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Formulation, *In Vitro* Characterization and Stability Studies of Self Microemulsifying Drug Delivery Systems of Domperidone

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ABSTRACT

Self-micro emulsifying drug delivery system (SMEDDS) is a novel and versatile approach for overcoming the formulation difficulties of drugs with poor aqueous solubility. The aim of the present study was to develop and evaluate the performance of SMEDDS for improving the oral delivery of domperidone. The solubility of drug was determined in various oils, surfactants and cosurfactants for selection of components of formulations. Phase behaviour of the selected components was investigated by construction of ternary phase diagrams. The SMEDDS were characterised for robustness to dilution, globule size, polydispersity index and zeta potential. The average globule size was in the range of 146-230 nm. The zeta potential of all the formulations was less then -30, indicating good stability. It was concluded that SMEDDS prepared with oleic acid, tween 80 and PEG 400 and surfactant co-surfactant ratio (3:1) is a promising approach to improve the solubility and dissolution rate of domperidone.

Keywords: Domperidone, self microemulsifying drug delivery systems, phase behaviour, oleic acid, tween 80, PEG 400.

INTRODUCTION

Low aqueous solubility of drugs is a serious concern as it leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Successful oral delivery of numerous drugs is hindered owing to their high hydrophobicity (Lipinski, 2002; Palmer, 2003). For successful oral delivery it is imperative to improve the solubility. Approaches for increasing the dissolution rate, and thereby oral absorption and bioavailability of poorly water-soluble drugs include solid dispersion, anti-solvent, complexation with cyclodextrin and lipid-based formulations (Weuts *et al.,* 2004; Ammar *et al.,* 2006; Muhrer *et al.,* 2006; Odeberg *et al.,* 2003).

In recent years, much attention has been focused on lipid-based formulations to improve the oral bioavailability of poorly water-soluble drug compounds.

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In fact, the most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles such as oils (Burcham *et al.,* 1997), surfactant dispersions (Serajuddin *et al.,* 1988), emulsions (Jumaa *et al.,* 2002), liposomes (Schwendener *et al.,* 1996), self-emulsifying formulations (Patil *et al.,* 2007), self-nanoemulsifying systems (Taha *et al.,* 2004; Sheikh *et al.,* 2007; Brusewitz *et al.,* 2007; Date and Nagarsenker, 2007), self-microemulsifying systems (Wu *et al.,* 2006). Most of them increase surface area of the drugs to improve solubilisation behaviour as well as permeation. From the viewpoint of oral drug delivery, lipids are studied as components of various oily liquids and dispersions that are designed to increase solubility and bioavailability of drugs belonging to the class II and IV of the biopharmaceutical drug classification system (Amidon *et al.,* 1995).

Numerous bioavailability studies carried out in animals and humans have suggested that hydrophobic drugs are better absorbed when administered in self-dispersing lipid formulations (Gershanik *et al.,* 2000; Hong *et al.,* 2006). There has been growing interest in the use of lipidic excipients in formulations and, in particular, in self-emulsifying lipid formulations (SELFs) because of their ability to solubilize poorly water-soluble

'lipophilic' drugs and overcome the problem of poor drug absorption.

Some of the potential advantages of these systems include better physico-chemical stability, enhanced oral bioavailability enabling reduction in dose, consistent temporal profiles of drug absorption, selective targeting of drug towards specific absorption window in GIT, ability to increase C_{max}, AUC, and reduced $t_{max,}$ linear AUC-dose relationship, reduced variability including effect of food, protection of sensitive drug substances, high drug payloads and flexibility of designing liquid or solid dosage forms.

Self microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of an oil, surfactant, cosurfactant (or solubilizer), and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions following dilution by aqueous phases which is provided by gentle agitation of the digestive motility of the stomach and intestine *in vivo* (Constantinides, 1995; Shah *et al*., 1994). The spontaneous formation of an emulsion upon drug release in the GI tract advantageously presents the drug in a dissolved form and the small droplet size provides a large interfacial surface area for drug absorption (Charman *et al*., 1992; Shah *et al*., 1994). For selecting a suitable self-emulsifying vehicle, it is important to assess; (a) the drug solubility in various components, (b) the area of self-emulsifying region in the phase diagram, and (c) droplet size distribution following self-emulsification (Kommuru *et al*., 2001).

SMEDDS are particularly useful when the poorly water-soluble compounds are to be pre-dissolved in a suitable solvent and filled into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem with this system is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). But alternatively, if the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets (Amidon *et al.*, 1995).

This bioavailability enhancing property has been associated with a number of *in vivo* properties of lipidic formulation including:

- The formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
- The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favor improved drug absorption.
- The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.

Certain lipidic excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver (Porter *et al.*, 2007).

MATERIALS AND METHODS

MATERIALS

Domperidone was kindly provided as a gift sample by S.K Kant Lab (Wapi, India). Oleic acid, Tween 80, PEG 400, propylene glycol, Span 80 and castor oil were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). All samples were used without any further purification.

METHODS

SOLUBILITY STUDIES

The drug used in this study for the preparation of SMEDDS, Domperidon, belongs to BCS Class II and therefore displays dissolution limited bioavailability (Borhade *et al.*, 2008; Patil *et al.*, 2007; Chen *et al.*, 2008). The solubility of domperidon was studied in various oils (Table.1).

SCREENING OF OILS

For the preparation of self emulsifying formulation the oils used were mainly vegetable oils and mineral oils. The oils were selected on the basis of propensity for self emulsification. The oil and surfactant (Tween 80) were mixed in a ration of 1:1. The mixture was subsequently checked for self emulsification by transferring 1 ml from each mixture to 5 ml of water and followed by agitation. The turbid solution obtained was observed under microscope for emulsion formation. The observations are shown in Table.2.

CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAMS

To obtain an optimum formula of the domperidone SMEDDS, which can form a microemulsion upon dilution with water, pseudo-ternary phase diagrams were constructed using the water titration method at ambient temperature. Based on preliminary experiments, oleic acid was used as the oil phase, tween 80 was used as the surfactant, and propylene glycol 400 was used as the cosurfactant. The surfactant/cosurfactant ratio used was 1/1, 2/1, 3/1, 4/1, 5/1. After domperidone was added to the mixture of oil, surfactant and cosurfactant, water was added drop by drop to this mixture. During the titration, the samples were agitated gently in order to reach equilibrium quickly. The phase boundary was determined by observing the changes in the sample appearance from turbid to transparent or from transparent to turbid. All the ratios in this study are reported as weight-to-weight ratios (W/W). The phase diagram was constructed by using Chemix software (Fig.1).

PREPARATION OF SELF MICROEMULSIFYING FORMULATION

Various formulations were prepared with a constant amount of domperidone (20mg) and varying ratios of oil, surfactant to cosurfactant. In brief, domperidone was dissolved in oleic acidin stoppered glass vials. Required amounts of Tween 80 and PEG 400 were added to the mixture and mixed well. These systems were warmed to 40°C using a water bath for 30 min with intermittent shaking to ensure complete mixing. The prepared

formulations were then stored until further use. The compositions of different SMEDDS formulations are Shown in Table.3.

ROBUSTNESS TO DILUTION

Robustness to dilution was studied by diluting it 100 and 1000 times with various dissolution media viz. 0.1N HCl and buffer pH 6.8. The diluted microemulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation. Robustness to dilution in 0.1N HCl and Phosphate buffer (pH 6.8) is shown in Table.4.

GLOBULE SIZE ANALYSIS

The globule size of the emulsions was determined by dynamic light scattering (DLS) by monitoring at 25°C at a scattering angle 173° (Zetasizer Nano-ZS, Malvern, UK), which measure size range between 6 nm to 0.6 µm. The nanometric size range of the particle was retained even after 100 times dilution with water which proves the compatibility of the system with excess water. Globule size of various formulations is shown in Table.5.

ZETA POTENTIAL

Zeta potential is used to identify the charge of the droplets. In conventional SMEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids (Gershanik *et al.*, 1996). Zeta potential determined by Zeta-meter was monitored at 25°C at a scattering angle 173° (Zetasizer Nano-ZS, Malvern, UK). The results are shown in Table.5.

DETERMINATION OF EMULSIFICATION TIME

Formulations were graded for self-emulsification time, according to the visual assessment criteria for self microemulsion formation listed in Table.6. The results of this visual assessment study are depicted in Table.7.

Table.1 Solubility profile of Domperidone in various oils and surfactants

S. No.	Oil/Surfactant	Solubility (mg/ml)
1	Oleic acid	27.24
2	Castor oil	9.10
3	Olive oil	18.20
4	Soya oil	16.30
5	Tween 80	12.61
6	Span 80	Insoluble
7	Propylene glycol	7.21
8	PEG 400	14.10

Table.2 Emulsification based screening of oils

Oils used	Emulsification
Oleic acid	Emulsifies
Castor oil	Emulsifies
Olive oil	Emulsifies
Soyabean oil	Emulsifies

STABILITY STUDY

The physical stability of the formulations was evaluated by visual inspection for physical changes such as phase separation and drug precipitation (Pang *et al*., 2007). The physical stability study was performed at 4˚C, 25˚C and 45˚C for 15 days. The results of stability study are presented in Tables.8-10.

DRUG LOADING EFFICIENCY

50 mg formulation was transferred to a 100 ml volumetric flask and the volume was made up with phosphate buffer (pH 6.8). The resultant solution was analysed spectroscopically following suitable dilution. The drug loading efficiency was determined by:

$$\text{Drug loading efficiency} = \frac{\text{amount of drug in known amount of formulation}}{\text{intial drug load}} \times 100$$

The results are recorded in Table.11.

***IN VITRO* DISSOLUTION PROFILE**

Dissolution profiles of the self-microemulsified formulations were determined using USP24 rotating paddle apparatus at 37±0.5˚C and a rotating speed of 100 rpm in 900 ml of 0.1N HCl and Phosphate buffer (pH 6.8). The self microemulsifying formulation was placed in a dialysis membrane bag held to the bottom of the vessel using copper sinkers. During the release studies, samples were withdrawn and subjected to spectrophotometric analysis. The sample volume was replaced each time with equal quantity of fresh medium. The results are presented graphicallyin Figure.2

Table.11 Drug content of various SMEDDS

Formulation	% Drug content
F-1	93.70
F-2	92.40
F-3	89.50
F-4	94.80
F-5	95.85

.

Table.3 Composition of various SMEDDS formulations of Domperidone

Formulation	Oil (Oleic acid) (mg)	Surfactant (Tween 80) (mg)	Cosurfactant (PEG 400) (mg)	Drug (Domperidone) (mg)
Formulation 1 S/CO-(1:1)	492	64	64	20
Formulation 2 S/CO-(2:1)	428	128	64	20
Formulation 3 S/CO-(3:1)	364	192	64	20
Formulation 4 S/CO-(4:1)	300	256	64	20
Formulation 5 S/CO-(5:1)	236	320	64	20

Table.4 Robustness to dilution of various SMEDDS

Formulation	Phase Separation		Drug Precipitation	
	0.1N HCl	Phosphate buffer (pH 6.8)	0.1N HCl	Phosphate buffer (pH 6.8)
F-1	-	-	--	--
F-2	-	-	--	--
F-3	-	-	--	--
F-4	-	-	--	--
F-5	-	-	--	--

(+ Phase separation, ++ Drug Precipitation, - No phase separation, -- No precipitation)

Table.5 Globule size, polydispersity index and zeta potential of various SMEDDS

Formulation	Average Globule size (nm)	Polydispersity Index	Zeta Potential (mV)
F-1	164.8	0.263	-40.9
F-2	162.6	0.272	-31.0
F-3	146.8	0.268	-58.2
F-4	175.8	0.356	-45.3
F-5	230.4	0.544	-42.0

Table.6 Visual assessment criteria for self microemulsification

Grade	Time required for microemulsion formation	Appearance
A	within 1 min.	Clear or slightly bluish
B	within 1 min	bluish white
C	within 2 min	bluish white, similar in appearance to milk
D	Longer than 2 min	Dull, ash emulsion, slightly oily appearance
E	Longer than 2 min	Poor or minimal emulsification ,large oil droplets present on the surface

Table.7 Visual assessment of various SMEDDS

Formulation	Grade based on visual observation	Time of emulsification in (Min: Sec)
F-1	A	00:25
F-2	A	00:35
F-3	A	00:40
F-4	B	00:55
F-5	B	00:60

Table.8 Stability profile of various SMEDDS following storage at 4˚C

Formulation	Storage stability at 4˚C after (days)		
	5	10	15
F-1	-, --		-,--
F-2	-,--		-,--
F-3	-,--		-,--
F-4	-,--		-,--
F-5	-,--		-,--

(+ Phase separation, + + Drug precipitation, - No phase separation, -- No precipitation)

Table.9 Stability profile of various SMEDDS following storage at 25˚C

Formulation	Storage stability at 25˚C after (days)		
	5	10	15
F-1	-, --		-,--
F-2	-,--		-,--
F-3	-,--		-,--
F-4	-,--		-,--
F-5	-,--		-,--

(+ Phase separation, + + Drug precipitation, - No phase separation, -- No precipitation)

Table.10 Stability profile of various SMEDDS following storage at 45˚C

Formulation	Storage stability at 45˚C after (days)		
	5	10	15
F-1	-, --		+,+
F-2	-,--		+,+
F-3	-,--		+,+
F-4	-,--		+,+
F-5	-,--		+,+

(+ Phase separation, + + Drug precipitation, - No phase separation, No precipitation)

RESULT AND DISCUSSION

Solubility studies indicated that domperidone does not display good solubility profile. It was found to be insoluble in water, soluble in many solvent such as acetic acid, 0.1N HCl, methanol, slightly soluble in acetone and dichloromethane and sparingly soluble in ethanol. Solubility studies of drug in oil indicated that it was more soluble in oleic acid, Tween 80, propylene glycol 400. Thus, these excipients were used for the preparation of SMEDDS. The screening studies based on self emulsification indicated that all the oils used were able to emulsify and could be used for preparation of self emulsifying formulation.

Pseudo-ternary phase diagrams were constructed using the water titration method at ambient temperature to determine the area of microemulsion existence. Based on preliminary experiments, ternary phase diagrams of F-3 illustrated microemulsion region and therefore, surfactant/co-surfactant ratio (3/1) was selected as optimum for SMEDDS.

Robustness to dilution was studied by diluting the system 100 and 1000 times with various dissolution media viz. 0.1N HCl and phosphate buffer (pH 6.8). The diluted microemulsions were stored for 12h and it does not indicate any signs of phase separation or drug precipitation.

Fig.1 Ternary Phase Diagram of Oleic Acid–Tween 80+PEG 400–Water System

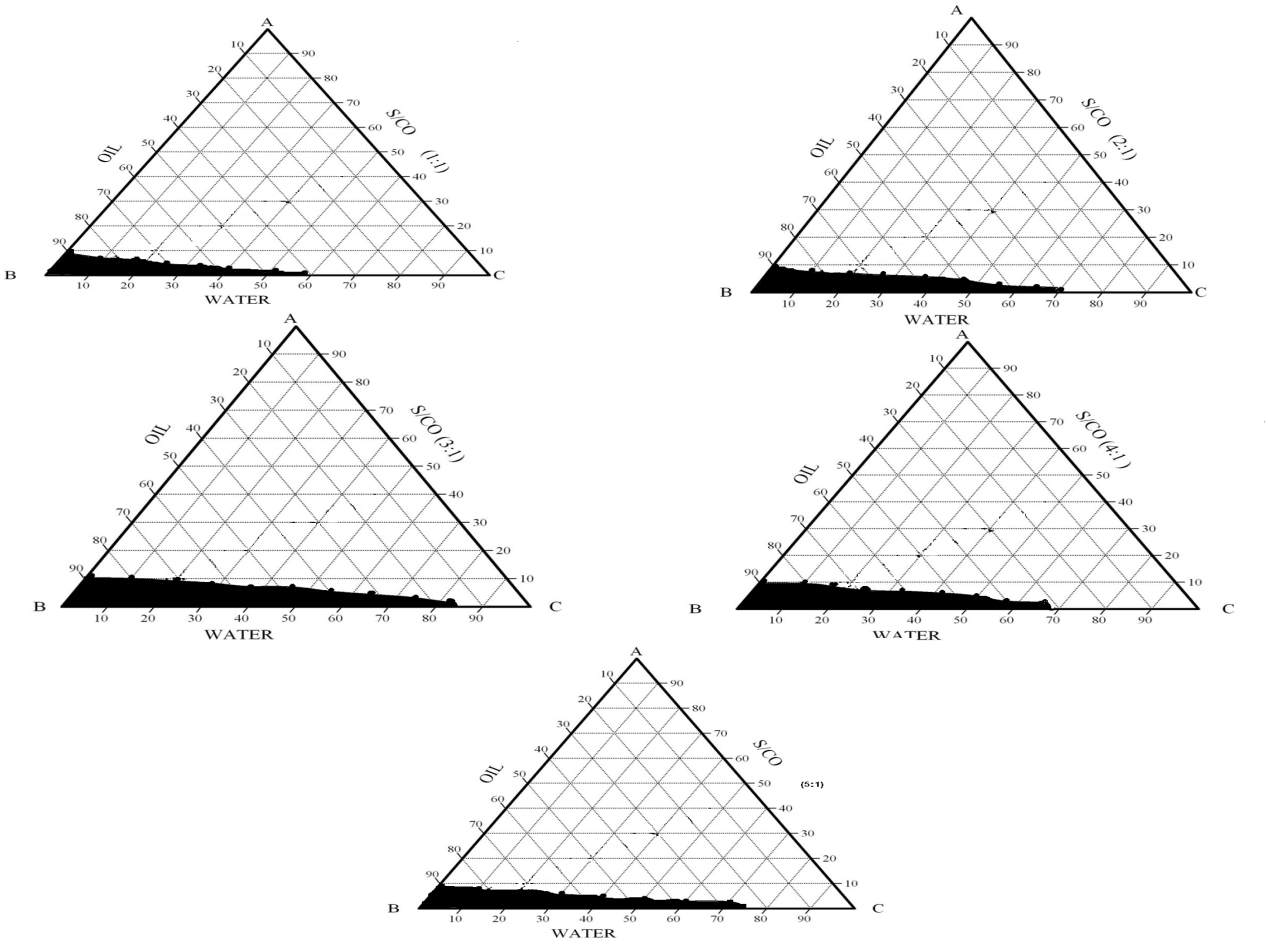
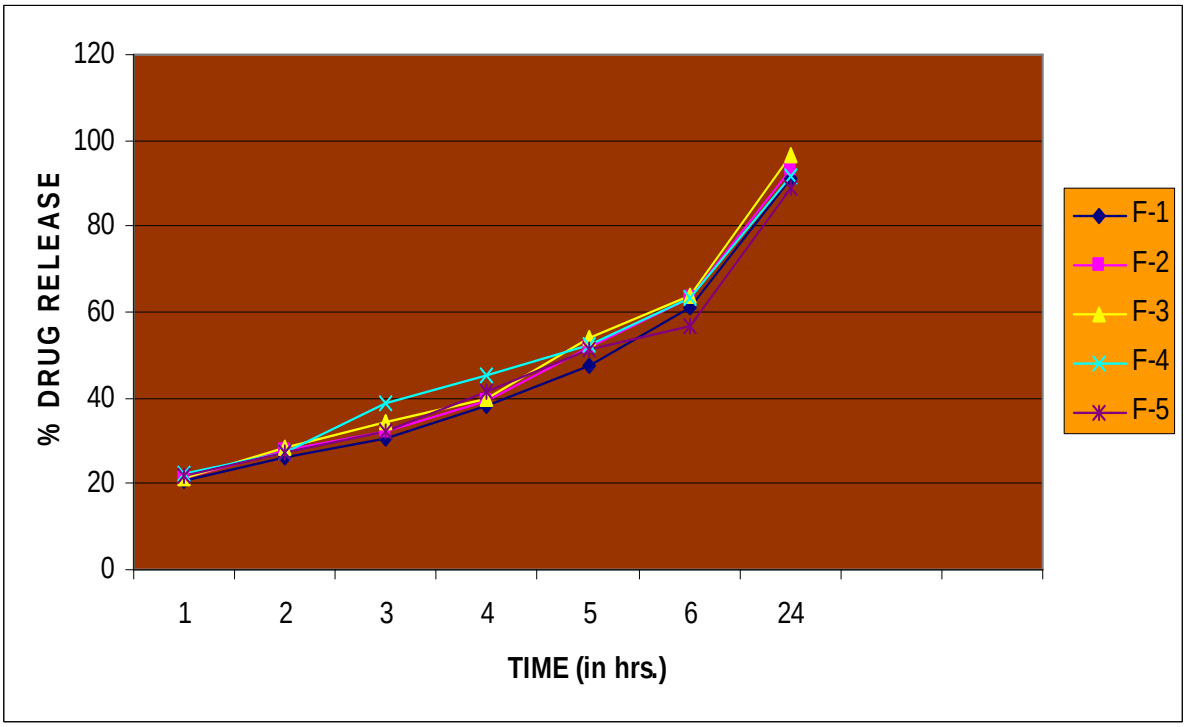


Fig.2 Cumulative % drug release from various Self microemulsifying formulations



The globule size and zeta potential were observed with the help of Malvern Zetasizer. The average globule size was taken into consideration. The average diameters of vesicles were in nano size range. From the observations it was clear that the size range was dependent on concentration of surfactant/co-surfactant ratio.

The zeta potential of the liquid systems is of considerable importance from the stability point of view. The systems having the zeta potentials in the range of +30 to -30 show poor stability profiles. In this study the zeta potentials of all the formulations were less then –30, indicating good stability.

Droplet size distribution is one of the most important characteristics of emulsion for stability evaluation and *in vivo* absorbtion. Poly dispersity index below 0.3 indicates good uniformity in the droplet size distribution after dilution with water. In this study the poly dispersity index below 0.3 was obtained for all formulations except F-4 and F-5.

The assessment of time of emulsification showed that with the increase in surfactant concentration the time of emulsification increases. Formulation F-4 and F-5 was bluish white and grade B but all other formulation were grade A and slightly bluish white.

The stability studied shows that all formulations were stable at 4^{o}C and 25^{o}C, but at 45^{o}C, formulations were unstable after 5 days as indicated by physical changes in terms of phase separation and drug precipitation.

Drug content of the formulation increased with increase of droplet size. Drug content of the F-3 formulation was very low as compared to other formulations and this can be attributed to their minimum droplet size.

As the droplet size decreased, surface area increased allowing more dissolution and drug release and accordingly, with formulation F-3 drug release was found to be highest.

CONCLUSION

The SMEDDS formulations of domperidon were successfully prepared by simple mixing method. F-3 formulation showed promising results. On the basis of emulsification study, as the concentration of surfactant and co-surfactant was optimum in F-3 formulation and time of emulsification was within 1 min. However, the drug content of the F-3 formulation was very low as compared to other formulations. As the droplet size decreases, surface area increases allowing greater dissolution and drug release formulation F-3 showed higher drug release. It could be concluded that SMEDDS formed from oleic acid, tween 80 and PEG 400 and surfactant co-surfactant ratio (3:1) is a promising approach to improve the solubility, dissolution rate and bioavailability of domperidone.

It is apparent that SMEDDS offers a good opportunity for the non-invasive delivery of drugs with poor water solubility, short half life, and poor bioavailability. In addition, drug release is not affected by lipid digestion process. Thus, it can be a logical conclusion that SMEDDS formulations possess promising future in effective delivery of poorly water soluble drug.

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