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Short communication

Development of a self-microemulsifying drug delivery system of domperidone: *In vitro* and *in vivo* characterization

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The main objective of this work was to prepare a self-micro emulsifying drug delivery system (SMEDDS) for enhancement of oral bioavailability of domperidone, a poorly water soluble drug. The solubility of the drug was determined in various vehicles. A pseudo ternary phase diagram was constructed to identify the self-micro emulsification region. The *in vitro* self-micro emulsification properties and droplet size analysis of SMEDDS were studied following their addition to water under mild agitation. Further, the resultant formulations were investigated for clarity, phase separation, globule size, effect of pH and dilutions (1:100, 1:500, 1:1000) and freeze-thaw stability. The optimized formulation, SMEDDS-B used for *in vitro* dissolution and bioavailability assessment, contained oil (Labrafac CC, 25 %, *m/m*), surfactant (Tween 80, 55 %, *m/m*), and co-surfactant (Transcutol®, 20 %, *m/m*). The preliminary oral bioavailability of domperidone from SMEDDS was 1.92-fold higher compared to that of domperidone suspension in rats. The $AUC_{0\text{-}24}$ and c_{max} values were 3.38 ± 0.81 μg h mL^{-1} and 0.44 ± 0.03 μg mL^{-1} for SMEDDS-B formulation in comparison with 1.74 ± 0.18 μg h mL^{-1} and 0.24 ± 0.02 μg mL^{-1} for domperidone suspension, suggesting a significant increase ($p < 0.05$) in oral bioavailability of domperidone from SMEDDSS.

Keywords: domperidone, SMEDDS, lipophilic drug delivery, particle size, enhanced oral bioavailability

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Domperidone, a dopamine D2 receptor antagonist, is used as a prokinetic and antiemetic agent for the treatment of gastroparesis, nausea and vomiting (1). It is a poor water soluble drug and is rapidly absorbed from the gastrointestinal (GI) tract. Its oral bioavailability was reported in a range of 13–17 % (2). Poor aqueous solubility and extensive first pass metabolism are the reasons for its low oral bioavailability. The approaches used to improve oral bioavailability were: incorporation of the active lipophilic component

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into inert lipid vehicles such as oils, surfactant dispersions, liposomes, emulsions and self-emulsifying formulations (3–5). Among these lipidic approaches, the self-emulsifying drug delivery system (SEDDS) was used for lipophilic drugs with poor aqueous solubility and low bioavailability after oral administration (6).

Self-emulsifying formulations comprise isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvent(s), which spontaneously emulsify when exposed to the GIT fluids to form oil-in-water emulsions or microemulsions (6–10). Self-emulsifying formulations also provide the advantage of increased drug loading capacity compared to lipid solutions, since the solubility of poorly water-soluble drugs with intermediate partition coefficients (log *P* 2–4) is typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents (11). Rapid emulsification of these systems under mild agitation and in the presence of aqueous media such as GI fluids also generates a high surface area of interaction between the formulation and the GI fluids and is thought to offer an improvement in the rate and extent of absorption and result in more reproducible blood concentration time profiles.

The main aim of this study was to develop a domperidone SMEDDS by varying the concentration of oils, surfactants, co-surfactant and optimization of the formulation by ternary phase diagram. The SMEDDS were prepared and characterized for self-microemulsification time, droplet size, and stability after dilution. Further, the optimized formulation was evaluated for oral bioavailability in male Wistar rats in comparison with domperidone suspension.

EXPERIMENTAL

Materials

Domperidone was a gift sample from Zydus Cadilla, India. Labrafac® CC, Labrafac Lipophile WL-1349, Lauroglycol® 90, Labrasol® and Transcutol® were kindly supplied by Gattefosse, USA. Captex-200, Capmul MCM were obtained from ABITEC Corporations, USA. Cremophore EL was obtained from BASF, India. Tween 80 was purchased from Merck (India). All other chemicals and solvents used were of analytical grade.

Methods

Solubility studies. – The solubility of domperidone in different oils, surfactant and cosurfactant combinations were determined. In brief, one mL of each vehicle was added to each capped vial containing an excess of domperidone (0.05 g) (12, 13). The mixture was heated for 2 min at 40 °C in a water bath and mixed using a vortex mixer. Then the mixtures were shaken with a shaker at 25 °C for 24 h. After reaching equilibrium, each vial was centrifuged at 4000 rpm for 10 min and excess insoluble domperidone was separated by filtration using a membrane filter (0.45 µm, Whatman, USA). The solubility of domperidone was determined by HPLC analysis (14).

The HPLC analysis system consisted of the mobile phase acetonitrile/doubly distilled water/triethylamine (30:70:0.25, pH 2.5 adjusted with orthophosphoric acid) and 20-µL aliquot was injected into the HPLC column Lichrospher® 100, RP-18e (5 µm), 4.6 mm × 250 mm

(Merck, Germany) in Shimadzu LC 20AD (Japan) solvent delivery pump and UV-Visible Detector. The eluate was monitored at λ_{max} 285 nm and the flow rate was 1 mL min^{-1}.

HPLC. – Mobile phase was used to get standard solutions for calibration: 0.05, 0.1, 0.3, 0.5, 1.0, 5.0, and 10.0 μg mL^{-1}. An aliquot of twenty μL of each solution was injected onto HPLC column, peak area and retention time were noted and a standard graph was plotted.

UV-Visible spectrophotometry. – Domperidone solutions of 100 μg mL^{-1} were prepared in 0.1 mol L^{-1} HCl, pH 1.2, and phosphate buffer pH 6.8. From these solutions, dilutions were made to obtain 5, 10, 15, 20, 25, 30, and 35 μg mL^{-1}. Absorbance of domperidone was measured with a UV–Visible Single Beam Spectrophotometer, Elico Ltd, India, at λ_{max} 283 nm.

Estimation of drug content in domperidone suspension. – About 40 mg of domperidone was added to 5 mL of 2 % (*m*/*V*) sodium carboxymethyl cellulose mucilage and the final volume was made up to 10 mL to produce 4 mg mL^{-1}. From this, serial dilutions were made. Drug content was estimated by HPLC.

Preparation of SMEDDS. – A series of self-micro emulsifying systems were prepared in each of the four formulations with varying concentrations of Labrafac CC (20–35 % *m*/*m*), Tween 80 (50–55 % *m*/*m*), and Transcutol (15–25 %, *m*/*m*) as oil, surfactant and co-surfactant. The SMEDDS were coded A, B, C and D (Table II). Domperidone was dissolved in a glass test tube containing Transcutol at 60 °C in a water bath to facilitate solubilization. Oil and surfactant were added and the final mixture was mixed by vortexing until a clear solution was obtained (12, 13). The mixture was stored at room temperature until used.

Estimation of drug content in SMEDDS. – Initially 1.64 g of SMEDDS formulation containing 40 mg of domperidone was diluted to 10 mL with doubly distilled water. From this, serial dilutions were made. Drug content was estimated by HPLC.

Visual observations and construction of the phase diagram. – A series of formulations were prepared with varying concentrations of oil (20–40 % *m*/*m*), surfactant (20–60 % *m*/*m*), and co-surfactant (10–60 % *m*/*m*). Oil (Labrafac CC), surfactant (Tween 80 or Labrasol) and co-surfactant (Transcutol) were added to the glass test tube and were mixed by vortexing until a clear solution was obtained (15, 16). The mixture was stored at room temperature until used.

A visual test to assess that self-microemulsification was reported (4) and it was adopted in this study after modification (15). Formulation (50 μL) was introduced into 50 mL of doubly distilled water in a glass beaker at 37 °C, and the contents were mixed gently with a magnetic stir bar at 100 rpm. The tendency to microemulsify spontaneously and microemulsion droplet formation as well as the final appearance of the microemulsion were monitored. The tendency to form a microemulsion was rated »good« when droplets were spread easily in water and formed a fine microemulsion that was clear or transparent in appearance, while it was rated »bad« when the corresponding performance was poor or there was less clear microemulsion formation, or emulsion formation. Phase diagrams were constructed identifying the good self-microemulsifying region using the Tri plot v1-4 software (Fig. 1) (13).

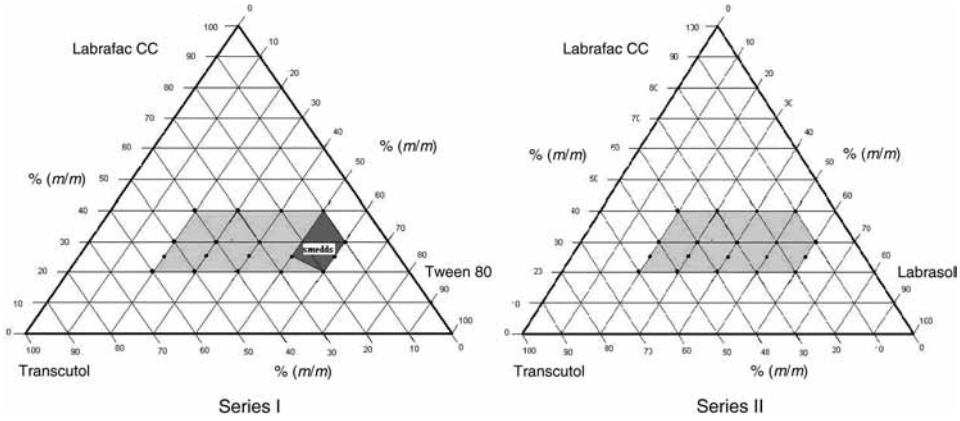

Fig. 1. Ternary phase diagram of series I consisting of Labrafac CC, Tween 80 and Transcutol and of series II consisting of Labrafac CC, Labrasol and Transcutol (dark shaded area indicates the SMEDDS formation and the light shaded area does not indicate SMEDDS formation.

In vitro *drug release studies.* – Drug release was studied by the dialysis bag method. Initially, the dialysis tubing was soaked in the specified medium for 1 h at 40 °C (12). The quantitative *in vitro* release test was performed in simulated gastric fluid (0.1 mol L^{-1} HCl, pH 1.2) and also in simulated intestinal fluid (pH 6.8). SMEDDS formulation (410 mg) containing 10 mg of domperidone was placed in the dialysis bag made up of the membrane having the molecular mass cut off 12,000–14,000 (Himedia, India) and then suspended in a 250-mL beaker containing 200 mL of the medium. The contents were mixed gently with a magnetic stir bar at 100 rpm and release patterns were studied at room temperature. At different time intervals up to 24 h, 1-mL samples of the medium were

Table I. Solubility of domperidone in different oils, surfactants and cosurfactant

Vehicle	Solubility (mg mL^{-1})
Captex-200P	2.64 ± 2.19
Lauroglycol 90	5.84 ± 3.13
Labrafac CC	31.49 ± 2.72
Labrafac Lipophile WL-1349	0.92 ± 0.88
Cremophore EL	2.29 ± 2.06
Labrasol	14.22 ± 4.42
Tween 80	12.16 ± 5.18
Capmul MCM	1.39 ± 1.22
Transcutol	288.08 ± 43.58

Mean ± SD, $n = 3$.

Table II. Formulation composition, droplet size and polydispersity index (PDI) and self-micro emulsification time of SMEDDS

Formulation	Labrafac CC (%, *m*/*m*)	Tween 80 (%, *m*/*m*)	Transcutol (%, *m*/*m*)	Droplet size (nm)	PDI	Self-micro emulsification time (s)
SMEDDS-A	20	55	25	46.28 ± 7.24	0.25 ± 0.18	20.96 ± 2.63
SMEDDS-B	25	55	20	25.47 ± 3.06	0.26 ± 0.06	25.55 ± 2.02
SMEDDS-C	30	50	20	74.74 ± 12.07	0.35 ± 0.13	30.46 ± 2.08
SMEDDS-D	35	50	15	87.86 ± 7.40	0.42 ± 0.15	32.27 ± 2.41

SMEDDS A, B, C and D belong to series I. PDI – polydispersity index

Table III. Effect of dilution with distilled water and pH media on the SMEDDS droplet size

Treatment	Droplet size (nm)			
	SMEDDS-A	SMEDDS-B	SMEDDS-C	SMEDDS-D
Water 1:10	39.70 ± 8.61	20.18 ± 7.45	112.10 ± 8.60	135.57 ± 6.88
1:100	46.60 ± 11.05	22.91 ± 5.28	86.64 ± 7.53	104.99 ± 10.62
1:500	42.15 ± 4.80	27.99 ± 3.07	73.49 ± 9.44	93.42 ± 5.80
1:1000	46.28 ± 7.24	25.47 ± 3.06	74.74 ± 12.07	87.86 ± 7.40
HCl, 0.1 mol L^{-1}, pH 1.2	49.17 ± 4.44	25.68 ± 4.28	73.41 ± 6.86	91.73 ± 6.59
Phosphate buffer, pH 6.8	49.10 ± 3.98	28.21 ± 3.92	82.18 ± 3.83	92.12 ± 3.30

Mean ± SD, $n = 3$.

collected and replaced with equal volumes of fresh medium. No enzymes were added to the medium. All the samples were analyzed at λ_{max} 283 nm after appropriate dilution.

Assessment of self-microemulsification time. – Evaluation of the self-microemulsifying properties of SMEDDS formulations was performed by visual assessment (13). The time taken for the microemulsion formation (until a transparent system was obtained) was noticed upon dropwise addition of 100 µL of SMEDDS into 100 mL of distilled water in a glass beaker at 37 °C, and the contents were stirred magnetically at 100 rpm (17).

Phase separation and stability study of microemulsion. – Each SMEDDS (50 µL) was added to a glass test tube containing 5 mL doubly distilled water at 37 °C (16). After 1 minute of vortex mixing, each mixture was stored for a period of 2 h and observed for phase separation and precipitation of the drug, if any. Further, observations were also made after 4, 6, 8, 12 and 24 h.

Droplet size analysis. – Formulation (50 µL) was introduced into 50 mL of doubly distilled water in a glass beaker at 37 °C, and the contents were mixed gently with a magnetic stir bar at 100 rpm (13, 15). The resultant microemulsion was then subjected to droplet

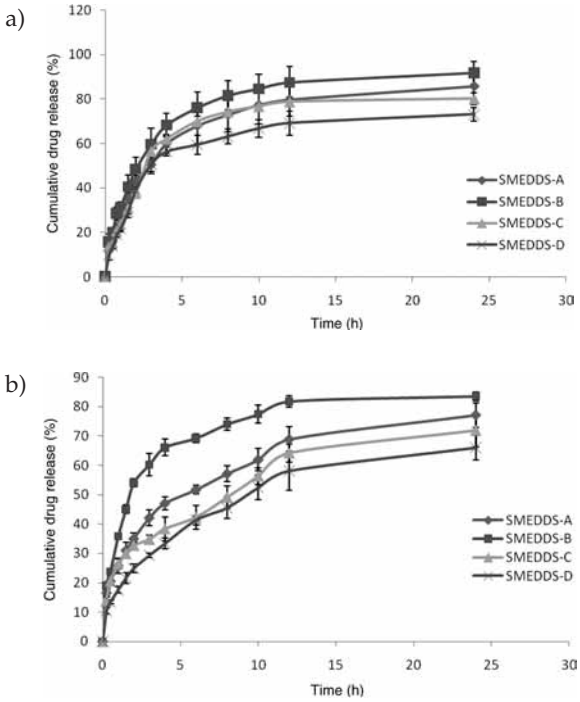

Fig. 2. a) Cumulative percent drug release from SMEDDS formulations at: a) pH 1.2, b) pH 6.8; Mean ± SD, n = 3.

size analysis. The size of the globule was measured at the 90° angle and at the temperature of 25 °C by a Malvern Zetasizer (Nano ZS90, Malvern, UK). The average of three readings was noted.

Effect of dilution and pH on droplet size. – To evaluate the effect of dilution on the droplet size of the resultant microemulsion, SMEDDS formulations were subjected to dilutions (1:10, 1:100, 1:500, and 1:1000) and size of globules was measured.

To evaluate the effect of pH, SMEDDS formulations were diluted (1:1000 dilution) with doubly distilled water, 0.1 mol L^{-1} HCl (pH 1.2) and pH 6.8 phosphate buffer. Then, the resultant microemulsions were subjected to droplet size analysis.

Physical stability of the SMEDDS during freeze and thawing and storage. – The formulations in Eppendorf tubes were subjected to 4 to 5 freeze-thaw cycles, which included freezing at –20 °C for 24 h followed by thawing at 40 °C for 24 h (13). After completion of 5 freeze-thaw cycles, the formulations were centrifuged at 3000 rpm for 5 min. The formulations were then observed for phase separation, and precipitation of the drug, if any. After completion of freeze thaw study, the same SMEDDS formulations were stored at room temperature for 6 months and observed for phase separation, and precipitation of the drug.

Pharmacokinetic study

Animals. – Healthy male Wistar rats (270–350 g) were used for the pharmacokinetic study. The animals were given a diet recommended by the National Institute of Nutrition, Hyderabad, India, and had free access to water. The studies were conducted with prior approval of institutional ethical committee, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India.

Study protocol. – The animals were divided into two groups (6 animals each) and were randomly administered each treatment. The following treatments were given at a single dose of 10 mg kg^{-1} body mass orally. The SMEDDS B formulation and suspension were administered after about 8 to 10 h of fasting to each group of animals. At appropriate predetermined time intervals after oral administration, blood samples were collected by puncturing the retro-orbital venous plexus. The blood was allowed to clot, centrifuged at 5000×*g* for 10 min and serum was collected. Serum samples were stored at –20 °C until analysis. Serum samples were extracted with dichloromethane and serum domperidone levels were estimated by HPLC. Drug content in serum samples was estimated by following the procedure that follows. To 100 µL of blank serum, 100 µL of domperidone standard solution in mobile phase was added, containing 0.2, 0.3, 0.5, 1.0 or 5.0 µg mL^{-1} of domperidone (14). One hundred fifty nanograms of propranolol in methanol (100 µL) as internal standard, 100 µL of 0.1 mol L^{-1} NaOH, and 3 mL of dichloromethane were added. The mixture was shaken for 10 min and centrifuged at 3000×*g* for 10 min, then the organic phase was transferred to another glass tube and evaporated to dryness using a vacuum evaporator. The dried residue was dissolved in 100 µL of mobile phase [acetonitrile/25 mmol L^{-1} phosphate buffer/trietylamine (35:65:0.25)] pH 2.5 was adjusted with orthophosphoric acid and twenty µL of aliquot was injected into the HPLC column. Peak area and retention time were noted for all samples and the standard graph was plotted. Pharmacokinetic parameters (PK) c_{max}, t_{max}, *AUC*, $t_{1/2}$ and mean residence time (*MRT*) were calculated using Kinetica software (18).

Statistical significance of observed differences in pharmacokinetic parameters of different groups was assessed by ANOVA. The pharmacokinetic data was expressed as mean ± SD, and two sample comparisons were performed using the unpaired *t*-test. $p < 0.05$ was considered to indicate statistically significant difference.

RESULTS AND DISCUSSION

Preparation of SMEDDS

Labrafac CC (oil), Labrasol and Tween 80 (surfactants) and Transcutol (co-surfactant) showed higher solubility for domperidone (Table I) when compared with the others agents tested. The self-micro emulsification region was mainly dependant on the concentration of Transcutol and Tween 80. SMEDDS were formed when the concentration of Tween 80 was 50–60 % (*m*/*m*), provided that the concentration of Transcutol was less or equal to 25 % (*m*/*m*), above which SMEDDS were not formed. From the phase diagrams (Fig. 1), it was observed that series I (consisting of Labrafac CC, Tween 80 and Transcutol) had a large self-

-micro emulsifying domain and series II (consisting of Labrafac CC, Labrasol and Transcutol) had no such domain. So series I, consisting of Labrafac CC (20–40 %, *m*/*m*), Tween 80 (50–60 %, m/*m*) and Transcutol (10–25 %, *m*/*m*) was selected for the further study.

It was observed that increasing the concentration of the co-surfactant, Transcutol, within the SMEDDS forming region increased the spontaneity of the self-microemulsification process. When a co-surfactant was added to the system, it further lowered the interfacial tension between the O/W interfaces and also influenced the interfacial film curvature, which thereby readily formed the micro-emulsions upon dilution.

In SMEDDS, increasing the surfactant Tween 80 concentration decreased the mean droplet size (Table II). The effect of co-surfactant concentration on the droplet size distribution in SMEDDS was similar to that of the surfactant Tween 80 when concentrations of transcutol changed from 10 to 25 % *m*/*m*. When a co-surfactant was added (in addition to surfactant) to the system, it lowered the interfacial tension, fluidized the hydrocarbon region of the interfacial film, and decreased the bending stress of the interface (19).

In vitro *drug release and stability*

The *in vitro* drug release studies were performed for SMEDDS A, B, C and D formulations. The cumulative percentage release (Figs. 2a and 2b) of domperidone from the SMEDDS-B formulation was significantly higher than that of other formulations, which might be due to the small droplet size.

In general, during the dilution studies with water no significant difference was found in the droplet size of A and B formulations, whereas, in case of formulations C and D it resulted in decreased droplet size (Table III). The different media pHs could not alter the droplet sizes significantly in any SMEDDS formulation (Table III). SMEDDS A and B resulted droplet size less than 50 nm. Diluted upto 1000 times either with water or media. Whereas in case of SMEDDS-C and -D the size was significantly higher. This difference in size was probably due to the relatively smaller oil portion and more surfactant and co-surfactant in case of SMEDDS A and B. SMEDDS-B showed almost 50 % lower size compared to SMEDDS-A. Thus, SMEDDS-B was found to be superior to the others.

The freeze-thaw studies of the SMEDDS formulation did not show any changes in the stability, *i.e.*, phase separation and precipitation of the drug even after storage for six months at room temperature. Stability of the resulting microemulsion after 1:100 dilution with distilled water was studied up to 24 h. During this period no phase separation and precipitation were noticed.

Bioavailability

Based on the self-emulsification properties, particle size, drug release data and stability of micro emulsion, formulation-B was selected for bioavailability studies. The plasma profiles of domperidone in rats following oral administration of the suspension and SMEDDS-B formulation were compared. The plasma concentration profiles of domperidone SMEDDS-B formulation showed higher drug levels at all time points than that of the suspension. As shown in Table IV, the AUC_{0-24} and c_{max} values were 3.37 ± 0.81 μg h mL^{-1} and 0.44 ± 0.03 μg mL^{-1} for SMEDDS-B formulation in comparison with 1.74 ± 0.18 μg h mL^{-1} and 0.24 ± 0.02 μg mL^{-1} for domperidone suspension, suggesting a significant increase

Table IV. The pharmacokinetic parameters of domperidone in rats

Parameter	SMEDDS-B	Domperidone suspension
c_{max} (μg mL^{-1})	0.44 ± 0.04[a]	0.24 ± 0.02
t_{max} (h)	0.58 ± 0.20	0.50 ± 0.00
AUC_{total}(μg h mL^{-1})	3.37 ± 0.81[a]	1.74 ± 0.18
$t_{1/2}$ (h)	6.68 ± 1.57	6.65 ± 0.61
MRT (h)	8.90 ± 1.72	8.04 ± 0.85

Mean ± SD, $n = 6$.
[a] Domperidone SMEDDS-B formulation significantly different from the suspension at $p<0.05$ (unpaired t-test).

($p < 0.05$) in oral bioavailability of the SMEDDS formulation**.** However, the t_{max}, $t_{1/2}$ and *MRT* values (in h) were: 0.58 ± 0.20, 6.68 ± 1.57, 8.9 ± 1.72 and 0.50 ± 0.00, 6.65 ± 0.61, 8.04 ± 0.85 for the SMEDDS-B and domperidone suspension respectively. The relative bioavailability of the SMEDDS-B formulation was 1.9-fold higher compared to the suspension. The reason for enhanced oral bioavailability of SMEDDS-B might be due to its lymphatic transport. It has been also reported that the long-chain oils promote lipoprotein synthesis and subsequent lymphatic absorption (20). The spontaneously formed emulsion, upon drug release in the GI tract, effectively presents the drug in a solubilised state, and the small droplet size would provide a large interfacial surface area for drug absorption (3). The main rate-limiting barrier for drug absorption/diffusion is the single layer of intestinal epithelial cells. High content of surfactants in SMEDDS could enhance the permeability by disturbing the cell membrane (21). The surfactant with the best enhancement ability requires both hydrophilic and lipophilic domains, such as Tween 80. Its structural characteristics impart both lipophilic and hydrophilic properties to the surfactant, allowing it to partition between lipid and protein domains. The surfactant was demonstrated to have a reversible effect on the opening of a tight junction and it might interact with the polar head groups of lipid bilayers, modifying hydrogen bonding and ionic forces between these groups. It may also insert itself between the lipophilic tails of the bilayers, resulting in disruption of the lipid-packing arrangement (22). Therefore, drug delivery using SMEDDS is a promising approach for the effective absorption and rapid onset of action after oral administration of this drug and for improvement of its oral bioavailability.

CONCLUSIONS

Domperidone, being a lipophilic drug, was formulated as SMEDDS based on the oil solubility studies and ternary phase diagrams. Optimal formulation, SMEDDS-B, was developed based on *in vitro* experiments, used in oral bioavailabilty studies in rats and compared with a suspension. The preliminary oral bioavailability study of SMEDDS-B showed improvement by a factor of 1.9 compared to the suspension in rats. Thus SMEDDS may be used for improvement of oral bioavailabilty of drugs with poor water solubility and low oral bioavailability.

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