BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **28**: 199–207 (2007)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/bdd.546

In Vitro and *In Vivo* Comparative Study of Itraconazole Bioavailability When Formulated in Highly Soluble Self-Emulsifying System and in Solid Dispersion

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ABSTRACT: A semisolid self-emulsifying system (SES) of itraconazole consisting of oleic acid, polysorbate 80 and coajuvant (citric acid) was prepared by a hot-melt technique and then compared with hydroxypropylmethylcellulose (HPMC) solid dispersion (SD) coated onto inert sugar spheres as a reference formulation for *in vitro* and *in vivo* disposition in rats. The optimal SES greatly increased dissolution rates in gastric (pH 1.2) and intestinal fluid (pH 6.8) by forming a microemulsion (150–250 nm), whereas that of SD was minimal. The tissue uptake of itraconazole from SES in whole intestine, liver and Peyer's patches of the rats was more favorable than that from SD and linearly increased as a function of administering dose. Interestingly, the uptake ratio of Peyer's patches relative to liver also increased linearly in the case of SES while that of SD was almost unchanged. After repeated dosing for 1 week, both SES and SD increased the areas of Peyer's patch region in intestinal tissues but no distinct histopathological damage of the intestine was observed except the hepatocytes. Due to the biopharmaceutical differences of SES in terms of efficient solubilization, easy dispersibility and higher lymphatic transport, the *in vivo* bioavailability of SES was about twice greater than that of SD in rats. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: self-emulsifying system (SES); solid dispersion (SD); comparative disposition; Peyer's patches; bioavailability

Introduction

Itraconazole is a synthetic triazole antifungal agent and is used to treat various fungal diseases, such as histoplasmosis, blastomycosis and onychomycosis [1,2]. Chemically, it is a basic drug and has low solubility (pKa = 3.7) in water and simulated intestinal fluid, but much higher solubility in acid media [2,3]. The oral bioavailability of itraconazole is also low due to its poor solubility and hepatic metabolism. Sporanox® capsule is commercially available worldwide.

Various solid dispersions (SD) of itraconazole have been investigated extensively to improve dissolution and bioavailability [4–8]. The SD carriers include hydroxypropylmethylcellulose (HPMC), Eudragits, polyvinylpyrrolidone (PVP) VA64, 2-hydroxypropyl-β-cyclodextrin, polyethylene glycol (PEG) and phosphoric acid. Alternatively, a self-emulsifying system (SES) containing a mixture of fatty acid and surfactant can be more efficient for increasing the dissolution rates of poorly water-soluble drugs by forming an emulsifying environment [9–11]. Furthermore, a long-chain fatty acid such as oleic acid in the SES may also increase the oral bioavailability of highly lipophilic drugs by forming chylomicrons (80–1000 nm) within the

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Received 17 August 2006
Revised 12 December 2006
Accepted 3 January 2007

enterocytes during the digestion and absorption of lipids, resulting in the stimulation of transport into Peyer's patches for systemic circulation directly without experiencing hepatic metabolism [12,13]. The physicochemical properties of the itraconazole semisolid dosage forms prepared using a hot-melt technique without using harmful organic solvents were recently observed [11]. So far, no detailed *in vitro* and *in vivo* evaluations of the SES dosage form of itraconazole have been done. The biopharmaceutical differences in the SES and SD dosage forms to modify the bioavailability of poorly water-soluble drugs are their efficiency of solubilization, easiness of dispersibility and possibility of tissue uptake, especially by Peyer's patches in the gastrointestinal tract. Concerning these points, it is interesting to compare the biopharmaceutical characteristics of SES and SD dosage forms containing itraconazole.

In this study, semisolid SES was prepared by a hot-melt technique consisting of oil (oleic acid), surfactant (polysorbate 80) and coajuvant (citric acid), which can easily constitute an emulsion/microemulsion in gastrointestinal fluid. The itraconazole SD with HPMC coated onto inert sugar spheres from a marketed Sporanox® capsule was chosen as a reference [5,7]. Thereafter, dissolution, *in vivo* tissue disposition and bioavailability of the SES were compared with itraconazole SD after oral administration to rats. For tissue dispositions, drug levels in the liver, intestine and Peyer's patches were determined. Histopathological changes in intestinal tissues (duodenum, jejunum, ileum and colon) and liver were also examined.

Materials and Methods

Materials

Itraconazole was obtained from Kukje Pharmaceutical Company (Seoul, Korea). *n*-Heptane, isoamyl alcohol, citric acid, oleic acid and polysorbate 80 were purchased from Sigma (St Louis, MO, USA). Acetonitrile (HPLC grade) was purchased from Fisher Scientific (Pittsburgh, PA, USA). Diethylamine was purchased from Showa (Kyoto, Japan). The econazole nitrate as an internal standard was obtained from Seoul Pharma (Seoul, Korea). Sulfuric acid was purchased from Shinyo Pure Chemicals (Kyoto, Japan). All other chemicals were of reagent grade and were used without further purification.

HPLC analysis of itraconazole

The Jasco HPLC unit (Tokyo, Japan) consisted of a pump (PU980), a UV-VIS spectrophotometric detector (UV-1575), an autosampler (AS-950-10) and a degasser (DG-980-50). Reverse phase columns, i.e. Haisil® 100 (C18, 5 μm, 150 × 4.6 mm, Higgins Analytical, Inc., Mountain View, CA) and Sinergi (C18, 4 μm Hydro-RP, 150 × 4.6 mm, Phenomenex® Torrance, CA) were used for plasma and tissue samples, respectively, to analyse the itraconazole concentration. The mobile phase consisting of acetonitrile and 0.1% diethylamine buffer (65: 35 v/v/%) was filtered using a 0.45 μm nylon membrane filter (Whatman®, England) and degassed under vacuum for 10 min. The flow rate of the mobile phase was 1 ml/min, and itraconazole concentrations were determined at 263 nm. Sample aliquots of 20 μl were injected into the HPLC system.

Preparation of SES

SES was prepared using a hot melt process without adding organic solvents. The weight ratio of drug, citric acid, oleic acid and polysorbate 80 was 1:1:0.5:*x* (w/w). The polysorbate 80 ratios used were 3, 4, 5, 6 and 7. The citric acid and polysorbate 80 (40% total weight) melted homogeneously without stirring at 150°C in temperature-controlled Pyrex. Itraconazole was added to the above transparent-yellow or brown melted mixtures without stirring. The mixtures were then immediately cooled to 60–80°C. The remaining polysorbate 80 (60% total weight) and oleic acid were then added and gently stirred. The resulting mixtures were degassed by sonication for 10–20 min and then aged for 24 h at room temperature. The SES obtained was then milled three times in a Three-Roll Milling Unit (Exakt Co., Norderstedt, German). The SES prepared was then filled in #0 hard gelatin capsules for *in vitro* dissolution studies.

DOI: 10.1002/bdd

Dissolution studies

Studies on the dissolutions of SES and SD containing itraconazole were carried out according to the USP guideline. The USP dissolution II paddle method was used at a rotation speed of 100 rpm in a DST-600A dissolution tester (Labfine Co., Seoul, Korea). The media used were 900 ml of dissolution media at $37 \pm 0.5^{\circ}C$, simulated gastric (pH 1.2 ± 0.1) and intestinal fluids (pH 6.8 ± 0.1). Aliquots (1 ml) of media were collected for 2 h in gastric fluid and for 6 h in intestinal fluid, respectively, and then replaced with equal volumes of fresh medium. The collected samples were centrifuged at 10 000 rpm for 2 min to remove any impurities in the suspension. The supernatants obtained were immediately diluted with acetonitrile. Itraconazole concentrations in media were determined by HPLC within 24 h as mentioned previously.

Animal treatment

Male Sprague-Dawley rats 7–10 weeks old, weighing 285–380 g, were purchased from Daehan Biolink Co. (Chungbuk, Korea). Rats were housed under a 12 h light-dark cycle (8:00–20:00) in temperature-controlled rooms ($25 \pm 2^{\circ}C$) and allowed free access to food and tap water. The animals were fasted for 24 h before the experiment but had free access to tap water. The detailed animal treatment was followed according to the Guide for the Care and Use of Laboratory Animals.

Comparative tissue dispositions

Rats were randomly divided into five rats per group. The SES or SD equivalent of 2.5, 5 or 10 mg of itraconazole per kg of body weight was administered p.o. by oral sonde together with 1 ml of water. The rats were killed by cervical dislocation at 4 h post-administration. The whole intestine and liver were carefully dissected and thoroughly rinsed with phosphate-buffer saline (pH 7.4). The Peyer's patches were also collected from the intestine of each animal and combined for tissue analysis. The number of Peyer's patches was about 18–20/animal. Buffer solution remaining on tissue surfaces was removed with blotting paper. Tissue samples were then stored in a deep freezer at $-70^{\circ}C$ for 24 h. The tissue specimens were then freeze-dried for 24 h.

Extraction and drug analysis in tissues and plasma

For calibration purposes, blank plasma or freeze-dried tissue samples (liver, Peyer's patches, small intestine) were spiked with known itraconazole solutions in acetonitrile (0.1–10 μg/ml itraconazole per mg tissue) into the HPLC unit. The peak area ratios of itraconazole to internal standard solution (320 μg/ml of econazole nitrate) were plotted as a function of drug concentration and used to assay the itraconazole concentration.

The extraction procedure used for itraconazole in plasma or tissue samples was a modification of a previously described method [14]. Freeze-dried tissue samples of liver (0.1 g), small intestine (0.02 g) or Peyer's patches (0.02 g) were weighed. 1 ml of acetonitrile/water (60:40 v/v %) was then added and vortexed for 40 s. For rat plasma samples, 270 μl of rat plasma was mixed with 30 μl of acetonitrile for 40 s. The resulting solution was mixed with 100 μl of an internal standard solution (320 μg/ml of econazole nitrate) and 500 μl of 0.05 M of phosphate buffer (pH 7.8), and vortexed for 40 s. 4 ml of *n*-heptane/isoamyl alcohol (98.5:1.5, v/v) was added, and the resulting solution was mixed for 40 s and then centrifuged at 2500 rpm for 10 min. This extraction procedure was then repeated twice. The combined organic layers were then extracted with 4 ml of 0.05 M sulphuric acid. After discarding the organic layer by centrifugation at 2500 rpm for 10 min, the aqueous acidic phase was alkalinized with 0.6 ml of concentrated ammonia to pH >9. The resulting solution was then re-extracted twice with 4 ml aliquots of the above *n*-heptane/isoamyl alcohol and centrifuged at 2500 rpm for 10 min. The organic layers were combined and then evaporated to dryness under a gentle stream of nitrogen at $40^{\circ}C$. The residues were redissolved in 100 μl of HPLC mobile phase (described above) and mixed for 40 s. Finally 20 μl aliquots were injected into the HPLC system. Itraconazole concentrations in tissue samples are expressed as μg/g of lyophilized tissue sample.

DOI: 10.1002/bdd

Histopathological examination

After the repeated dosing of SES or SD (equivalent to 10 mg of itraconazole/kg) for 1 week once a day, the rats were killed by cervical dislocation. The four different intestinal sites (duodenum, jejunum, ileum and colon) and liver were carefully dissected and then immediately dipped in 10% formalin solution. Formalin-fixed and paraffin-embedded tissues were sectioned at 4 μm using a microtome and then stained with Harris hematoxylin-eosin solution. Histopathological examination was carried out using an Olympus Bx microscope (Tokyo) linked with imaging software (Baumer Twain Ver. 1.0, Humin Tech Corp., Seoul) in the Central Laboratory, Kangwon National University at a magnification of $\times 40$. Areas of Peyer's patch regions were determined visually.

Comparative pharmacokinetics of dosage forms

Under anesthesia induced by ether inhalation, a polyethylene cannula (i.d. 0.58 mm: o.d. 0.96 mm, Dural Plastics) was surgically introduced into the left femoral artery to obtain blood samples (0.5 ml) at various sampling times (0.25, 0.50, 1, 2, 3, 4, 5, 6, 7 and 8 h) after oral dosing. Blood samples were centrifuged at 10 000 rpm for 10 min to obtain plasma samples. The itraconazole concentrations in plasma were then determined as described above. Noncompartmental pharmacokinetic parameters were obtained as follows. The maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) were directly read from the plasma concentration-time profiles of itraconazole. Areas under the plasma concentration-time curve ($AUC_{0-8\,h}$) were calculated using the classical trapezoidal method.

Statistical analysis

All data were presented as mean $\pm$ standard deviation. The statistical significance of differences was performed using analysis of variance (ANOVA) test and then assessed by a Duncan's multiple range test. A probability level at 5% ($p < 0.05$) was considered to be statistically significant.

Results and discussion

Comparative dissolution

According to the Biopharmaceutic Classification System, itraconazole is a class II compound due to its low solubility and high intestinal permeability (P_{eff} 3.8×10^{-6} cm/s) [7]. Low water solubilities and poor dissolution rates may result in low and variable bioavailabilities. Thus enhanced dissolution rates improve the bioavailability of itraconazole. The effect of the ratio of polysorbate 80 and oleic acid on the dissolution of itraconazole from SES in simulated intestinal fluid (pH 6.8) is shown in Figure 1. As the ratio of polysorbate 80 and oleic acid was increased, dissolution rates at 1 and 2 h gradually increased. The present study showed that the solubility of itraconazole could be improved by increasing polysorbate 80 levels in the SES by so-called micellar solubilization. The increased dissolution by the polysorbate 80 in SES was due to forming a more efficient emulsifying environment [10,11].

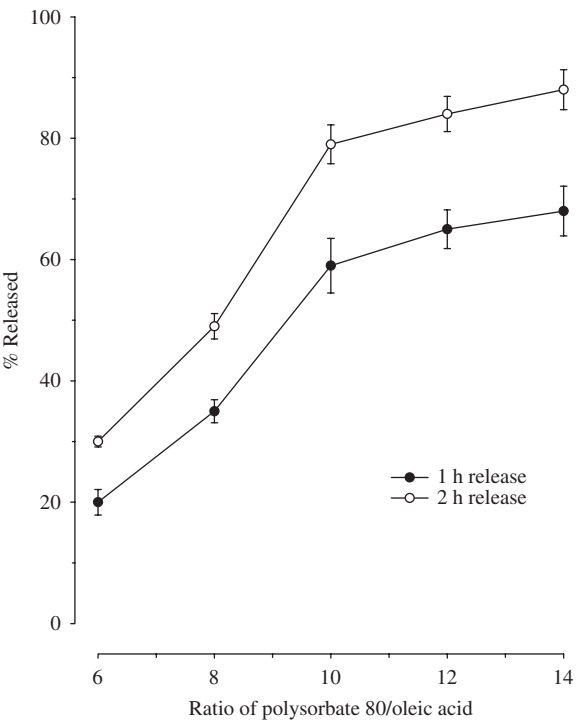

Figure 1. Effect of ratio of polysorbate 80 and oleic acid on the dissolution of itraconazole from SES in simulated intestinal fluid (pH 6.8)

DOI: 10.1002/bdd

Maximal dissolution was achieved when the ratio of polysorbate 80 to oleic acid was 10. So the optimal ratio of polysorbate 80 and oleic acid in SES was invariably fixed at 10.

The dissolution profiles of the SES were compared with SD in simulated gastric and intestinal fluid (Figure 2). The dissolution rate of SES and SD was comparable in the gastric fluid. The dissolution rate of SD was over 70% and the optimal SES was almost 100% over 2 h in gastric fluid. However, the dissolution rate of SD was nearly zero in simulated intestinal fluid, whereas the optimal SES had a highly increased dissolution rate of 80% after 2 h. The main reason for forming the SES microemulsion was to increase dissolution rates. A physical change of itraconazole in the semisolid preparations from crystalline to amorphous forms would also be a contributing factor as discussed previously [11].

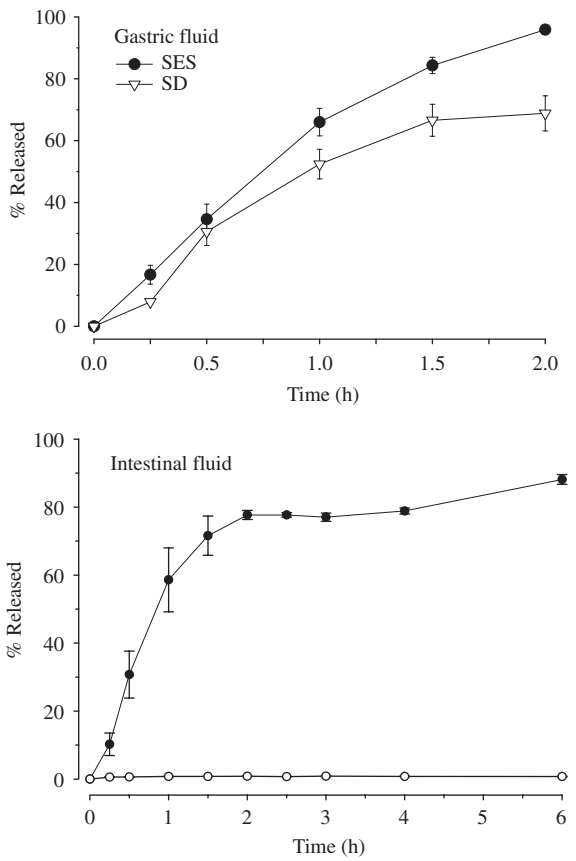

Figure 2. Comparative dissolution of the SES and SD in simulated gastric and intestinal fluids

In the case of SES, the microemulsion solution turned transparent and slightly turbid. The mean size of the formed emulsion in gastric fluid was about 150–200 nm, whereas the mean size in the intestinal tract was about 200–250 nm (as determined by laser scattering).

Comparative tissue dispositions

Tissue disposition of itraconazole in the intestine, liver and Peyer's patches after a single oral administration of SES or SD to rats is compared in Figure 3. The tissue uptake of itraconazole from SES in whole intestine, liver and Peyer's patches was more favorable than that from SD. This tissue uptake increased with increasing doses from 2.5 to 10 mg/kg in SES, suggesting passive uptake. The uptake of SES was almost 2.1 times higher in intestine and 1.4 times in liver compared with SD at the same doses. The main reason for the higher uptake of SES was its higher solubilization in the intestinal tract and easy dispersibility. Although the bioavailability is determined by the uptake over the intestinal membrane and first-pass metabolism, this tissue distribution can be an indirect way to compare the biopharmaceutical differences of the SES and SD dosage forms.

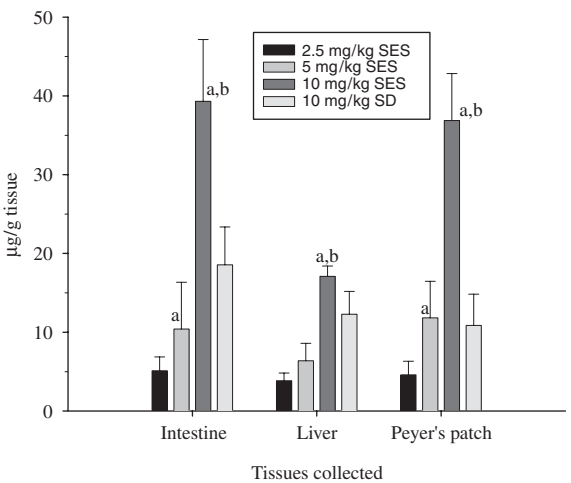

Figure 3. Tissue dispositions of itraconazole in whole intestine, liver and Peyer's patches 4 h after a single oral administration of SES or SD to rats ($n = 5$). [a]$p < 0.05$, significantly different from 2.5 mg/kg dose SES; [b]$p < 0.05$, significantly different from SD

DOI: 10.1002/bdd

The Peyer's patches, a part of M-cell with irregularly shaped microfolds are collections of sub-epithelial lymphoid follicles burgeoning among villi and distributed throughout the small intestine [15]. In this study, the number of Peyer's patches collected from the small intestine of each rat was about 18–20 and combined for tissue analysis. The uptake of SES in Peyer's patches was about 3.4 times higher than that of SD. It is assumed that the SES provided an increased exposure to Peyer's patches due to its higher solubilization and easy dispersion. It was reported that enhanced lymphatic uptake may be a function of efficient solubilization, enhanced absorption leading to increased membrane permeability and the partitioning of drugs into lymph chylomicron/lipoprotein [12,13].

For drugs experiencing first-pass hepatic metabolism via the mesenteric vein, the uptake ratio of Peyer's patches relative to liver ($C_{\text{Peyer's patch}}$)/(C_{liver}) could provide an index of bypassing hepatic metabolism. The ratio of the cumulative amount of itraconazole taken up in Peyer's patches and liver ($C_{\text{Peyer's patch}}/C_{\text{liver}}$) as a function of the SES dose administered p.o. to rats is compared in Figure 4. Interestingly, as the administered dose of drug was increased, the $C_{\text{Peyer's patch}}/C_{\text{liver}}$ ratio also increased linearly in the case of SES, while the SD was almost unchanged. It was evident that the SES should

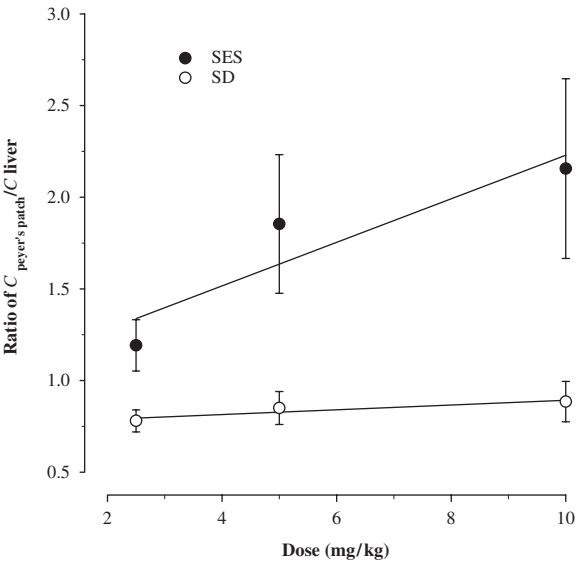

Figure 4. The ratio of cumulative amount of itraconazole taken up in Peyer's patches and liver ($C_{\text{Peyer's patch}}/C_{\text{liver}}$) as a function of SES doses administered p.o. to rats

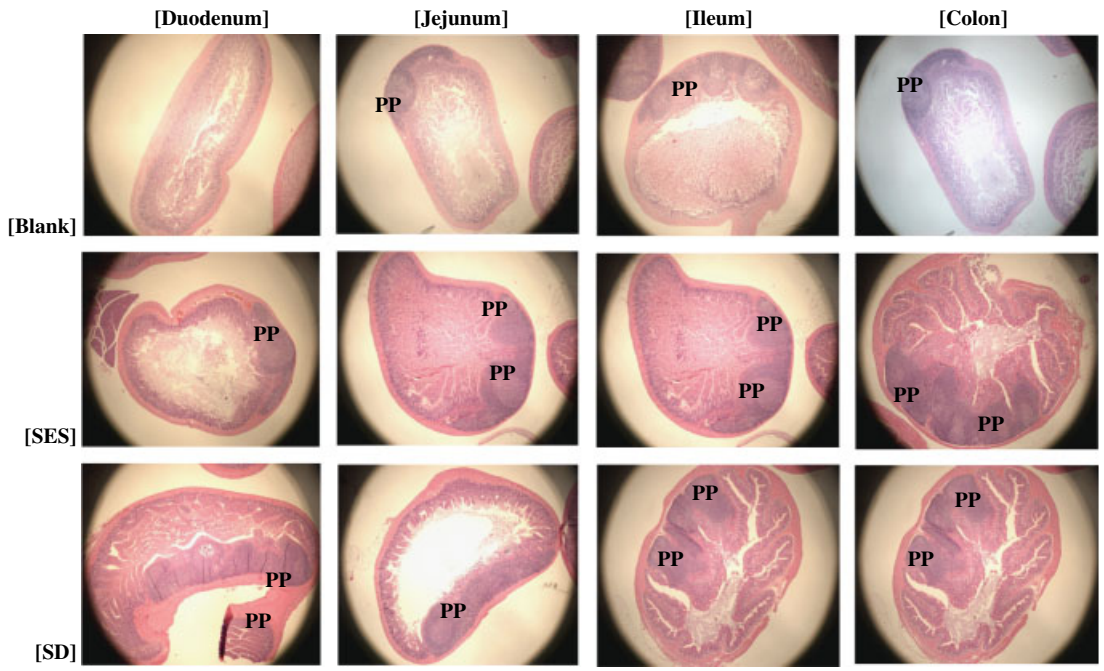

Figure 5. Histopathological views of duodenum, jejunum, ileum and colon tissues after repeated oral administrations of SES or SD for 1 week. A Peyer's patch is indicated by PP

DOI: 10.1002/bdd

be more favorable than the SD for lymphatic absorption.

Histopathological view

Although enhanced dissolution and uptake by intestine, Peyer's patches and liver were clearly observed, the SES or SD could potentially induce histopathological changes in intestinal epithelia and hepatic cellular membranes and alter Peyer's patch function by repeated dosing. The incorporation of pharmaceutical excipients in SSD such as polysorbate 80, oleic acid and citric acid is unlikely to cause any histological changes in these areas, because these excipients are known to be safe and not to induce any hepatotoxicity even at high concentrations. The oral lethal doses $(LD)_{50\%}$ of polysorbate 80, oleic acid and citric acid in rats are 25 g, 74 g and 3 g/kg, respectively [16].

So, it is also very desirable to examine protein or lipid release from membranes at the cellular level. However, in this study, any potential histopathological changes of tissues were visualized for preliminary information.

Histopathological views of duodenum, jejunum, ileum and colon tissue after oral administration of SES or SD are shown in Figure 5. After repeated dosing, no distinct evidence of histopathological damage was observed in intestinal enterocytes. No Peyer's patch regions were observed in blank duodenum tissue.

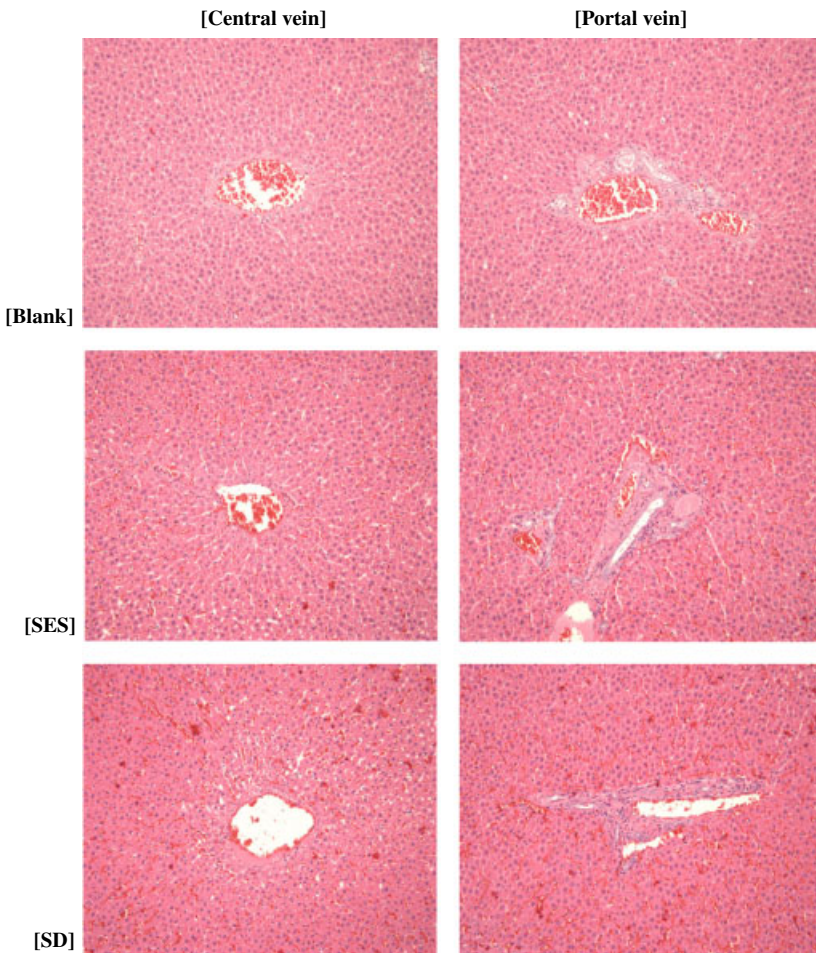

Figure 6. Histopathological views of the hepatic central and portal vein areas after repeated oral administrations of SES or SD to rats for 1 week, equivalent to 10 mg itraconazole/kg ($n = 5$)

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Contrarily, fractional Peyer's patch regions of blank jejunum, ileum and colon tissues comprised 15%, 25% and 15%, respectively. Interestingly, both SES and SD increased the areas of Peyer's patch region in intestinal tissues. Fractional Peyer's patch regions in duodenum, jejunum, ileum and colon were 25%, 30%, 35% and 35%, respectively, when SES was administered. For SD, fractional Peyer's patch regions in duodenum, jejunum, ileum and colon tissue were 35%, 35–40%, 45% and 25%, respectively.

Although microparticles or soluble lipid-based formulations can deliver drugs to the systemic circulation via Peyer's patches, no report on the proliferation of Peyer's patch regions by repeated dosing is available. Peyer's patch fractions after SES and SD formulations showed no significant differences, although the uptake of SES through Peyer's patches was about 3.39 times greater than that of SD at the same doses.

Itraconazole is metabolized by the liver to produce the active metabolite, hydroxyitraconazole. It is well-known that itraconazole should be avoided in patients with hepatic disease due to possible hepatotoxicity [17]. Histopathological views of the hepatic central and portal vein areas were compared after an oral administration of SES or SD (Figure 6). Hepatocytes from the tissues of untreated rats showed no significant congestion or inflamed monocytes in these areas. However, SES induced minor congestion in these regions. Minor inflamed monocytes were also observed. On the other hand, severe congestion and extension of sinusoids in the central vein areas were observed when SD was administered. Severe congestion and inflamed monocytes also occurred in portal vein tissues. The SES showed less hepatic damage than the SD, possibly by avoidance of hepatic uptake by passing an alternative route through Peyer's patches (see Figure 3). The detailed mechanism of the hepatotoxicity and histopathology of itraconazole by the difference of dosage formulations should be validated at the molecular level in the future.

Comparative bioavailability

Mean plasma concentration-time profiles following a single oral administration of SES or SD to rats are shown in Figure 7. Pharmacokinetic parameters are summarized in Table 1. The *AUC* and C_{max} of SES were about 2.2 and 2.4 times higher than those of SD. The T_{max} of SES was smaller than that of SD. It was evident that the bioavailability provided by SES was much improved versus SD, due to its increased dissolution, easy dispersion and improved uptake into intestines as well as high possibility of Peyer's patch absorption.

In conclusion, the SES were more favorable than the SD in terms of dissolution and tissue uptake in whole intestine, liver and Peyer's patches of itraconazole. After repeated dosing for 1 week, both SES and SD increased Peyer's patch fractions in intestinal tissues but their histopathologies were not altered by the different delivery systems, except those of hepatocytes.

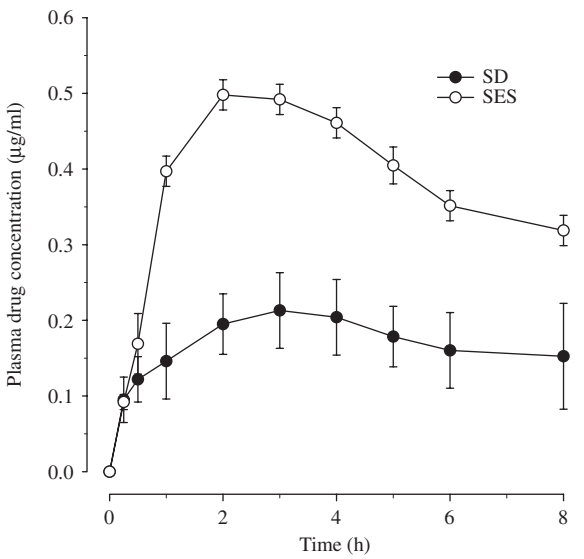

Figure 7. Mean plasma concentration-time profiles following a single oral administration of SES or SD, equivalent to 10 mg itraconazole/kg ($n = 5$)

Table 1. Summary of pharmacokinetic parameters after a single oral administration of SES or SD to rats, equivalent to 10 mg itraconazole/kg ($n = 5$)

Parameter	SES	SD
C_{max} (μg/ml)	0.50 ± 0.08[a]	0.221 ± 0.09
T_{max} (h)	2.50 ± 0.12	3.50 ± 0.51
AUC_{0-8h} (μg-h/ml)	3.09 ± 0.14[a]	1.36 ± 0.26

[a] Significantly different from SD.

DOI: 10.1002/bdd

These biopharmaceutical differences of SES resulted in much higher bioavailability than the SD. The current SES dosage forms would be preferable to SD to improve the bioavailability of poorly water-soluble drugs.

Acknowledgements

This work was partially supported by a grant of the Ministry of Science and Technology-NRL program (M10300000-06J0000-31910). The authors are very grateful to Mr Yin-Yuan Piao for his helpful contributions to the experiments. We also thank the Research Institute of Pharmaceutical Sciences, Kangwon National University for allowing the use of the Three-Roll Milling Unit.

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DOI: 10.1002/bdd