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Solubilized Formulation of Olmesartan Medoxomil for Enhancing Oral Bioavailability

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Olmesartan medoxomil (OLM) is an antihypertensive angiotensin II receptor blocker. OLM has a low bioavailability (BA), approximately 26% in humans, due to its low water solubility and efflux by drug resistance pumps in the gastrointestinal tract. Self-microemulsifying drug delivery system (SMEDDS), which is easily emulsified in aqueous media under gentle agitation and digestive motility, was formulated to increase the oral BA of OLM. Among the surfactants and oils studied, Capryol 90, Tween 20, and Tetraglycol were chosen and combined at a volume ratio of 1:6:3 on the basis of equilibrium solubility and phase diagram experiments. The mean droplet size of SMEDDS was 15 nm. In an oral absorption study in rats, SMEDDS formulation brought faster absorption compared to suspension, showing a T_{max} value of 0.2 hr. The C_{max} and AUC values of SMEDDS formulation were significantly higher than those of suspension, revealing a relative BA of about 170%. Our study demonstrated the potential usefulness of SMEDDS for the oral delivery of poorly absorbable compounds, including OLM.

Key words: Olmesartan medoxomil, SMEDDS, Solubilization, Bioavailability, Oral delivery

Selected by Editors

INTRODUCTION

Many attempts have been made to improve the oral bioavailability (BA) of poorly absorbable drugs via solubilization including self-microemulsifying drug delivery system (SMEDDS) (Kim et al., 2001; Shah et al., 1994). SMEDDS is an isotropic mixture of oils, surfactants, or alternatively, one or more hydrophilic solvents or surfactants. Upon mild agitation followed by dilution in aqueous media, including gastrointestinal fluids, this system can form fine droplets of oil-in-water (o/w) microemulsions (Gursoy and Benita, 2004). The resultant small droplet size provides a large surface area for drug release and absorption (Driscoll, 2002). In addition, the absorption of both hydrophobic and hydrophilic drugs can be increased by increasing membrane fluidity to facilitate transcellular absorption, opening tight junctions to allow paracellular transport, and inhibiting efflux pumps like P-glycoprotein (Haus et al., 1994; Gursoy et al., 2004).

Olmesartan medoxomil (5-methyl-2-oxo-1, 3-dioxolen-4-yl) methoxy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazol-5-yl)-phenyl] phenyl} methyl imidazol-5carboxylate) is a novel selective angiotensin II receptor blocker that is approved for the treatment of hypertension (Warner and Jarvis, 2002). It is a prodrug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite, olmesartan. Clinical trials in hypertensive patients revealed excellent pharmacological actions and a good tolerance without serious adverse effects (Neutel et al., 2002). However, the oral BA of olmesartan medoxomil was only 26% in healthy humans due to low solubility in water and unfavorable breakage of the ester drug to a poorly permeable parent molecule in the gastrointestinal fluids (Nakagomi-Hagihara et al., 2006). Efflux pumps in the gastrointestinal tract

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also interfere with drug absorption (Matsushima et al., 2001; Laeis et al., 2001).

Olmesartan dose-dependently reduces blood pressure through arterial vasodilation and reduced sodium retention, as do other angiotensin receptor blockers (Bruner and Nussberger, 2001). Thus, improving oral BA of olmesartan medoxomil can increase clinical efficacy or reduce the oral dosage required to achieve the same effect. No attempts have been reported to improve the intestinal absorption of olmesartan medoxomil. Therefore, we use SMEDDS formulation with Capryol 90 as an oil, Tween 20 as a surfactant, and Tetraglycol as a cosurfactant, to enhance the oral BA of olmesartan medoxomil. We tested the phase diagrams of the selected formulation, measured droplet size, and determined pharmacokinetics after oral administration in rats.

MATERIALS AND METHODS

Materials

Olmesartan medoxomil (OLM) and olmesartan (OL) were purchased from Estech Pharma Co., Ltd. Capryol 90 and Cremophor EL were kindly provided by BASF Korea, Ltd. Tween 20, Tetraglycol and telmisartan were purchased from Sigma-Aldrich. Labrafac lipophile 1349 and Labrafil M 1944 CS were provided by Gattefosse, and Capmul was purchasd from Abitec Corp. Hydrochloic acid (HCl), sodium carboxylmethylcellulose (Na-CMC), PEG 400, and glycerin were provided by Duksan Pure Chemical Co., Ltd., and tert-butyl-methyl-ether (TBME) was purchased from Across Organics. Acetonitrile and methanol were of HPLC grade and purchased from J. T. Baker. All other chemicals used were of analytical grade and used as received.

Equilibrium solubility determination

An excess amount of drug was added to oil, surfactant, or cosurfactant and vortexed. The mixture was then kept at ambient temperature for 3 days to reach equilibrium under intermittent shaking. The supersaturated sample was centrifuged at 12,000 rpm for 10 min to separate the undissolved OLM. The supernatant was then filtered using a membrane filter (0.45 μm, Whatman) and diluted with methanol to quantify the OLM by HPLC. The determination of OLM was performed by HPLC using acidic aqueous solution (0.2% acetic acid)-acetonitrile (70:30, v/v) as a mobile phase at a flow rate of 1.0 mL/min. The HPLC system consisted of a pump (L-2130), UV detector (L-2400), a data station (LaChrom Elite, Hitachi), and a C_{18} column (Shiseido). The column eluant was monitored at 260 nm, and the OLM peak was separated with a retention time of 13.0 min.

Pseudo-ternary phase diagram for SMEDDS formulation

The pseudo-ternary phase diagram of oil, surfactant/cosurfactant, and water was constructed using a water titration method in the presence of drug (Li et al., 2005). The mixtures of oil (Capryol 90) with a combination of surfactant (Tween 20) and cosurfactant (Tetraglycol) (2:1, v/v) were prepared at ratios of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:10 into different tubes. Water was added to the mixture in 5% step-wise increments. Following every water addition, the mixture was gently stirred and maintained at 37°C for 2 hr. The resultant mixture was evaluated visually for phase clarity. Regions of transparent and bluish-white were microemulsions, or milky dispersions were emulsions. The SMEDDS formulation was prepared by initially dispersing OLM in the cosurfactant and the addition of oil and surfactant. The mixture was vortexed to get a clear solution (OLM 20 mg/SMEDDS mL).

Particle size determination

An aliquot of SMEDDS formulation containing 20 mg of OLM was added to 200 mL of simulated intestinal fluid (pH 6.8) and then gently stirred. A photon correlation spectrometer using laser light scattering (Malvern zeta sizer) was employed for droplet size determination. The samples were loaded into a cuvette in a thermostatic chamber. Light scattering was monitored at a 90° angle at 25°C.

BA study in rats

The animal study was performed in accordance with the NIH guideline "Principles of Laboratory Animal Care" (NIH publication No.85-23, revised 1996) and approved by the Institutional Animal Care and Use Committee of Chung-Ang University in Seoul, Korea. Male Sprague-Dawley rats, 6-week-old and weighing 200-250 g, had free access to diet and water until 12 hr prior to being used in the experiments. Rats were anesthetized with chloroform before cannulation. Polyethylene cannulas were inserted in the femoral artery for blood sampling. Two formulations, SMEDDS dispersion and a 0.2% Na-CMC suspension, were administered via oral gavage at 1 mg/kg as OLM. Blood samples of about 0.3 mL were collected with heparinized tubes at predetermined time intervals and centrifuged at 12,000 rpm for 10 min. Plasma samples were stored at -20°C until analysis by LC-MS/MS.

Olmesartan assay in plasma samples

An LC-MS/MS assay was developed to determine the concentrations of OL in rat plasma. A 100 μL aliquot of plasma was transferred into a glass tube, followed by the addition of 50 μL of telmisartan as an internal standard (500 ng/mL), 200 μL of 1 M HCl, and 5 mL of extraction solvent TBME. The mixture was vortexed for 10 min to extract OL and the internal standard from plasma and then centrifuged at 3000 rpm. The upper organic phase was transferred into a glass tube and evaporated to dryness at 40°C under a gentle stream of nitrogen gas. The residue was reconstituted with 100 μL of methanol and was injected into the LC-MS/MS system. HPLC was performed on an Agilent 1100 Series HPLC system. Detection was performed with an API 3200 Triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex) with electrospray ionization (ESI) in positive ion mode for ion production, which was controlled by Analyst Software version 1.4.2. Chromatography was performed isocratically on an X-terra C_{18} column (50 mm × 2.1 mm, 3.5 μm, Waters). The mobile phase was 5 mM ammonium formate- acetonitrile (15:85, v/v) at a flow rate of 0.25 mL/min. The injection volume was 10 μL. Chromatography was performed at 20°C. The ion-spray potential was set at 5.5 kV and the source temperature was 500°C. Multiple reaction monitoring (MRM) was performed using nitrogen as the collision gas. The analytes were detected by monitoring the transitions *m/z* 447.3→207.2 and 515.3→276.2, with collision energy of 29 and 67 eV for OL and telmisartan, respectively. The analytical time for each run was 4 min in total. The calibration equation was determined by least-squares linear regression (weighting 1/x) over the range 5-4000 ng/mL in plasma. The precision and accuracy of the method were determined at five quality control sample levels.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using a BA Calc 2002 pharmacokinetic analysis computer program (Korea Food & Drug Administration). Area under the curve (AUC) was calculated using the linear trapezoidal rule by the program. Maximum plasma concentration (C_{max}) and the time needed to reach the maximum plasma concentration (T_{max}) were determined directly from concentration-time data. The elimination rate constant (K_{el}) was obtained from the terminal slope using regression analysis, and the half-life ($t_{1/2}$) of the drug was calculated by a relationship of $0.693/K_{el}$. The relative bioavailability was calculated as percentage of the AUC of SMEDDS to drug suspension.

Statistical analysis

All data are expressed as the mean ± S.D. Statistical significance was checked by Student's *t*-test at a threshold of $p < 0.05$, unless otherwise indicated

RESULTS AND DISCUSSION

Formulation development

The drug-loading capacity of SMEDDS, which contains oil and (co)surfactant, depends on the solubility of the drug in the formulation. The solubility of OLM in various solvents is presented in Table I. Tetraglycol, a solubilizing agent with good dissolution properties (Bechgaard et al., 1996) showed the highest OLM solubility (24 mg/mL). Tween 20 and Capryol 90 also showed the high solubility of OLM, 11 mg/mL and 1 mg/mL, respectively. Therefore, we selected Tetraglycol, Tween 20, and Capryol 90 to prepare the SMEDDS system.

We constructed pseudo-ternary phase diagrams in the presence of OLM to obtain the optimum ratio between components. In a fine dispersion of the oil droplet, surfactant and cosurfactant are preferentially located at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The mixing ratio of oil to surfactant/cosurfactant (S/CoS) influences microemulsion formation (Groves, 1976). Various S/CoS ratios, including 2:1, 1:1, and 1:2, are usually tested for phase behaviors (Patel et al., 2007; shah et al., 1994). Hydrophilic solvents such as PEG 400 and ethanol can be rapidly redistributed to the water phase and cause drug precipitation, which can be resolved by increasing the surfactant proportion in SMEDDS (Patel and Vavia, 2007; de Campo et al., 2004). Therefore, we used 2-fold greater amount of Tween 20 than Tetraglycol (S/

Table I. Solubility of olmesartan medoxomil in various solvents

Solvent	Solubility (mg/mL)*
Water	–[a]
Capryol 90	1.29 ± 0.32
Labrafac lipophile 1349	0.29 ± 0.02
Labrafil M 1944 CS	0.05 ± 0.01
Capmul MCM C8	0.26 ± 0.01
Tween 20	11.81 ± 0.23
Cremophor EL	8.44 ± 0.21
Tetraglycol	24.03 ± 2.92
PEG 400	6.98 ± 1.08
Glycerin	2.39 ± 0.56

[a] Practically insoluble.
* Data are expressed as the mean ± S.D. (n = 3).

CoS ratio of 2:1) to achieve a stable dispersion for OLM. The combination of Tween 20, Tetraglycol, and Capryol 90 yielded a large microemulsion region, and increasing the concentration of S/CoS increased the spontaneity of the self-emulsification region (Fig. 1). Dispersion was stable for at least 2 hr without drug precipitation or phase separation. The ratio of oil to S/CoS at 1:9, representing a wide microemulsion region, was selected. Finally, we optimized the SMEDDS formulation for solubilizing OLM with Capryol 90, Tween 20, and Tetraglycol (10:60:30).

Droplet size measurement

As shown in Fig. 2, droplet size was measured as approximately 15 nm on average, with a narrow and homogeneous size distribution. The high ratio of surfactants produced small droplets by decreasing the surface free energy and forming a closely packed system. Increasing the S/CoS ratio and decreasing the oil ratio lead to a proportional decrease in droplet size (Levy et al., 1990). The droplet size of the emulsion influences self-emulsification performance because it determines the rate and extent of drug absorption as well as *in vivo* stability (Shah et al., 1994; Tarr and Yalkowsky, 1989). Droplet sizes below 50 nm causes formation of stable isotropic microemulsions with high absorption rates (Grusoy and Benita, 2004). Because our SMEDDS formulation produced droplet sizes below 50 nm, this property should enhance the absorption of OLM after oral administration.

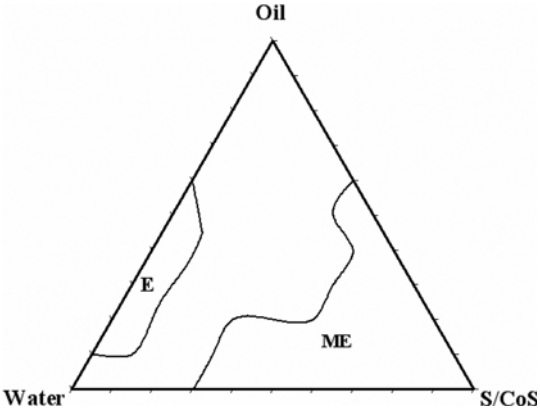

Fig. 1. Pseudo-ternary phase diagrams indicating a microemulsion existence range with a ratio of surfactant/cosurfactant (S/CoS) 2:1 (v/v). ME and E indicate microemulsion and emulsion area, respectively.

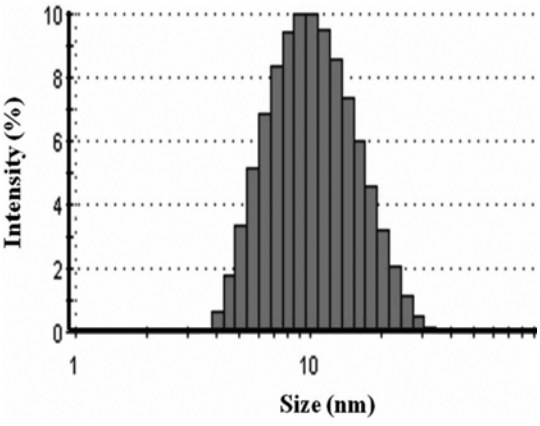

Fig. 2. Droplet size distribution of the SMEDDS formulation in buffer solution.

LC-MS/MS determination of olmesartan in rat plasma

Representative chromatograms obtained from blank plasma and plasma samples spiked with OL and telmisartan are presented in Fig. 3. The retention times for OL and telmisartan were 0.62 and 0.77 min, respectively. No endogenous serum components or pharmaceutical excipients eluted at the retention times of the peaks of interest. The calibration curves were constructed by spiking drug-free plasma with known amounts of OL at 5-4000 ng/mL. The standard calibration curve (n = 5) was linear, with a correlation coefficient of 0.9935. The samples were quantified using a peak height ratio of OL over the internal standard, telmisartan.

The analysis method was validated for precision (CV %) and accuracy. Five quality control samples at each concentration level (5, 10, 50, 100 and 500 ng/mL) were analyzed, and the intra- and inter-day precision and accuracy data are summarized in Table II. In plasma, intra and inter-day precisions ranged from 1.91% to 13.53%, and accuracies ranged from 94.79% to 110.07%.

BA evaluation in rats

We next performed an in vivo oral BA study in rats to evaluate how SMEDDS influenced the absorption of OLM, which is rapidly hydrolyzed in vivo to OL, an active metabolite. Plasma OL levels were measured to assess the pharmacokinetic parameters. Because hydrolysis of OLM in human plasma is extremely rapid, OL levels reflect OLM pharmacokinetics (Kobayashi et al., 2000). The mean plasma OL levels were higher following oral administration of the SMEDDS formulation than the suspension formulation (Fig. 4). Pharmacokinetic parameters for OL such as the maximum plasma concentration (C_{max}), the peak time (T_{max}), and the area under the concentration-time curve (AUC), are listed in Table III. The T_{max} of OL for SMEDDS was 0.2 hr, which was faster than the suspension. The C_{max} and AUC of the

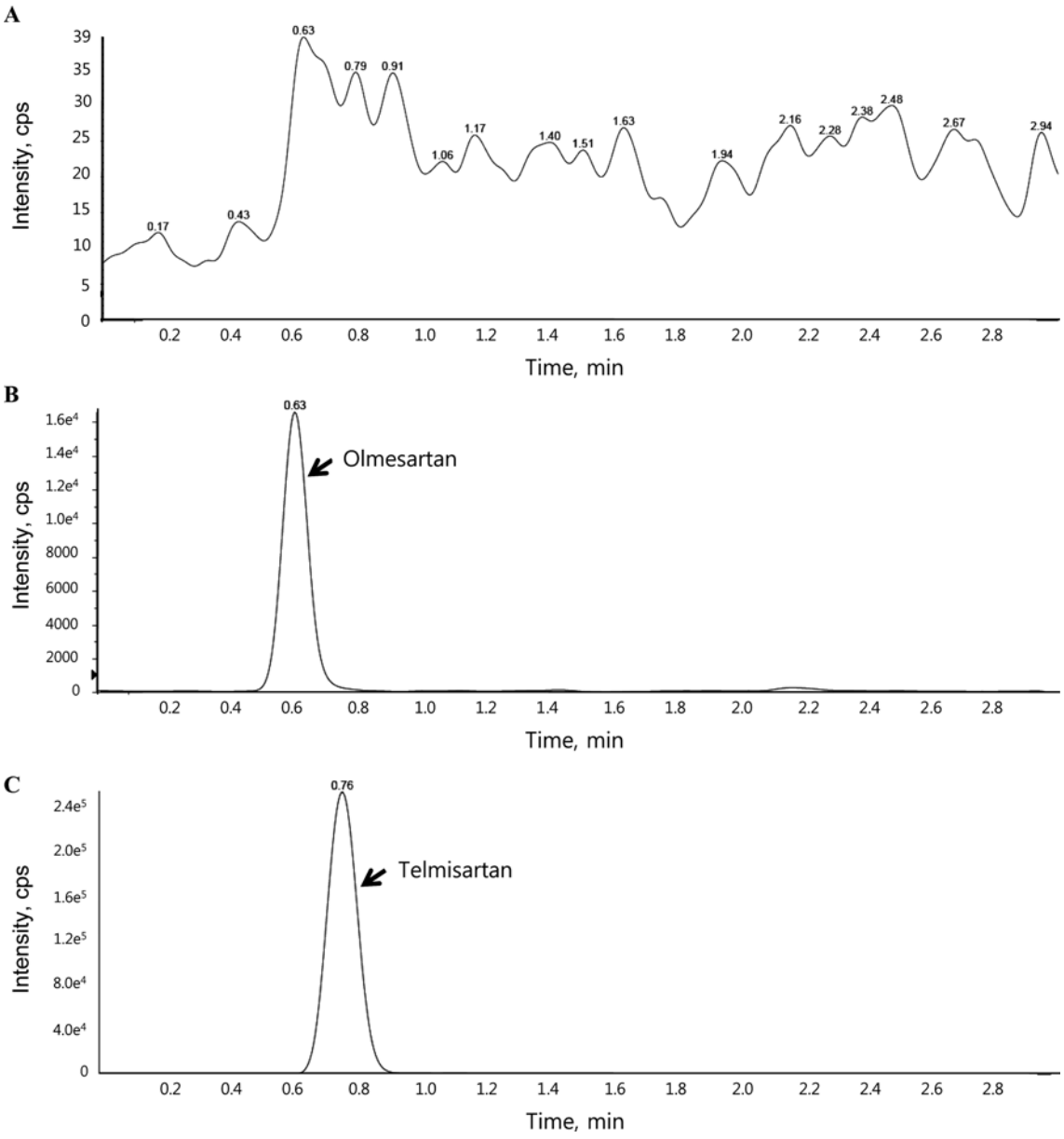

Fig. 3. LC-MS/MS chromatograms of (**A**) blank rat plasma, (**B**) and (**C**) blank rat plasma spiked with olmesartan and telmisartan, respectively.

Table II. Precision and accuracy for the LC-MS/MS analysis of olmesartan in plasma

Conc. (ng/mL)	Intraday			Interday		
	Conc. Found (ng/mL) (mean ± S.D.)	Precision (%)[a]	Accuracy (%)[b]	Conc. Found (ng/mL) (mean ± S.D.)	Precision (%)[a]	Accuracy (%)[b]
5	4.74 ± 0.64	13.53	94.79	4.98 ± 0.08	12.09	99.74
10	9.96 ± 1.16	11.69	99.58	11.00 ± 2.50	5.02	110.07
50	52.61 ± 7.05	13.41	105.21	51.16 ± 5.85	8.81	102.32
100	102.84 ± 9.28	9.03	102.84	98.16 ± 6.14	4.79	98.16
500	492.90 ± 3.46	7.60	98.58	480.40 ± 12.08	1.91	96.08

[a] Expressed as the relative standard deviation.
[b] Expressed as (mean observed concentrations/nominal concentrations) ×100.

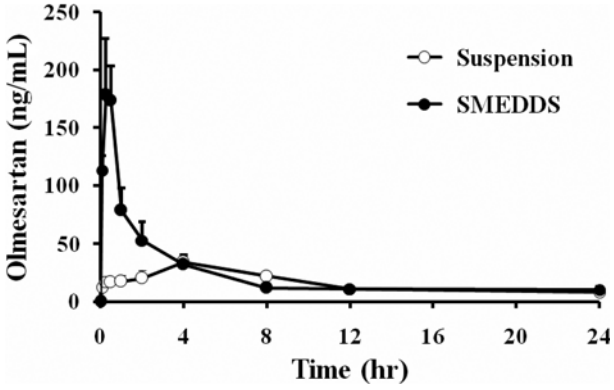

Fig. 4. The plasma concentration-time profiles of olmesartan following oral administration of olmesartan medoxomil suspension and SMEDDS formulation to rats at a single dose of 1.0 mg/kg (n = 5).

Table III. Comparison of the mean pharmacokinetic parameters of olmesartan from SMEDDS formulation compared to suspension after a single 1.0 mg/kg oral dose in rats

	Suspension	SMEDDS
$AUC_{(0\text{-}24h)}$ (ng·hr/mL)	375.9 ± 88.3	588.2 ± 113.2
$AUC_{(0\text{-}\infty)}$ (ng·hr/mL)	491.6 ± 146.9	843.4 ± 119.7
C_{max} (ng/mL)	34.2 ± 4.8	178.3 ± 48.9
T_{max} (hr)	4.0 ± 0.8	0.2 ± 0.1
$t_{1/2}$ (hr)	12.1 ± 1.7	13.7 ± 0.8
Relative Bioavailability (%)	-	171.7

*Data are expressed as the mean ± S.D. (n = 5)

SMEDDS formulation were also significantly higher than those of the suspension. The relative BA of OLM in SMEDDS was about 170% higher than the suspension, indicating the feasibility for further development of an efficient oral delivery system.

The plasma OL level peaked 4 h after oral administration of OLM in suspension, and then slowly declined up to 24 hr. The $AUC_{(0\text{–}24\ hr)}$ and $AUC_{(0\text{–}\infty)}$ were only 375 and 490 ng·h/mL, respectively, because *slower dissolution* of OLM particles in suspension is the rate-limiting step for intestinal absorption. OLM in 0.5% Na-CMC delivered orally (3 mg/kg; 3-fold higher than here) to streptozotocin-induced diabetic rats produced a T_{max} of 4 hr, a C_{max} of 95 ng/mL, and an $AUC_{(0\text{–}24\ hr)}$ of 650 ng·hr/mL (Nakamura et al., 2005). These results show the same T_{max} with dose proportionality in C_{max} and AUC.

The SMEDDS formulation improved AUC and C_{max} values as well as a faster T_{max}. Thus, solubilization of OLM in SMEDDS improves oral BA by avoiding the dissolution step. Also, Tween 20 may improve absorption by acting as an efflux pump inhibitor (Zhang et al., 2003). A transcellular transport assay using double transfectants indicated that OLM was a substrate of efflux pumps, including multidrug resistance 1 (MDR1), breast cancer resistance protein (*BCRP*), and *multi*-drug resistance-associated protein 2 (MRP 2), which may interfere with its intestinal absorption (Yamada et al., 2007). Tween 20 can modulate these efflux pumps. In mice, Tween 20, given orally 15 min before topotecan administration, increased the AUC 1.8-fold after oral administration by inhibiting BCRP function in the small intestine (Lo, 2003; Yu et al., 1999). Furthermore, oils and surfactants can increase drug permeability by interfering with the lipid bilayer of the epithelial cells.

CONCLUSION

We developed a SMEDDS system containing OLM using Capryol 90, Tween 20, and Tetraglycol (10:60:30), with a small droplet size of about 15 nm. The SMEDDS formulation showed a relative oral BA of 170% compared to suspension, putatively by increasing solubility and permeability, and possibly by inhibiting efflux pumps. Our study illustrated the potential usefulness of SMEDDS for the oral delivery of poorly soluble and poorly permeable compounds, including OLM.

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