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Research Article

A Self-microemulsifying Drug Delivery System (SMEDDS) for a Novel Medicative Compound Against Depression: a Preparation and Bioavailability Study in Rats

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ABSTRACT. AJS is the code name of an untitled novel medicative compound synthesized by the Tasly Holding Group Company (Tianjin, China) based on the structure of cinnamamide, which is one of the Biopharmaceutics Classification System (BCS) class II drugs. The drug has better antidepressant effect, achieved by acting on the 5-hydroxytryptamine receptor. However, the therapeutic effects of the drug are compromised due to its poor water solubility and lower bioavailability. Herein, a self-microemulsifying drug delivery system (SMEDDS) was developed to improve its solubility and oral bioavailability. AJS-SMEDDS formulation was optimized in terms of drug solubility in the excipients, droplet size, stability, and drug precipitation using a pseudo-ternary diagram. The pharmacokinetic study was performed in rats, and the drug concentration in plasma samples was assayed using the high-performance liquid chromatography-electrospray tandem mass spectrometry (HPLC-MS/MS) method. The optimized formulation for SMEDDS has a composition of castor oil 24.5%, Labrasol 28.6%, Cremphor EL 40.8%, and Transcutol HP 2.7% (co-surfactant). No drug precipitation or phase separation was observed from the optimized formulation after 3 months of storing at 25°C. The droplet size of microemulsion formed by the optimized formulation was 26.08±1.68 nm, and the zeta potential was −2.76 mV. The oral bioavailability of AJS-SMEDDS was increased by 3.4- and 35.9-fold, respectively, compared with the solid dispersion and cyclodextrin inclusion; meanwhile, the C_{max} of AJS-SMEDDS was about 2- and 40-fold as great as the two controls, respectively. In summary, the present SMEDDS enhanced oral bioavailability of AJS and was a promising strategy to orally deliver the drug.

KEY WORDS: bioavailability; HPLC-MS/MS; self-microemulsifying drug delivery system; solubilization; stability.

INTRODUCTION

An oral formulation is preferentially adopted as a drug delivery system due to its convenience and acceptance by patients, reducing hospital visits and the danger of infections (1, 2). However, the potential pharmacological activities of novel compounds developed via the high-throughput screening technology are always limited because of their poor water solubilities (3, 4). Methods of drug solubility enhancement including solid dispersion, liposomes, polymer micelles, nanoemulsions, cyclodextrin (CD) inclusion, and self-emulsifying drug delivery system (SEDDS) (5–10) are adopted to develop the oral drug delivery system. Among these methods, SEDDS is one of the most promising approach to improve oral bioavailability of poorly water-soluble drugs because it maintains the drug in a solubilized state in the gastrointestinal tract (11). In fact, several SEDDS formulations containing cyclosporin A, ritonavir, or saquinavir have been approved by the Food and Drug Administration (FDA) (12).

SEDDS is a stable mixture of drug, oil, surfactant, and co-surfactant; while self-microemulsifying drug delivery system (SMEDDS) is SEDDS which can form fine oil-in-water droplets with a diameter size of less than 50 nm under mild agitation of the gastrointestinal tract without the dissolution process (13). SMEDDS has the potential to deliver poorly water-soluble drugs because the microemulsion droplets of SMEDDS provide 100% of the capacity to entrap a drug (14) and protects the drug from gastrointestinal degradation. The increased surface area and small droplets that results in transporting the drug substance through the unstirred water layer to the gastrointestinal membrane contribute to a significant increase in drug absorption (15, 16). Moreover, the droplets can be rapidly dispersed in blood as well as lymph (13), and the lymphatic drug transport can avoid the first-pass effect (17). Additionally, the SMEDDS formulation is suitable for filling in gelatin capsules as the unit dosage container and stored at room temperature.

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AJS is the code name of an untitled novel medicative compound synthesized by the Tasly Holding Group Company (Tianjin, China) based on the structure of cinnamamide, which is one of the Biopharmaceutics Classification System (BCS) class II drugs. AJS, whose chemical structure is presented in Fig. 1, shows an antidepressant effect achieved by acting on the 5-hydroxytryptamine receptor that is linked to mood and anxiety disorders as well as depression (18, 19) and the noradrenergic nerve system (a key factor of depression) (20). However, its solubility in water is very poor, and its solubilities in 100 mL of water, 0.1 M HCl, and phosphate buffer (pH 7.2) are 0.49, 0.51, and 0.24 mg, respectively. These low solubilities reduce the oral bioavailability and discount the therapeutic effect. Unfortunately, no strategy is used to enhance its solubility until now. Thus, a formulation that can enhance its bioavailability is highly desirable.

To overcome the drawbacks of AJS and improve the therapeutic outcome, herein, the goal of this paper was to develop the AJS-SMEDDS to improve solubility and oral bioavailability. Thus, the present study sought to (I) prepare the SMEDDS for AJS and optimize its formulation in terms of drug solubility in the excipients, droplet size and stability and (II) evaluate the bioavailability in rats. AJS was a novel medicative compound with lower water solubility, which was developed by Tasly Holding Group Company (Tianjin, China); until now, there was no report about its formulation for dosage forms, especially about the strategies of drug solubility enhancement.

MATERIALS AND METHODS

Materials

The AJS sample was supplied by the Tasly Holding Group Company (Tianjin, China). Labrasol, Labrafil M 1944CS, Peceol, Maisine 35–1, Transcutol HP, Labrafac CC, and Oleique CC 497 were purchased from Gattefosse Co. Ltd. (Lyons, France). Cremphor EL was purchased from BASF SE (Ludwigshafen, Germany). Lipoxol 400 Med Liquid (PEG 400) was purchased from Sasol Ltd. (Sasolburg, South Africa). Caprylic/capric triglyceride (Crodamol Gtcc) was purchased from Croda Ltd. (Cowick Hall, Yorkshire, UK). Castor oil was purchased from Hunan Erkang Medicine Co. Ltd (Liuyang, Hunan, China). Span 80 was purchased from Tianjin Weichen Chemical Reagents Co. Ltd. (Tianjin, China). Hydroxypropyl methyl cellulose (HPMC E5) was purchased from Shanghai Colorcon Co. Ltd (Shanghai, China). β-cyclodextrin (β-CD) was purchased from Beijing Fenglijingqiu trade and Commerce Co. Ltd. (Beijing, China). Sodium dodecyl sulfate (SDS) was purchased from Tianjin Kermel Chemical Reagents Co. Ltd. (Tianjin, China).

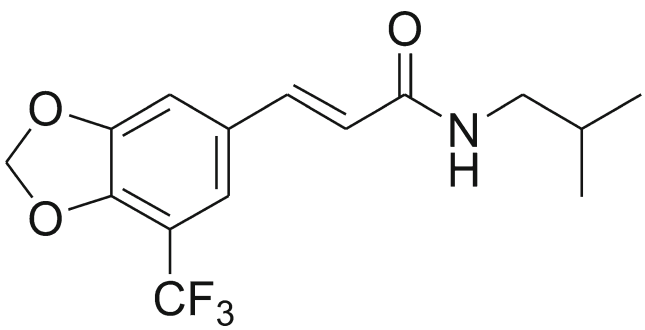

Fig. 1. Chemical structure of AJS

Solubility Studies

The solubility study was performed as previously reported with a minor modification (10). Briefly, excess amount of AJS was added into each test tube containing 2 mL of the vehicles, including oils, surfactants, and co-surfactant. The chemicals were then mixed for 10 min with a vortex mixer (Qilinbeier instrument Co. Ltd., Haimen, Jiangsu, China). The samples were then incubated in a shake water bath (GFL1092, GFL Company, Hanover, Germany) at 25°C for 48 h and then centrifuged at 3000×*g* for 10 min to separate the undissolved drug. The supernatants were filtered with a 0.45-μm filter membrane, and the drug content was quantified by high-performance liquid chromatography (HPLC) method.

The determination of AJS in samples was conducted using an Agilent 1260 HPLC system (Agilent Technologies, Inc., California, USA) with an Agilent ZORBAX SB-C18 column (250×4.6 mm, 5 μm, Agilent Technologies, USA). The mobile phase contained 58% of acetonitrile and 42% of phosphoric acid aqueous solution (0.1% of volume fraction) with a flow rate of 1.0 ml/min at 30°C. Detection was conducted at a wavelength of 220 nm. The injection volume was 20 μL.

Construction of Pseudo-ternary Phase Diagram

A series of bi-surfactants were prepared with various weight ratios of two selected surfactants, and the bi-surfactants were then mixed with selected oil at weight ratios from 10:0 to 0:10. The mixture was then blended with a fixed amount of Transcutol HP (co-surfactant). After mixing homogeneously, the sample was titrated with distilled water (100-fold greater than the mixture by weight) with a homothermal magnetic stirrer (EMS-9B, Ounuo instrument Co. Ltd, Tianjin). A visual observation was made simultaneously to identify the spontaneity of self-microemulsification. The formulations whose dilution showed phase separation or coalescence of oil droplets were judged as poor self-microemulsifying formulations, while those that were capable of forming a clear, uniform emulsion were chosen to construct the self-microemulsifying region. The self-microemulsifying region was adopted for choosing the potential formulations.

Preparation of SMEDDS, Solid Dispersion, and β-CD Inclusion

A series of formulations were chosen within the self-emulsification region of the pseudo-ternary phase diagram (21, 22). The formulations were prepared by formulating the fixed amount of AJS in the mixture of surfactant, oil, and co-surfactant at 25°C (Table I). A clear solution was obtained with the help of a vortex mixer. The signs of phase separation or drug precipitation of the formulations were examined after being sealed and were stored at room temperature for 24 h. The emulsification properties were assessed by adding the prepared SMEDDS into 900 mL distilled water under stirring conditions. The studied emulsification properties included the

Table I. Formulations and Their Scores of Self-microemulsifying Properties

Formulation	API (g)	Transcutol HP (g)	Labrasol (g)	Cremphor EL (g)	Castor oil (g)	Score
F1	2.0	1.6	34.4	54.4	30.4	4.2
F2	2.0	1.6	20.8	33.6	20.0	4.6
F3	2.0	1.6	18.4	28.0	12.0	4.2
F4	2.0	1.6	12.0	19.2	8.0	3.4
F5	2.0	1.6	12.8	19.2	8.8	3.4
F6	2.0	1.6	9.6	15.2	9.6	3.2
F7	2.0	1.6	16.8	24.0	14.4	4.8
F8	2.0	1.6	9.6	16	14.4	3.0
F9	2.0	1.6	28	44	24.0	4.4

emulsifying speed, appearance, total weight, and stability of emulsion performed by placing the formulations in a water bath (Ounuo instrument Co. Ltd., Tianjin, China) for 2 h at 37°C. Each formulation was scored according to the scoring system shown in the section below (formulation screening, pseudo-ternary phase diagram).

Two controls, solid dispersion and β-CD inclusion of the drug, were prepared and used in *in vivo* performance.

The solid dispersion was prepared by dissolving 10 g AJS, 100 g HPMC E5, and 200 mg SDS in 1250 mL 75% (*w*/*w*) ethanol (23). After the drug completely dissolved, the ethanol was then removed under vacuum (30–40 mbar) rotary evaporation at 50°C for 0.5 h.

The β-CD inclusion was done by adding AJS (31.7 mM, 10 g) and β-CD (31.7 mM, 36.02 g) in water (40 mL), following by grinding for 2 h, drying at 60°C, and passing through a 60-mesh screen (24, 25). To remove the excess drug, the suspension was filtered through a 0.22-μm filter membrane after grinding.

Stability and Viscosity of SMEDDS

The sealed formulations were stored at 25 and 4°C for 3 months, and the sample was collected once a month to examine the signs of phase separation or drug precipitation and emulsifying properties.

The viscosity of the formulations was tested using a rotational viscometer (Viscotester E, Thermo Electron, Karlsruhe, Germany).

Droplet Size of Microemulsion

The aliquot of chosen formulations (F1, F2, F3, F7, and F9) was diluted with water in a volumetric flask under stirring conditions. The droplet size of the diluted formulations was determined with a Zetasizer nano S (Malvern Instruments, Worcestershire, UK) at 25°C. Experiments were repeated five times.

Morphology and Structure of Microemulsion

The morphology of the emulsion droplet of the optimized formulation was observed using transmission electron microscope (TEM, JEM 100CX electron microscope, with an acceleration voltage of 100 kV). After dilution, one drop of the sample was deposited on a copper mesh and dried at 25°C (26).

In Vivo Pharmacokinetics

The animals used in the experiments received care in compliance with the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals. The experiments followed a protocol approved by the China Pharmaceutical University Institutional Animal Care and Use Committee.

In addition to the optimized formulation of SMEDDS, HPMC E5-based solid dispersion and β-CD inclusion of drug were also orally administered to rats to study oral bioavailability. Eighteen Wistar rats (250±20 g) were divided into three groups (six rats for each group) randomly and were fasted for 12 h prior to the experiment. The three groups were orally administered with SMEDDS, solid dispersion, and β-CD inclusion, respectively, at a dose of 5 mg/kg of AJS based on the weight of the rat. Five hundred microliters of blood samples were collected in heparinized tubes at predetermined time points (0.083, 0.17, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h). Supernatant plasma was obtained by centrifuging the blood samples at 4780×*g* for 10 min and then storing at −70°C for further analysis. The plasma concentration was assayed by the high-performance liquid chromatography-electrospray tandem mass spectrometry (HPLC-MS/MS) method described below.

Sample Preparation and Analytical Methods

The plasma sample (50 μL) was blended with 20 μL of internal standard (IS; 1 μg/mL of diazepam in methanol), 10 μL of methanol, and 400 μL of ethyl acetate. After being vortexed for 3 min, the mixture was centrifuged at 18,063×*g* with a high-speed centrifuge (Hettich MIKRO 220R, Hettich, Germany) for 10 min, and then 300 μL of the supernatant was collected. The supernatant was dried with a stream of nitrogen, and the dried sample was redissolved with 100 μL of mixture of distilled water and methanol (1:1, *v*/*v*), vortexed for 1 min and centrifuged at 12,780×*g* for 10 min. Ten microliters of the supernatant was injected into the HPLC-ESI-MS/MS system for analysis.

The concentration of drug in samples prepared above was detected with a HPLC-MS/MS system that consisted of two Shimadzu LC-20AD pumps (Shimadzu, Japan), a Shimadzu SIL-20AC constant temperature automatic sampler, a Shimadzu CTO-20A column oven, a Shimadzu CBM-20A communication bus module, and an API 4000 quadrupole mass spectrometer, (AB SCIEX, Massachusetts, USA)

equipped with an ESI ion source and an Analyst Software 1.5.2 chromatograph workstation.

HPLC isolation was performed on an Agilent ZORBAX XDB-C18 column (2.1×50 mm, 3.5 μm, Agilent Technologies, USA) at 30°C. The samples were gradient eluted with 0.1% formic acid in water (A) and 0.1% formic acid in methanol (B) at a flow rate of 0.5 mL/min and monitored at 316 nm for AJS and 285 nm for diazepam beginning at a composition of 80% A and 20% B. The gradient program was listed as follows: 0–0.5 min, 80% A and 20% B; 0.5–2.5 min, 2% A and 98% B; and 2.51–4.0 min, 80% A and 20% B. The total run time was 4.0 min.

The conditions for MS detection were set as follows: spray voltage, 5000 V; capillary temperature, 550°C; ion source gas 1, N2; pressure, 60 psi; ion source gas 2, N2; pressure, 55 psi; curtain gas, N2; pressure, 20 psi; declustering potential, 91 V for AJS and 106 V for diazepam (internal standard); and collision energy, 31 eV for AJS and 39 eV for diazepam, precursor ion, *m*/*z* 316.174→m/z 243.2 for AJS and *m*/*z* 285.199→m/z 154.1 for diazepam. The linear range of LC-MS detection was 0.2–200 ng/mL, and the lower limit of quantitation was 0.2 ng/mL. The method for the detection of drug concentration in plasma was specific, selective, and accurate.

Data Analysis and Statistics

In the pharmacokinetic study, the maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (T_{max}) as well as the area under the plasma concentration-time curve (AUC) were calculated by DAS 2.0 software (Pharmacology Institute of China) based on noncompartmental analysis. The AUC and C_{max} values were log-transformed to normalize the distributions and assessed by a two-tailed *t* test. The data are expressed as the mean±the standard deviation, and differences were considered statistically significant when the *P* values were less than 0.05.

RESULTS

Solubility Studies

To obtain the maximum drug loading, the excipients should have a high solubilizing capacity for the drug (13, 17). Herein, we optimized the type of oil phase and surfactants in terms of drug solubility. As shown in Table II, the AJS solubility in castor oil, Transcutol HP, Labrasol, and Cremphor EL was higher than others; thus, castor oil was formulated as oil phase, Labrasol and Cremphor EL were chosen as combined surfactants, and Transcutol HP was added as co-surfactant in our next study.

Formulation Screening

Pseudo-ternary Phase Diagram

The pseudo-ternary diagram was utilized to identify the self-microemulsifying region as well as the phase behavior of chosen vehicles. As shown in Fig. 2, the shadow area represents the self-microemulsifying region where the clear and homogeneous mixture was obtained through gentle stirring.

Table II. Solubility of AJS in Various Vehicles

Vehicles	Solubility (mg/g)
Labrafil M 1944CS	3.00
Peceol	2.50
Maisine 35-1	3.43
Labrafac CC	2.36
Crodamol Gtcc	3.43
Castor oil	9.81
Labrasol	25.04
Oleique CC 497	2.54
Cremphor EL	18.86
Lipoxol 400	3.40
Span 80	2.40
Transcutol HP	142.85

Nevertheless, a concentration of surfactants that is too high would lead to the irritation of the gastrointestinal tract (27); intersolubility and tendency of forming SMEDDS should also be of a concern. Thus, we further optimized the formulations of SMEDDS (F1–F9, Table I) by a scoring system as reported previously with minor modification (28). The scoring system was built on the visual efficiency assessment system by using weighing factor instead of grades (28). It was accurate to optimize the SMEDDS formulations because more influencing factors were involved, including emulsion stability, which is important to make the drug totally absorbable. This is the crucial factor for formulation assessment and should be given the highest weighing factor (28). Other factors such as the emulsifying time, appearance of emulsion, and weight of formulation were also contained in the system (Table III).

The score of each formulation is shown in Table I. The formulations of F1–F3, F7, and F9 exhibit higher scores (more than 4) than the others according to the scoring system discussed above, while the formulation F7 earned the highest score. Among these optimized formulations, the amount of surfactants (Labrasol and Cremphor EL) used in F7 was smallest, therefore having potential to reduce the toxicity. Thus, F7 was selected in the *in vivo* performance.

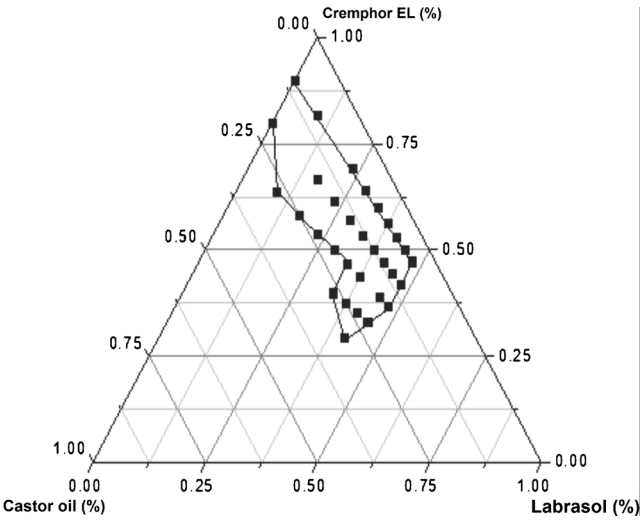

Fig. 2. Pseudo-ternary diagram of chosen vehicles

Table III. Scoring System of Chosen Formulations

	Weighting factors	Phenomena 5 score	Phenomena 4 score	Phenomena 3 score	Phenomena 2 score	Phenomena 1 score
Emulsifying speed	0.2	Totally emulsified within 5 s	Totally emulsified between 5 and 10 s	Totally emulsified between 10 and 15 s	Totally emulsified between 15 and 20 s	Time for totally emulsifying is longer than 20 s
Appearance of emulsion	0.2	Clear, blue emulsion	Clear, white-blue emulsion	Uniform but milky emulsion	Gray emulsion	Poor emulsified formulation with large oil globules
Total weight of formulation of therapeutical dose	0.2	<0.6 g	0.6–0.8 g	0.8–1.1 g	1.1–1.5 g	>1.5 g
Stability of emulsion	0.4	No drug precipitation or crystallization	–	Slight drug precipitation or crystallization	–	Much drug precipitation or crystallization

Table IV. Average Droplet Size, PDI, and Zeta Potential of Tested Formulations (n=5)

Formulation	Average size (nm)	PDI	Zeta potential (mV)
F1	34.23±3.17	0.322±0.04	−2.86±0.66
F2	40.26±2.25	0.363±0.02	−4.79±0.67
F3	27.96±1.77	0.299±0.02	−3.76±0.44
F7	26.08±1.68	0.264±0.01	−2.76±0.27
F9	33.56±1.11	0.399±0.04	−2.85±0.36

Stability and Viscosity of SMEDDS

To study the stability of SMEDDS, aliquots of SMEDDS formulations (F1–F9) were sealed and stored at 25°C and 4°C for 3 months to examine their stability. The aliquots were sampled for examination once a month. No drug precipitation or phase separation was observed from the formulations F1–F7 and F9 after 3 months of storing at 25°C, while F8 showed phase separation after 2 months of storing. The proportion of the oil phase in F8 was shown to be higher than the other formulations, and our further experiment indicated that phase separation occurred when the weight ratio of oil in the formulation was higher than 0.3.

All of the formulations were present as a solid state, as the samples were stored at 4°C. Upon being thawed and placed at room temperature for 1 h, the formulations F1–F3, F7, and F9 did not show any phase separation or drug precipitation, whereas significant drug precipitation at 1 month of storage was observed from F6, and slight drug precipitation was seen at 3 months of storage from F4 and F5. These findings thus indicated that the drug solubility in F4–F6 was saturated and drug precipitation would happen once the compounds were digested by the lipase in the gastrointestinal tract, therefore compromising the absorption.

The viscosity of F7 and other formulations was approximately 264 and 350 cP; thus, F7 had a better liquidity and was more convenient for administration and further capsule filling.

Based on the above results, the formulation F7 possessed the optimal emulsifying properties among all examined formulations. The results show that F7 is capable of pharmaceutical preparation of the drug. Therefore, the formulation was selected as the optimized formulation for further studies.

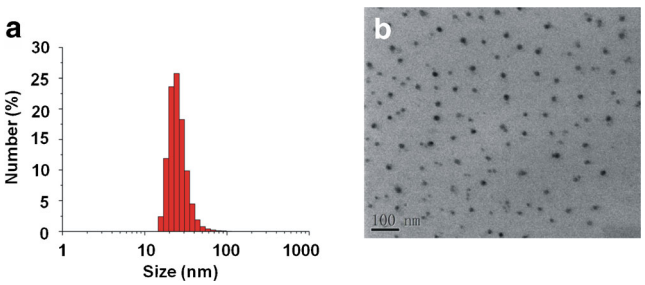

Fig. 3. Droplet size distribution (**a**) and (**b**) TEM image of droplet SMEDDS

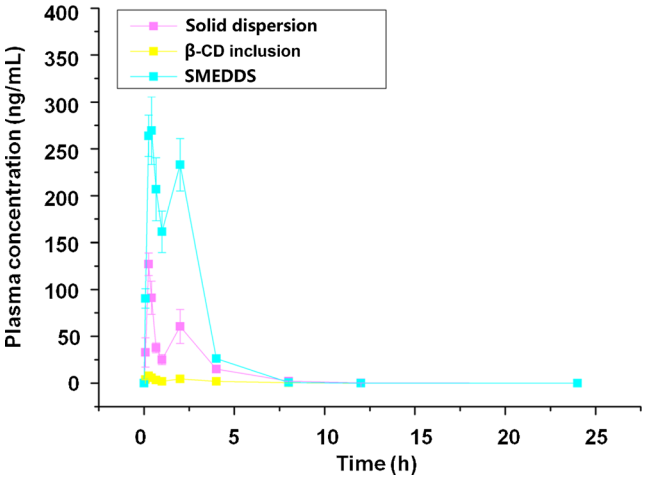

Fig. 4. Plasma drug concentration *versus* time after administration of AJS formulations (solid dispersion, β-CD inclusion, and SMEDDS)

Droplet size and Morphology

The average microemulsion droplet size and polydispersity index (PDI) are shown in Table IV. The average particle size of optimized formulation F7 was 26.08±1.68 nm with PDI of 0.264±0.01. These findings thus indicated that the formulation formed a microemulsion after dilution and the droplet size within the formulation was uniform (Fig. 3a). The TEM image of F7 showed that the droplets were a spherical shape with an average size in diameter of approximately 25 nm (Fig. 3b), which comprise the result of size measurement.

Bioavailability Study in Rats

The plasma concentration of AJS *versus* the time profiles in rats administered with the SMEDDS formulation (F7), solid dispersion, and β-CD inclusion are shown in Fig. 4. The pharmacokinetic parameters are presented in Table V. The oral bioavailability of AJS from SMEDDS, β-CD inclusion, and solid dispersion formulations were approximately 42,636.95±4469.26, 1188.00±157.03, and 12,497.86 ±2876.61 ng h/mL, respectively. The bioavailability of SMED DS was 35.9- and 3.4-fold as great as that of the β-CD inclusion and solid dispersion formulations. In other words, the oral bioavailability of the drug in SMEDDS was increased by 35.9- and 3.4-fold compared with the other two formulations. Moreover, significant increase in C_{max} was observed from the SMEDDS compared with the two controls. The bioavailability of solid dispersion was 10.52-fold as great as that of the β-CD inclusion. This result might be due to the enhanced intestinal permeability and an inhibition effect on P-gp activity by SDS (29, 30).

DISCUSSION

The higher oral bioavailability in SMEDDS was ascribed to larger surface area obtained from oral administration of the SMEDDS formulation, high concentration of surfactant contained in SMEDDS, and the promotion of lymphatic transport through transcellular pathway (11, 27, 31). The microemulsion droplets formed by the movements of the gastrointestinal tract after oral administration would closely contact with the apical membrane and then transfer across the intestinal gut wall (32). This effect could be further promoted by the high content of surfactant within SMEDDS that was able to disturb the membrane and subsequently open the tight junctions of the intestinal epithelium and increase the permeability of the intestinal barrier (33). Especially, some surfactants such as Labrasol involved in our present SMEDDS helped to open the tight junctions via an interaction with F-actin and actin-anchoring protein (ZO-1) (34, 35).

Intestinal lymphatic transport obtained across the systemic circulation without passing through the liver was an important absorptive pathway after oral administration of lipid formulations (36). The transport was more profound for the SMEDDS formulations, which was evident in that using the SMEDDS, the lymphatic pathway contributed more than 30% and 60% to the oral bioavailability for the candesartan and cyclosporine A, respectively (37). Further experiments should be performed to examine what the lymphatic transport contributed to the increased oral bioavailability.

Interestingly, a double-absorption curve of the two peak concentrations were similar to what was observed from the SMEDDS formulation and solid dispersion, indicating the hepatoenteral circulation of the drug. The second peak concentration might be related with the intestinal lymphatic transport because a drug with high lipophilicity has been reported to be considered as a substrate for lymphatic transport (38). This result thus further indicated the presence of intestinal lymphatic transport for the drug.

CONCLUSIONS

The SMEDDS formulation for AJS, a novel medicative compound against depression that is one of the BCS class II drugs, was prepared successfully, and its microemulsion

Table V. Pharmacokinetic Parameters of AJS in the Formulations of Solid Dispersion, β-CD Inclusion, and SMEDDS (n=6)

Parameters	Solid dispersion	β-CD inclusion	SMEDDS
$T_{1/2}$ (min)	76.5±7.35	134.00±4.24	58.90±1.13
C_{max} (ng/mL)	127±12.00	7.71±2.03	274.05±29.93
T_{max} (h)	0.27±0.03	0.25±0.01	0.36±0.08
AUC_{0-t} (ng h/mL)	12,497.86±2876.61	1188.00±157.03	42,636.9 5±4469.26
MRT_{0-t} (min)	130.50±0.70	195.00±1.41	105.20±11.03
CL (mL/min)	421.00±106.22	4425.00±746.61	124.90±14.41

Abbreviations: AUC_{0-t} area under the plasma concentration-time curve up to the last time point, C_{max} maximum plasma concentration, T_{max} time of maximum concentration, MRT mean retention time, $T_{1/2,}$ elimination half-life, CL clearance

droplets were less than 30 nm with a narrow size distribution. By using the formulation, the AJS bioavailability was increased by 35.9- and 3.4-fold compared with the β-CD inclusion and solid dispersion formulations. In conclusion, the present SMEDDS improved the oral bioavailability of AJS dramatically and was a promising strategy for the drug's oral delivery.

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