. However, due to the limited solubilization capacity, these PEG-based SDs showed dissolution rates, below 50% in this study, under sink conditions. The PEG-based SD, with no pharmaceutical excipients incorporated, increased the maximum plasma concentration (C_{max}) and area under the plasma concentration curve ($AUC_{0\text{-}6h}$) two-fold compared to the drug only. The bioavailability was more pronounced in the cases of solubilizing and microemulsifying PEG-based SDs. The thermograms of the PEG-based SDs showed the characteristic peak of the carrier matrix around 60°C, without a drug peak, indicating that the drug had changed into an amorphous structure. The diffraction pattern of the pure drug showed the drug to be highly crystalline in nature, as indicated by numerous distinctive peaks. The lack of the numerous distinctive peaks of the drug in the PEG-based SDs demonstrated that a high concentration of the drug molecules was dissolved in the solid-state carrier matrix of the amorphous structure. The utilization of oils, fatty acid and surfactant, or their mixtures, in PEG-based SD could be a useful tool to enhance the dissolution and bioavailability of poorly water-soluble drugs by forming solubilizing and microemulsifying systems when exposed to gastrointestinal fluid.

Key words: Solid dispersion, Pharmaceutical excipients, Solubilizing and microemulsifying, Dissolution rate, Bioavailability, Crystal structure

INTRODUCTION

Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability. Solid dispersions (SDs) have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs (Chiou and Riegelman, 1971; Alden *et al.*, 1993; Betageri *et al.*, 1996; Mura *et al.*, 1996; Serajuddin, 1999; Franco *et al.*, 2001; Joshi *et al.*, 2004). SDs refer to the dispersion of one or more drugs in inert and solid water-soluble carriers, either molecularly or as fine particles. Mechanisms to improve the solubility and dissolution properties of SDs include change of the drug crystal structure into an amorphous structure, reduction of aggregation and increased wetting and solubilization of drugs by the

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carriers (Chiou and Riegelman, 1971; Serajuddin, 1999; Franco *et al.*, 2001; Verheyen *et al.*, 2002). As soluble carriers dissolve, poorly water-soluble drugs are exposed to dissolution media as very fine particles or dispersions that enhance their dissolution and absorption. One of most widely used carriers in the preparation of SDs is solid-type polyethylene glycols (PEGs), such as PEG 4000, 6000, and 8000 (Betageri *et al.*, 1996; Mura *et al.*, 1996; Owusu-Ababio *et al.*, 1998; Franco *et al.*, 2001; Verheyen *et al.*, 2002). PEG-based SD are commonly prepared using the fusion (or melting) method, due to its convenience, ease and pulverization over a shorter period, without the use of organic solvents (Chiou and Riegelman, 1971; Betageri *et al.*, 1996; Owusu-Ababio *et al.*, 1998; Serajuddin, 1999).

However, due to the limited solubilizing capability of carriers, various pharmaceutical excipients, such as solubilizers, surfactants, oils and fatty acids, or in the form of mixtures, can be added into the SDs to further improve the drug solubility and dissolution rate (Morris *et al.*, 1992; Alden *et al.*, 1993; Sheen *et al.*, 1995; Owusu-Ababio *et al.*, 1998; Kim *et al.*, 2002; Cao *et al.*, 2003; Joshi *et al.*, 2004). Furthermore, isotropic mixtures of oil, a surfactant, and possibly one or more hydrophilic solvents or co-surfactants, known as self-microemulsifying drug delivery systems (SMEDDS), can be incorporated into the SDs. This SMEDDS forms a transparent and thermodynamically stable isotropic solution of microemulsion (ME) when exposed to aqueous media, which have recently been used to improve the dissolution and absorption of lipophilic drugs (Constantinides, 1995; Attama *et al.*, 2003).

Although the physical and structural properties of the PEG-based SDs, incorporating surfactants and solubilizers, were investigated as vehicles, little work has been carried out to investigate the dissolution and bioavailability of poorly water-soluble drugs in the SDs incorporating solubilizing and microemulsifying pharmaceutical excipients. Depending on the type of pharmaceutical excipient, the PEG-based SDs can readily form a solubilizing or emulsifying/micro-emulsifying system for the enhanced dissolution and absorption of insoluble drugs when exposed to aqueous media.

The purpose of this study was to prepare PEG 6000-based SDs, by incorporating various pharmaceutical excipients or microemulsion systems, using the fusion method, and compare the dissolution rate and bioavailability of ketoconazole (KT) in rats. The amorphous structure of the drug in the SD was also characterized by powder X-ray diffractometry (XRD) and differential scanning calorimetry (DSC). KT was selected as a model drug, which was the first antifungal agent in a series of azole derivatives used to treat a wide variety of superficial and systemic mycotic infections (Baxter *et al.*, 1986). It is known that KT has significant individual variations and a low bioavailability when given orally, due to its low solubility.

MATERIALS AND METHODS

Materials

The KT was supplied by Choong Wae Pharmaceutical Company (Seoul, Korea) and the PEG 6000 was purchased from Shinyo (Osaka, Japan). The oleic acid and polysorbate 80 (Tween 80) were purchased from Showa (Tokyo, Japan). The polyoxy 35 cator oil (Cremophor-EL) was purchased from BASF (Germany). The isopropyl myristate (IPM) and butyl paraben were purchased from Sigma (St. Louis, MO, USA). Liquid-paraffin was purchased from Junsei (Tokyo, Japan). Deionized water was used throughout the experiments. All other chemicals were of reagent grade and used without further purification.

Preparation of SDs

The PEG 6000 solution was melted over a calibrated hotplate at a temperature of 75°C. Mixtures of the drug and various excipients were preheated, stirred with a magnetic bar, and then added to the above melted PEG solution. After sufficient mixing for 1 h, the melts were allowed to cool at ~40°C. The solidified masses were further dried for 12 h at 30°C, and then pulverized in a pestle. The powders were passed through a 300mm sieve and then collected. The incorporated pharmaceutical excipients (%) for the solubilizing and microemulsifying PEG-based SDs are shown Table I.

Two different lipid-based delivery systems, SMEDDS and ME, were prepared and incorporated into the SDs for comparison, depending on the presence of water. It was proved that the SMEDDS could readily form a ME when

Table I. Compositions of incorporating pharmaceutical excipients (g) for solubilizing and microemulsifying the PEG-based SDs

Codes	Drug	PEG 6000	Oils	Surfactant
D	10	--	--	--
P	--	90	--	--
SD1	10	90	--	--
SD2	10	90	5 (Oleic acid)	--
SD3	10	90	5 (Isopropyl myristate)	--
SD4	10	90	5 (Mineral oil)	--
SD5	10	90	--	5 (Cremophor EL)
SD6	10	90	--	5 (Polysorbate 80)
SD7	10	80	5 (Oleic acid)	5 (Polysorbate 80)
SD8	10	80	5 (Isopropyl myristate)	5 (Polysorbate 80)
SD9	10	80	5 (Mineral oil)	5 (Polysorbate 80)
SD10	10	80	5 (Oleic acid)	10 (Polysorbate 80)
SD11	10	80	10 (Oleic acid)	10 (Polysorbate 80)
SD12	10	80	5 (Oleic acid)	20 (Polysorbate 80)

exposed to intestinal fluid, giving a particle size of 90-400 nm (250 ± 90 nm), as determined by dynamic laser scattering method.

The SD (SMEDDS)-drug (1.0 g), oleic acid (0.5 g), cremophor EL (0.6 g), ethanol (3.5 g) and transcutol (0.1 g) were homogeneously mixed, and then added into the melted PEG solution (7.8 g) to form the SD.

The SD (ME)-drug (1.0 g), oleic acid (0.5 g), cremophor EL (0.6 g), ethanol (3.5 g) and transcutol (0.1 g) were mixed and dispersed with water (138 mL). The ME was then left at 60°C for 5 h to evaporate the alcohol and water. The melted PEG 6000 solution (7.8 g) was then added to the above concentrated ME. The PEG-based SDs were finally prepared according to the previously described procedure.

Solubility of SDs

The solubility of KT in various solubilizing and micro-emulsifying PEG-based SDs, as shown in Table I, was determined in 10 mL of distilled water at 37°C. The solution, tightly sealed with parafilm, was shaken for 3 days at 37 °C. Aliquots were filtered through a 0.45 μm membrane filter (Millipore, MA, USA) and the drug concentration determined, using a HPLC system, from a standard curve.

Dissolution of SDs

In vitro dissolution tests of the powdered SDs (0.3 g) were performed in duplicate, using the dissolution apparatus (Fine scientific DST-600A, Korea) type II paddle method at 37 ± 0.5°C for 6 h, with a stirring rate of 50 rpm, in 500 mL of a dissolution medium of enzyme-free simulated intestinal fluid (pH 6.8±0.1). Dissolution samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 h, with replacement of an equal volume of temperature equilibrated dissolution medium. The samples were filtered through a 0.45 μm membrane filter, and the concentration of KT dissolved analyzed using a HPLC system, and determined as a function of time from a standard curve.

In vivo bioavailability of SDs in rats

Male Sprague-Dawley rats, weighing 250-350 g, fasted overnight, but with free access to water, were used in the experiments. Under anesthesia by inhalation of ether, a polyethylene cannula (inner diameter, 0.58 mm; outer diameter, 0.96 mm; dural plastics) was surgically introduced into the left carotid artery, and blood samples obtained at various times. After 2 h, SDs, equivalent to 35 mg KT per kg of rat body weight, were orally administrated using a sonde. After oral dosing with various SDs, heparinized blood samples (about 200 μL) were collected from the left carotid artery, at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 h and then centrifuged to collect plasma samples. The plasma samples were stored in a freezer, at a -40°C, until analyzed using HPLC.

Noncompartmental pharmacokinetic parameters were obtained as follows. The maximum plasma concentration (C_{max}) and the time to reach that concentration (T_{max}) were directly read from the plasma concentration-time profiles of KT. The area under the plasma concentration curve ($AUC_{0\text{-}6h}$) was calculated by the classical trapezoidal method.

Analytical method of plasma samples

The frozen plasma samples were melted at room temperature, an equal volume of acetonitrile added into 100 μL of the melted plasma and then spiked with 20 μL butyl paraben solution as an internal standard (10 μg in 1 mL acetonitrile). The samples were mixed for 5 min, centrifuged for 5 min and 50 μL aliquots injected into the HPLC system to determine the plasma KT concentration.

A reverse phase HPLC system (Jasco, Tokyo, Japan) was used for the KT analysis, consisting of a pump (PU-980), UV-Vis spectrophotometric detector (UV-975) and an autosampler (AS-950-10) linked to a data workstation (Borwin 1.20 software). A reverse phase column, Inertsil ODS-3, 5 μm, 4.6×150 mm, was used. The mobile phase, consisting of 80% methanol in 0.02 M KH_2PO_4 (pH 6.8), was filtered, under vacuum, through a 0.45 μm nylon memzbrane filter (Gelman sciences, USA) and then degassed. The flow rate of the mobile phase was 1.0 mL/min. The KT concentration was determined at a wavelength of 254 nm. 20 or 50 μL aliquots, for *in vitro* and *in vivo* experiments, respectively, were injected using the autosampler. Good linearity was observed for the standard calibration curve (correlation coefficient >0.9999). Typical HPLC chromatograms of the drug-free rat plasma, spiked with butyl paraben (10 μg/mL) as an internal standard (left), rat plasma, spiked with drug (50 μg/mL) (middle), and rat plasma 15 min after an oral administration equivalent to 35 mg drug per kg of rat body weight (right), are given in Fig. 1. The peaks were well resolved, and separated with high accuracy and precision, which were above the 0.1 mg/mL detection limit. Also, no interfering peaks were observed in the drug-free plasma samples.

Physical characterization of SDs

DSC

The thermal behaviors of KT, PEG 6000, and PEG-based SDs were investigated using a Dupont DSC (Dupont, U.S.A). An approximately 5 mg sample was weighed in a standard aluminum pan, with a pinhole in the lid, which allows the removal of any residual water. Dry nitrogen was used as the purge gas, at a flow rate of 50 mL/min. An empty pan of same type was utilized as a reference. The samples were heated from room temperature to 200°C, at a heating rate of 5°C/min. Calibrations of

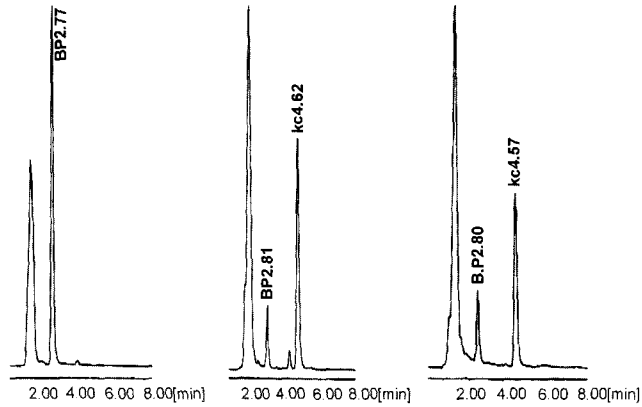

Fig. 1. HPLC chromatograms of drug-free rat plasma, spiked with butyl paraben (10 μg/mL) as an internal standard (left), rat plasma, spiked with the drug (50 μg/mL) (middle) and rat plasma 15 min after a single oral administration of the SD, equivalent to 35 mg drug per kg of rat body weight (right)

the temperatures and enthalpy (heat flow) were performed with pure indium and gallium.

Powder X-ray diffraction

The scanning powder X-ray diffraction patterns of KT, PEG 6000 and PEG-based SDs were obtained using a D5005 (Bruker, Germany), and were used to characterize the physical state of the drug in the SDs. The radiation was generated by a copper Kα filter, with a wavelength of 1.5418 Å, at 35 kV, and 30 mA. Samples were scanned over a range of 2θ values, from 10 to 70°, at the scan rate of 2.0°/min, for 30 min per sample.

RESULTS AND DISCUSSION

Solubility of SDs

The water solubilities of the KT in the solubilizing and microemulsifying PEG-based SDs incorporating pharmaceutical excipients were compared, and are shown in Fig. 2, along with that of pure KT as a reference. The solubilities of the KT were greatly increased with solubilizing excipients incorporated into the PEG-based SDs. The hydrophilic excipients, such as polysorbate 80 and cremophor EL, were more efficient than lipophilic excipients, such as oleic acid, IPM and mineral oil, possibly because they provided a good surrounding for the physical interaction with water.

Most of all, a remarkable enhancement in the solubility was observed when lipophilic and hydrophilic excipients were combined and then incorporated into the PEG-based SDs. When the PEG-based SDs incorporating oleic acid and polysorbate 80 were exposed to water, they readily formed an emulsion/microemulsion; so, enhanced solubility was expected. Conversely, PEG-based SDs

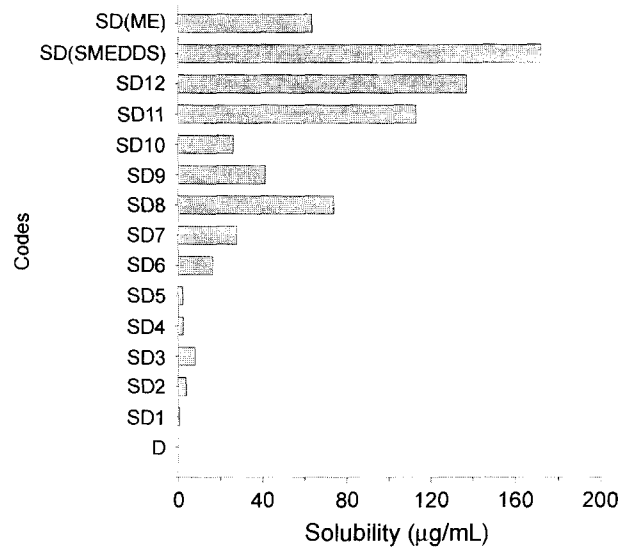

Fig. 2. The water solubilities of KT in the solubilizing and microemulsifying PEG-based SDs incorporating pharmaceutical excipients

incorporating microemulsion systems (SMEDDS or ME) also showed increased solubility due to its readily re-dispersible characteristics when exposed to water.

Release characteristics of SDs

Fig. 3 shows the dissolution rates of solubilizing PEG-based SDs incorporating pharmaceutical excipients in a simulated intestinal fluid (pH 6.8). Due to the good wetting

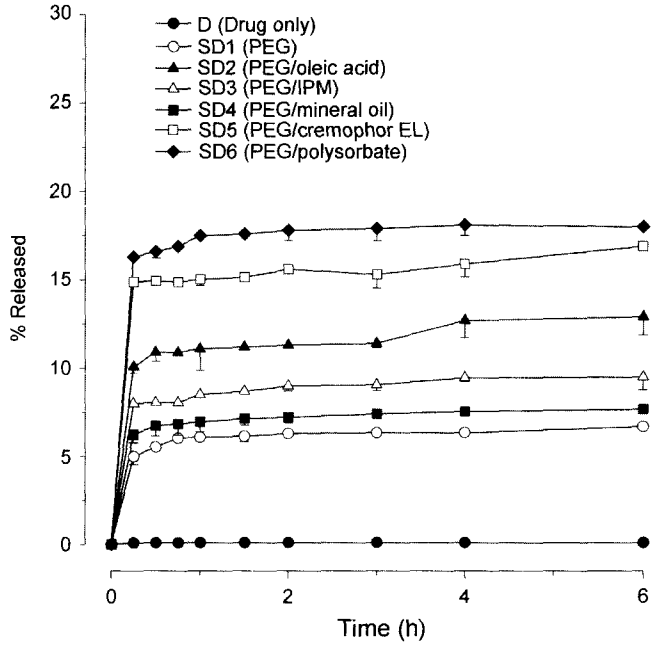

Fig. 3. The dissolution rates of the solubilizing PEG-based SDs incorporating pharmaceutical excipients, in simulated intestinal fluid (pH 6.8)

of the SDs, an initial burst release was shown in the dissolution rate, which then reached the saturating solubility throughout the study. The dissolution rate of pure KT was very low. However the initial dissolution rate of the KT in the solid dispersion, up to about 1h, increased sevenfold compared to pure KT alone. The dissolution rate of KT increased when solubilizing excipients were incorporated into the SDs. Even though lipophilic excipients, such as oleic acid, IPM or mineral oil, were added, the dissolution rate tended to increase. The oleic acid showed the highest dissolution rate.

The enhancing efficiency of the dissolution rates was more pronounced in cases with hydrophilic surfactants, such as polysorbate and cremophor EL. The polysorbate 80 gave a slightly higher dissolution rate than cremophor EL. It is well known that hydrophilic surfactants in the SDs could play a key role as solubilizers and wetting agents for poorly water-soluble drugs (Alden *et al.*, 1993; Morris *et al.*, 1992; Sheen *et al.*, 1995; Owusu-Ababio *et al.*, 1998; Joshi *et al.*, 2004). The surfactants could increase the wettability and spreadability of the precipitated drug by reducing aggregations in the readily soluble state.

The dissolution rates of microemulsifying PEG-based SDs incorporating lipophilic oils and polysorbate 80 in simulated intestinal fluid (pH 6.8) are given in Fig. 4. Although hydrophilic surfactants were incorporated to enhance the dissolution of the PEG-based SD or surface-active and emulsifying carriers, such as Gelucire (Gattefosse Corp., Westwood, NJ, USA), the SD containing both oils and surfactants, with the aim of forming a microemulsion, have not been widely investigated. When hydrophilic and lipophilic excipients were combined and incorporated into PEG-based SDs, the dissolution rates were markedly enhanced. The dissolution rate was also increased with increasing amount of hydrophilic surfactant (polysorbate 80) or lipophilic oleic acid. When the PEG-based SDs incorporating oleic acid and polysorbate 80 were exposed to the dissolution medium, an emulsion/microemulsion, trapping poorly water-soluble drug as very fine particles or dispersions, could be formed to enhance the dissolution. However, the ratio of hydrophilic surfactants and lipophilic oils can be crucial in optimizing the solubilizing capacity and physical properties of SDs. SDs with more than 10% oleic acid and 20% polysorbate in their composition were difficult to pulverize and sieve due to their stickiness and fluidity.

The optimized compositions of SMEDDS or ME were incorporated into the PEG-based SDs. The dissolution rates of the PEG-based SDs incorporating SMEDDS or ME in simulated intestinal fluid (pH 6.8) are also compared in Fig. 5. Although the microemulsifying PEG-based SDs incorporating oils and surfactants were useful in improving the dissolution rates, the PEG-based SDs containing SMEDDS and ME were also very efficient. The solid self-emulsifying systems, using thermo-sensitive goat fat and polysorbate, which were intended to show a combination of emulsion and micelle formation, have also shown increased dissolution of lipophilic diclofenac, but in a near zero-order fashion (Attama *et al.*, 2003). The PEG-based

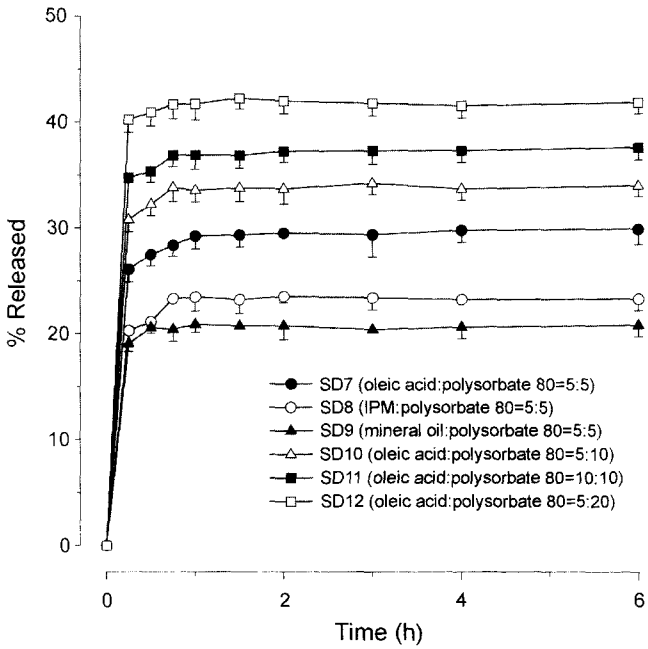

Fig. 4. The dissolution rates of the microemulsifying PEG-based SDs incorporating lipophilic oils and polysorbate 80, in simulated intestinal fluid (pH 6.8)

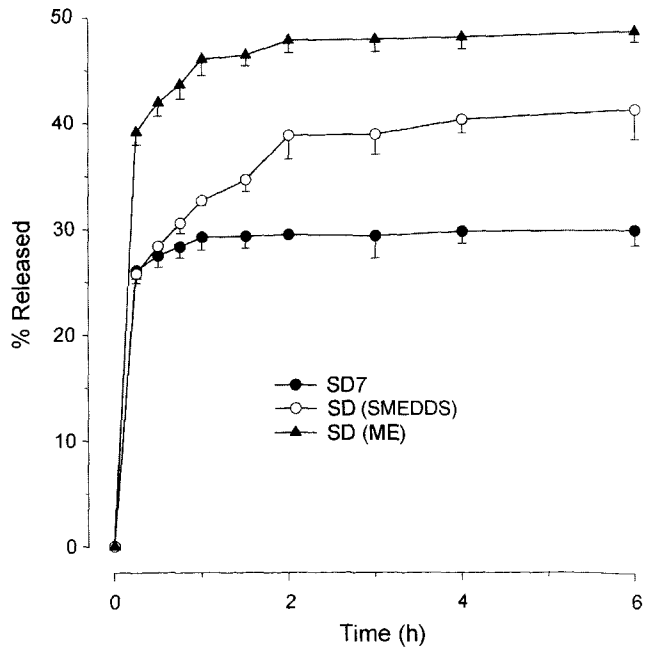

Fig. 5. The dissolution rates of the PEG-based SDs incorporating SMEDDS or ME, in simulated intestinal fluid (pH 6.8)

SD having ME showed the highest dissolution rate, due to the readily re-dispersible properties and more favorable physical interaction with aqueous medium. Although the ME was heated, to evaporate the water, and added to the melted PEG solution, a small amount of water might have been a factor in the greatly increased dissolution rate compared to the SD (SMEDDS). It was also expected that the PEG-based SDs incorporating SMEDDS or ME could form a microemulsion or dispersible particles in the aqueous medium. The initial dissolution rate tended to be delayed, possibly due to the sustaining effect of ME in the aqueous medium. However, due to their limited solubilization capacity, the PEG-based SDs used in this study showed dissolution rates below 50% under the sink conditions.

In vivo bioavailability of SDs in rats

The plasma concentration-time profiles of various PEG-based SDs, following a single oral administration to rats (n=5), are shown in Fig. 6. The pharmacokinetic parameters following a single oral administration of various PEG-based SDs, equivalent to 35 mg per kg of rat body weight (n=5), are also compared in Table II. *In vivo* data of the SD (SMEDDS) was excluded, as the dissolution rate was lower than that of the SD (ME). Although the PEG-based SD showed twofold increases in the C_{max} and AUC compared to the drug only, the bioavailability was more pronounced in the cases of solubilizing and microemulsifying PEG-based SDs and the PEG-based SD (ME). Unexpectedly, the solubilizing PEG-based SDs incorporating

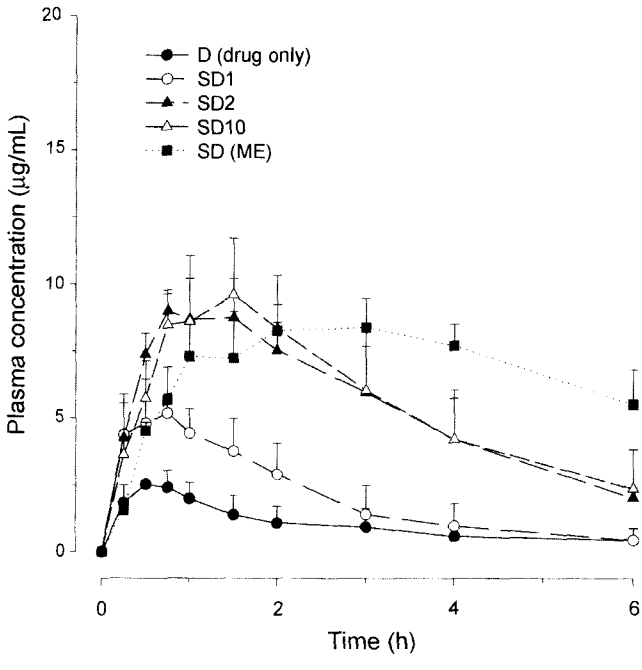

Fig. 6. Plasma concentration-time profiles of various PEG-based SDs, following a single oral administration, in rats (n=5)

Table II. Comparison of pharmacokinetic parameters following a single oral administration of various PEG-based SDs, equivalent to 35 mg per kg of rat body weight (n=5).

Codes	C_{max} (μg/mL)	t_{max} (h)	AUC (μg-h/mL)
D (drug only)	2.64 ± 0.63	0.67 ± 0.14	7.39 ± 2.8
SD1 (PEG)	5.43 ± 1.08[a]	0.75 ± 0.25[a]	14.17 ± 6.29[a]
SD2 (PEG/oleic acid)	9.11 ± 2.54[a,b]	1.0 ± 0.43	37.30 ±11.15[a,b]
SD10 (PEG/oleic acid/ polysorbate)	9.26 ± 2.59[a,b]	1.33 ± 1.53[a,b]	38.58 ± 3.18[a,b]
SD (ME)	9.62 ± 4.12[a,b]	2.53 ± 0.29[a,b]	51.17 ± 8.96[a,b]

[a]Significantly different from D, $p<0.05$.
[b]Significantly different from SD1, $p<0.05$

lipophilic oleic acid only (SD2) had similar bioavailabilities to the microemulsifying PEG-based SDs incorporating lipophilic oleic acid and the hydrophilic surfactant (SD10). It has been recognized that a long chain fatty acid, i.e., oleic acid, in a dosage form, can be used to enhance the solubility of poorly water soluble drugs and reduce hepatic metabolism, by forming chylomicrons that enhance the lymphatic delivery, resulting in an increased bioavailability (Burns *et al.*, 1995; Barnwell *et al.*, 1996). The long chain fatty acid in the formulation was re-esterified to triglycerides within the intestinal cell, incorporated into the chylomicrons with a lipoprotein, and then secreted into the lymph vessels due size limitation. Chylomicrons are basically related to the lymphatic transport of various lipophilic drugs from the small intestine (Caliph *et al.*, 2000; Porter and Charman, 2001). Due to the contributing effect of oleic acid in solubilizing drug and for lymphatic delivery, the bioavailability of KT from solubilizing and microemulsifying SDs could be improved. In the case of the PEG-based SD containing a microemulsion (SD-ME), the AUC was significantly higher compared to the other SD preparations. It was also noted that the plasma concentration profiles were somewhat sustained. Unlike the solubilizing or microemulsifying PEG-based SDs, the SD (ME) could entrap drug molecules inside the microstructure, which would then be released in a sustained fashion when exposed to gastrointestinal fluid (see also Fig. 5), resulting in delayed plasma concentration profiles. Therefore, the AUC was drastically increased, with the aid of an enhanced dissolution and a sustaining absorption.

From these findings, it was evident that PEG-based SD, incorporating oils, fatty acid, surfactant or their mixtures, significantly enhanced the dissolution and bioavailability of the poorly water-soluble drug due to the formation of a solubilizing and microemulsifying system when exposed to gastrointestinal fluid. The mechanism for this enhanced dissolution and bioavailability could include the change in the crystal structure of the drug and the increased wetting and solubilization capacity due to incorporating excipients

or their mixtures into the SDs (Morris *et al.*, 1992; Sheen *et al.*, 1995; Owusu-Ababio *et al.*, 1998; Franco *et al.*, 2001; Verheyen *et al.*, 2002; Joshi *et al.*, 2004). The more favorable physical interaction, *via* hydrogen bonding, of the drug with carriers, and the readily redispersible properties of PEG-based SD when exposed to gastrointestinal fluid, could also be factors. Further solubilization by bile salts in the gastrointestinal tract can occur, which could facilitate absorption into the enterocytes (Joshi *et al.*, 2004). In addition, it was noted that a number of excipients commonly added to pharmaceutical formulation may play key roles in modifying the pharmacokinetic profiles of drugs, due to changes in the dissolution rate, function of intestinal P-glycoprotein, oral absorption *via* lymphatic systems and the hepatic metabolism (Cornaire *et al.*, 2004; Wang *et al.*, 2004).

Physical characterization of SDs

To elucidate the enhanced dissolution and bioavailability, the physical state of the drug crystals in the PEG-based SD was investigated using instrumental analysis. It is widely known that the PEG-based SD can improve the dissolution rates of poorly water-soluble drugs by changing the crystalline structure into a high-energy state, i.e. an amorphous state, which are extensively characterized using instrumental techniques, such as XRD and DSC (Morris *et al.*, 1992; Sheen *et al.*, 1995; Franco *et al.*, 2001; Verheyen *et al.*, 2002).

The DSC thermograms of various PEG-based SDs are compared in Fig. 7. The drug has an intrinsic single peak at 148.6°C. The thermograms of the PEG-based SDs showed the characteristic peak of the carrier matrix around 60°C, but without the drug peak, indicating that the drug had changed into its amorphous structure. However, additional peaks were observed around 60-63°C, which suggested the drug was not completely dissolved in the PEG carrier.

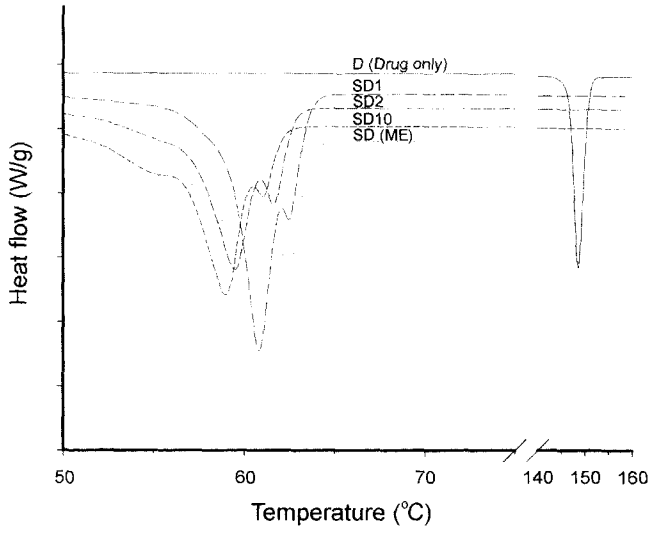

Fig. 7. Comparison of the DSC thermograms of various PEG-based SDs

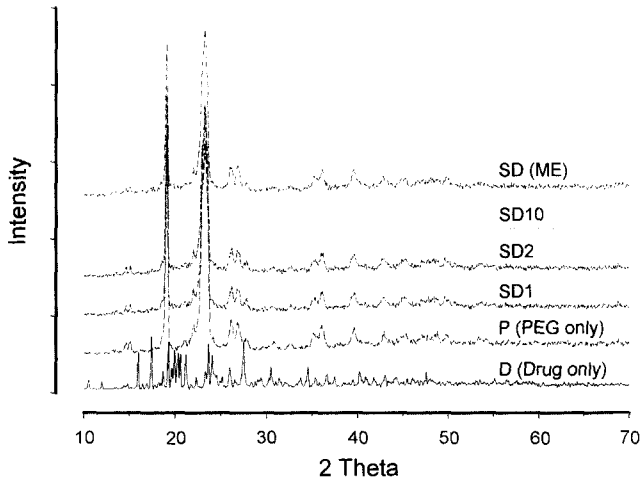

Fig. 8. Comparison of the powder XRD patterns of various PEG-based SDs

The powder XRD patterns of various PEG-based SDs are also compared in Fig. 8. The diffraction pattern of the pure drug showed its highly crystalline nature, as indicated by the numerous distinctive peaks. The PEG 6000 alone exhibited two high intensity peaks at 19°C and 23°C. The lack of the numerous distinctive peaks of the drug in the PEG-based SDs demonstrated that a high concentration of the drug was dissolved in the solid-state carrier matrix in an amorphous structure. It was very difficult to identify the amorphous and partially crystallized drug from the XRD patterns. However, there were no significant differences in the DSC thermograms and XRD patterns of the PEG-based SDs incorporating solubilizing and microemulsifying excipients, or in the SD containing ME, although the dissolution rates were quite variable, as discussed previously. The structural properties of polysorbates with various PEGs were well characterized by the DSC and XRD, indicating that these mixtures may be used as SD vehicles for the complete dissolution of poorly water-soluble drugs (Morris *et al.*, 1992; Sheen *et al.*, 1995; Owusu-Ababio *et al.*, 1998;). However, amorphous and partially crystallized drug molecules might be present in the PEG-based carrier matrix. This was another reason the dissolution rate of KT was below 50%, as discussed previously.

CONCLUSION

The utilization of oils, fatty acid and surfactant, or their mixtures, in PEG-based SDs could be a useful tool to enhance in the vitro dissolution and *in vivo* bioavailability

of poorly water-soluble KT, by forming solubilizing and microemulsifying system when exposed to aqueous media. The drug crystalline structure was changed into a high-energy state, i.e. an amorphous state, as characterized by the DSC and XRD. These changes in the crystal structure of KT in the PEG-based SD, coupled with the high dissolution rate in the presence of solubilizing and microemulsifying excipients, were responsible for the enhanced bioavailability.

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