

# Development and evaluation of a self-emulsifying drug delivery system of amphotericin B

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Amphotericin B is a polyene antifungal antibiotic belonging to Class IV of Biopharmaceutics Classification System which is not absorbed from the gastrointestinal tract after oral administration. The aim of this research work was to develop a self-emulsifying drug delivery system (SEDDS) of amphotericin B and to evaluate the dissolution and permeability of amphotericin B from the formulation. The solubility of amphotericin B in various oils, surfactants and cosurfactants was determined. Various SEDDS formulations were prepared with varying amounts of oil, surfactant and co-surfactant. Evaluation parameters for formulation optimization were drug content, self-emulsification, droplet size analysis, and precipitation studies. *In vitro* dissolution was studied in comparison to the pure drug. Permeability was studied using non-everted intestinal sac method. The optimized formulation consisted of glycerol mono-oleate (10%, w/w), tween 80 (36%, w/w), polyethylene glycol 400 (27%, w/w), and propylene glycol (27%, w/w) with a drug content of about 8 mg per ml. The self-emulsifying formulation showed 100% dissolution within 30 minutes whereas the pure drug exhibited a very poor rate of dissolution. *In vitro* intestinal permeability was studied by noneverted intestinal sac method using rat intestine. The self-emulsifying formulation showed 100% drug permeation within 30 minutes compared to negligible permeation from the drug suspension. The study demonstrates that SEDDS approach may be useful for enhancement of dissolution and intestinal permeation of amphotericin B belonging to class IV of Biopharmaceutic Classification System.

**Key words:** Amphotericin B, dissolution, intestinal permeability, self-emulsifying drug delivery system

## INTRODUCTION

Lipid-based formulation approaches, specifically the self-emulsifying drug delivery system (SEDDS), are well accepted as potential alternative strategy for delivery of poorly water soluble drugs, which are associated with low oral bioavailability owing to poor aqueous solubility.<sup>[1-7]</sup> SEDDS formulations are commonly isotropic mixtures of oil, a surfactant, a cosurfactant, and a drug. This system forms fine oil-in-water (o/w) emulsion under gentle agitation following dilution by aqueous phase. The motility of the gastrointestinal tract provides the agitation required for self-emulsification *in vivo*.<sup>[5]</sup> This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption.<sup>[8]</sup> Apart from solubilization, the presence

of lipid and surfactants in the formulation further helps improve bioavailability by affecting membrane permeability and *p*-glycoprotein mediated efflux.<sup>[7]</sup>

Amphotericin B (AmB) is a polyene antifungal antibiotic, which still remains the single most reliable drug in the treatment of life threatening systemic fungal infections.<sup>[9]</sup> The incidences of systemic fungal infections are rapidly rising with the widespread proliferation of HIV-AIDS all over the world. Systemic fungal infections are also cause for grave concern among immunocompromised patients such as cancer, diabetes and organ transplant recipients. AmB is also the most effective treatment available for resistant cases of kala-azar and mucocutaneous leishmaniasis.<sup>[10]</sup> AmB is conventionally used parenterally as a bile salt complex. Intravenous administration of conventional AmB is

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associated with severe infusion-related side effects. Newer lipid formulations including AmB lipid complex and liposomal AmB are relatively safe, but their high cost limits their use in countries like India. Amphotericin B has low water solubility (2--4 mcg/ml),<sup>[11]</sup> poor membrane permeability and is unstable at gastric pH, posing problems in the development of a suitable oral formulation. Several techniques have been tried by researchers for oral delivery of the drug. Solid dispersion,<sup>[12]</sup> mixed micelle,<sup>[13]</sup> nanosuspension,<sup>[14]</sup> cyclodextrin complex,<sup>[11]</sup> oral cochleate,<sup>[15,16]</sup> and lipid based delivery systems have been developed<sup>[17,18]</sup> and antifungal activities following oral administration have been studied.<sup>[18]</sup> The role of lymphatic transport and p-glycoprotein mediated efflux in intestinal absorption of AmB dispersed in Peceol (glycerol monooleate) has been investigated.<sup>[17]</sup> The plasma and tissue distribution of AmB resulting from oral administration of the lipid based delivery systems have also been reported.<sup>[19,20]</sup>

The objectives of the study were to develop a SEDDS formulation containing amphotericin B and evaluate the potential of the formulation in increasing the dissolution and intestinal permeability of the drug.

## MATERIALS AND METHODS

### Materials

Amphotericin B was obtained as a gift sample from Synbiotics Ltd (Vadodara, India). Labrafac CC and Peceol (glycerol mono oleate) was obtained as a gift sample from Colorcon Asia (Goa, India). Labrasol was donated by Gattefosse (Mumbai, India). Capmul MCM (medium chain mono and di glycerides), Captex 100, Capmul GMO-50 (glycerol mono oleate), were received as gift samples from Abitech Corporations (Columbus, USA). Propylene glycol, Tween 80, polyethyleneglycol 400 (PEG 400), dimethylacetamide, and oleic acid were purchased from Qualikems Fine chemicals Pvt. Ltd., New Delhi, India. Cremophor EL was purchased from Sigma Aldrich Inc, Germany. Olive oil, corn oil, cottonseed oil, and castor oil were purchased from Across Organics, Belgium. All chemicals were used as received. Deionized water was prepared by a DQ 3 water purification system from Millipore (Molsheim, France). Methanol and acetonitrile used in the present study was of high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical reagent grade.

Empty HPMC capsule shells were generously donated by Capsugel Ltd (Mumbai).

### Methods

#### Solubility studies

The solubility of AmB was determined by adding excess amount of AmB to various oils, surfactants, and co-surfactants in screw capped glass vials. After vortex mixing, the mixtures were kept at ambient temperatures for 7 days for equilibration. The equilibrated samples were centrifuged at 4000 rpm for 10 minutes to remove the undissolved AmB. The supernatants were taken and diluted with methanol. The amount of AmB in the methanolic solutions thus obtained was quantified by UV spectroscopy at 382 nm using a double beam UV-visible spectrophotometer (Shimadzu, UV-1700).

#### Preparation of SEDDS formulations

A series of SEDDS formulations were prepared using glyceryl mono oleate or oleic acid as oil phase, tween 80 as surfactant and a 1:1 blend of propylene glycol and PEG 400 as cosurfactant [Table 1]. AmB was accurately weighed in screw capped glass vials and dispersed in the co-surfactant blend by stirring using a magnetic stirrer. The surfactant and the oil was then added and the mixture was stirred for 15--20 minutes. The mixture was then sonicated using an ultrasonicator probe (Bendell, Germany) for 2 minutes at 60% power. Undissolved AmB was separated by centrifugation at 2500 rpm for 10 minutes. The supernatants were collected, filled in screw capped glass vials and stored in 4°C until further use.

#### Drug content of SEDDS formulations

Drug content of the prepared formulations were quantified by UV spectrophotometry after appropriately diluting the formulations with methanol. The effect of processing on the stability of AmB was assessed by UV spectral shift analysis by scanning in the wavelength range of 250-500 nm using a double beam UV-visible spectrophotometer (Shimadzu, UV-1700).

#### Self-emulsification and precipitation assessment

Evaluation of the self-emulsifying properties of SEDDS formulations was performed by visual assessment as previously reported.<sup>[7]</sup> In brief, different compositions were categorized on speed of emulsification, clarity, and apparent stability of

**Table 1: Composition of SEDDS formulations**

Formulation code	Components (mg)				Total (g)
	GMO*/Oleic acid	Tween 80	PG/PEG(1:1)**	AmB	
1	200	400	400	10	1.010
2	200	267	533	10	1.010
3	200	533	267	10	1.010
4	100	450	450	10	1.010
5	100	300	600	10	1.010
6	100	360	540	10	1.010
7	100	600	300	10	1.010

\*Glycerol mono oleate \*\*1:1 mixture of propylene glycol and PEG 400

the resultant emulsion. Visual assessment was performed by addition of 0.1 ml of SEDDS into 250 ml of distilled water. This was done in a glass beaker at 37°C, and the contents were gently stirred magnetically at about 50 rpm. The formulations were then categorized as 'good' when the droplets spread easily on the water without any further coalescence within one minute of addition and produced a clear emulsion with a bluish tinge. All other cases were categorized as bad. Phase diagram was constructed identifying the 'good' self-emulsifying regions as reported earlier.<sup>[7]</sup>

Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were categorized as stable when there was no precipitation at the end of 24 hours.

#### Emulsion droplet size analysis

One hundred microliters of SEDDS formulation was diluted to 100 ml with water in a volumetric flask and gently mixed by inversion. The resultant emulsion was then subjected to droplet size analysis using Malvern Zetasizer Nano ZS (Worcestershire, UK) with a particle size measurement range of 0.6 nm to 6 µm. All studies were repeated in triplicate, with good agreement being found between measurements.

#### In vitro dissolution studies

The quantitative *in vitro* release test was performed in 900 ml of phosphate buffer pH 6.8 using US Pharmacopeia XXXII dissolution apparatus 2 at 50 rpm. 1 g of the optimized SEDDS formulation was filled in HPMC capsules as well as hard gelatin capsules of size 00 and used for drug release studies. The procedure was repeated with plain AmB. During the release studies, a 5 ml sample of medium was taken out and subjected to drug analysis using HPLC after filtering through 0.22 µm membrane filter. The volume was replaced each time with 5 ml of fresh medium.

#### HPLC analysis of AmB

The concentration of AmB in the samples was determined by HPLC. The HPLC analysis system consisted of an Adept CE4100 Dual Piston Pump and Adept CE 4201 UV-Visible Variable Wavelength Detector (Cecil, U.K.). The chromatographic column was a Princeton SPHER ODS-5 (5 µm) 4.6 mm × 250 mm. The mobile phase used was a mixture of methanol:acetonitrile:0.0025M EDTA (50:35:20, v/v)<sup>[21]</sup> at a flow rate of 1.3 ml/min. Injection volume was 20 µl, detection was performed at 405 nm and retention time of AmB was 3 minutes 30 ± 7 seconds with a runtime of 5 minutes.

#### In vitro Intestinal Permeability Assessment

Intestinal permeability was studied by *ex vivo* non-inverted intestinal sac method.<sup>[22,23]</sup> The study protocol was approved by Institutional Animal Ethics Committee (IAEC) (992/a/06/CPCSEA, date of approval-13<sup>th</sup> August, 2010, document no.- RKGIT/CPCSEA/IAEC/Aug.13,2010/01). A male Wistar rat weighing about 250 g was sacrificed by cervical dislocation

after overnight fasting with free access to water. The abdomen was cut open and the intestine was surgically removed and flushed with ice cold saline. Equal lengths of 5 cm of the ileum were cut. One hundred microlitres of the SEDDS was dissolved in 100 ml pH 7.4 Tyrode's solution. The resultant emulsion (1 ml) was filled in the normal sac (mucosal side), and both ends of the sac were ligated tightly. The sac containing SEDDS solution was immersed in 40 ml of Tyrode's solution. The medium was pre-warmed at 37°C and pre-oxygenated with 5 % CO<sub>2</sub> / 95 % O<sub>2</sub> for 15 minutes. Under bubbling with a CO<sub>2</sub> / O<sub>2</sub> mixture, the transport of AmB from mucosal to serosal surfaces across the intestine was measured by sampling the serosal medium periodically for 120 minutes. The samples of 1 ml were collected at predetermined time intervals from the serosal medium and replenished with fresh buffer. The procedure was repeated for plain AmB by using AmB suspension in Tyrode's solution with a concentration of 0.08 mg/ml. The drug transported was measured using high performance liquid chromatography (HPLC) method as described above. All experiments were performed in triplicate.

## RESULTS

#### Solubility studies

The results of solubility studies are depicted in Figure 1. Based on the solubility result, the 1:1 mixture of propylene glycol and PEG 400 was selected as the co-surfactant, tween 80 was chosen as the surfactant and glycerol mono oleate and oleic acid both were chosen as oils.

#### Preparation and evaluation of SEDDS formulations

Self-emulsifying formulations using different ratio of oil, surfactant and cosurfactant were prepared by simple mixing followed by sonication. Translucent yellow homogeneous formulations without any visible particulates were generated. The formulations were optimized on the basis of drug content and self-emulsification.

#### Drug content

The drug content of the formulations was found to increase with decrease in oil content and increase in co-surfactant content. Formulations containing oleic acid had somewhat less drug content when compared to formulations containing glycerol mono oleate.

The relation between drug content and cosurfactant concentration is depicted in Figure. 2.

The UV spectra of the prepared formulations diluted with methanol exhibited the characteristic peaks of AmB at 405 nm, 382 nm, 364 nm, and 344 nm with peaks at 405 nm and 382 nm having the greatest amplitude, indicating presence of monomeric AmB in the formulations. When AmB becomes self-associated the peaks shift to 420 nm, 390 nm, 368 nm, and 333 nm with the peak at 333 nm having the greatest amplitude.<sup>[24]</sup>

### Self-emulsification and precipitation assessment

Results of self-emulsification studies indicated that formulations containing more than 40% oil had poor self-emulsifying properties. Increasing the cosurfactant concentration hastened the self-emulsification, whereas increasing the surfactant concentration led to an increase in the time required for efficient self-emulsification owing to gel like layer formation. The compositions corresponding to 'good' self-emulsification are identified in the phase diagram [Figure 3]. Formulations containing oleic acid required more time and agitation for self-emulsification as compared to formulations containing glycerol mono oleate and, therefore, were not categorized as 'good'.

Results of precipitation studies indicated that decreasing the oil concentration and increasing the co-surfactant concentration led to increased drug precipitation. Based on the above evaluations on drug content, self-emulsification and precipitation, the formulation containing 10% glycerol mono oleate, and a surfactant/co-surfactant (S/CoS) ratio of 2:3 was selected for further studies.

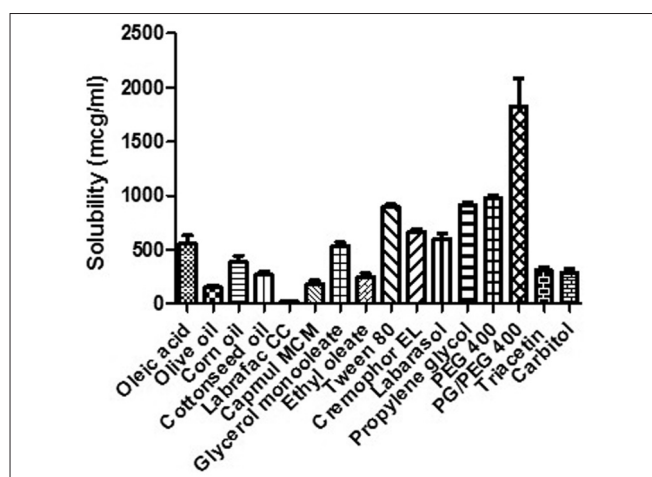


Figure 1: Solubility of Amphotericin B in different oil, surfactant, and cosurfactants ( $n = 3$ ; data are represented as mean  $\pm$  S.D)

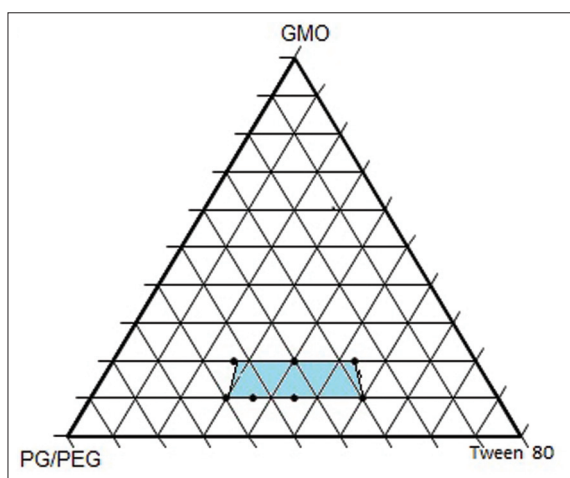


Figure 3: Ternary phase diagram identifying good self-emulsifying region (GMO stands for glycerol mono oleate)

### Emulsion droplet size analysis

Average droplet diameter of the selected formulation was found to be 349.6 nm with a PDI of 0.749. The distribution was bimodal with 65% population with a mean diameter of  $664.8 \pm 264.4$  nm and rest with a mean diameter of  $149.7 \pm 50.2$  nm.

### In vitro dissolution studies

The results of comparative dissolution of the optimized formulation filled in HPMC capsules and hard gelatin capsule are shown in Figure 4. The dissolution was found to be affected by the capsule type. Formulation filled in hard gelatin capsule released 100% AmB within 10 minutes whereas HPMC capsules showed a lag time of 20 minutes and 100% release was observed after 30 minutes.

### Intestinal permeability assessment

The pure drug was found to be nonpermeable through the intestinal mucosa even after 2 hours whereas 100% permeation occurred within 30 minutes with the SEDDS formulation.

## DISCUSSION

Amphotericin B belongs to class IV of Biopharmaceutic classification system (BCS). It is almost negligibly absorbed from the gastrointestinal tract after oral administration.

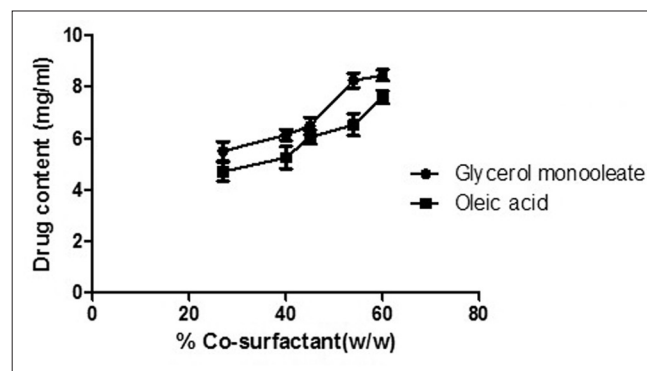


Figure 2: Effect of cosurfactant concentration on AmB content of different compositions ( $n = 3$ ; data are represented as mean  $\pm$  S.D)

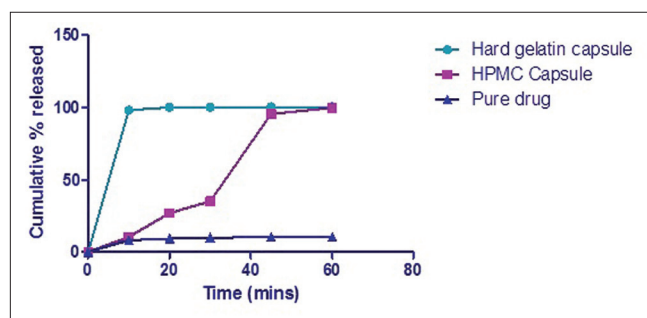


Figure 4: Dissolution of optimized SEDDS formulation in pH 6.8 phosphate buffer from hard gelatin capsule and HPMC capsule in comparison to pure drug ( $n = 3$ , with 0.5-3.0% variation)



Although a number of studies have proved the utility of SEDDS approach for improvement of oral bioavailability of BCS class II drugs, till date not much work has been done for BCS class IV drugs. SEDDS formulation for AmB has been earlier reported but it was not studied in detail owing to its poor drug content (0.5 mg/ml).<sup>[18]</sup> Lipidic formulations consisting of dispersion of AmB in Peceol and AmB in Peceol-DSPE-PEG2000<sup>[17-20]</sup> have been studied in detail and were found to be promising in terms of both oral bioavailability and eradication of fungal and leishmanial load in animal models. In the present study, we have tried to formulate a SEDDS formulation with increased drug content and dissolution rate. It is evident from the results of the solubility studies that AmB has a solubility of less than 1 mg/ml in all the oils, surfactants and co-surfactants studied except only the 1:1 mixture of propylene glycol and PEG 400. Although AmB has a very good solubility of more than 20 mg/ml in dimethylacetamide (DMA) (data not shown), the drug degraded rapidly in the SEDDS blend composed of glycerol mono oleate, tween 80 and DMA. The use of a cosurfactant blend consisting of propylene glycol and PEG 400 and ultrasonication of the SEDDS blend was found to improve drug content considerably as all the studied formulations had a drug content of at least 4.5 mg/ml with the optimized formulation having a drug content of  $8.11 \pm 0.50$  mg/ml. Whereas the same formulations when prepared by only stirring and mild heating at 40°C, had a drug content of 1.5-3.0 mg/ml. The contribution of ultrasonication on drug content may be because of increased solubility in the SEDDS blend as well as particle size reduction. The prepared formulations were not true solutions but rather colloidal dispersion of AmB in the SEDDS blend as was clear from their translucent rather than transparent appearance. The time for sonication and power intensity was carefully monitored to ensure that AmB does not degrade during processing as the drug may degrade at high temperatures resulting from the sonication process. The optimal separation of coarse particles was achieved by centrifugation at  $2500 \pm 200$  rpm for 10 minutes. Increasing the speed of centrifugation led to decrease in drug content whereas decrease in centrifugal speed led to settling of visible drug particles on storage.

Although, the solubility of AmB in glycerol mono oleate and oleic acid was nearly same, the drug content and self-emulsification properties of formulations containing glycerol mono oleate were better. We have used both Peceol and Capmul GMO-50 as the oil phase and they were found to be similar with respect to drug solubility and self-emulsification properties.

Evaluation of intestinal permeability was carried out using the non-everted intestinal sac method. AmB in SEDDS was found to have 100% intestinal permeability within 30 minutes, whereas the pure drug was non-permeable even after 2 hours. The increase in permeability may be attributed to the increase in dissolution rate as well as permeability enhancement. It has been speculated previously that poor permeability of AmB may

be due to p-glycoprotein mediated efflux. The excipients Tween 80 and PEG 400 present in the SEDDS formulation are known to be inhibitors of p-glycoprotein mediated efflux and may play a role in increased permeation of AmB from the SEDDS.<sup>[25,26]</sup>

The results of the present study show that SEDDS approach can be successfully applied to amphiphilic drugs like AmB to increase both dissolution rate and permeability. All the SEDDS formulations described in literature are clear solution of the drug in oil, surfactant, co-surfactant blend whereas the present SEDDS formulation is a sub-micron dispersion of AmB. The results of dissolution study indicate that the lack of presence in soluble form does not affect the dissolution. The preparation of this formulation has been achieved by sonication in the present study, but it may be achieved by homogenization techniques as well.

## CONCLUSIONS

SEDDS formulations containing AmB was successfully prepared and evaluated. The components of the SEDDS were chosen by solubility studies. A number of SEDDS formulations were prepared using glycerol mono oleate, Tween 80 and a mixture of propylene glycol and PEG 400 (1:1). Sonication was used to increase the drug content. The formulations were evaluated in terms of drug content, self-emulsification, and drug precipitation on dilution. The optimized formula had good self-emulsification properties with a small mean droplet diameter, rapid dissolution and high intestinal permeability. The results of this study demonstrate that BCS class IV drugs like AmB can be successfully formulated as SEDDS formulation to increase its dissolution and permeability. Oral administration of lipid based AmB formulation containing 2.5 mg/ml of AmB, have been previously studied for antifungal and antileishmanial activity in animals and have been demonstrated to be of considerable efficacy at a dose of 10 mg/kg. The present formulation with considerably higher drug content needs to be evaluated further for *in vivo* antifungal activity as well as renal toxicity.

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