



## Formulation and Evaluation of Solid Self-microemulsifying Drug Delivery System of A Selective Second Generation Cephalosporin Antibiotic

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### ABSTRACT

The objective of the present work was to formulate and evaluate novel solid self micro emulsifying drug delivery system (S-SMEDDS) of poorly soluble drug Cefuroxime Axetil, a selective second generation cephalosporin antibiotic. The liquid SMEDDS consisted of Capryol 90<sup>®</sup>, Labrasol<sup>®</sup>, Lutrol E400 and Cefuroxime Axetil. The solid SMEDDS were prepared by adsorption technique using Aerosil 200<sup>®</sup> as solid carrier. The solid SMEDDS were characterised for droplet size, zeta potential, *in vitro* release, SEM, DSC and XRD studies. The results demonstrated that the solid SMEDDS improve the dissolution profile thereby providing an aid to enhance the bioavailability by spontaneously forming micro emulsion after dilution in gastric fluids *in vivo*. The results indicate that the solid intermediates of SMEDDS have the potential to greatly enhance the dissolution profile of the poorly solubility drug.

**Keywords:** Cefuroxime Axetil, Globule size, PDI, SMEDDS, Zeta potential.

### INTRODUCTION

The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility. For this class of compounds, defined by Amidon *et al.*,<sup>1</sup> as 'low solubility/high permeability class', dissolution in the environmental lumen is the rate-controlling step in the absorption process.<sup>1</sup> Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy.<sup>2</sup>

Self-micro emulsifying drug delivery systems (SMEDDS) are fine oil in water emulsions, often are studied for the enhancement of bioavailability of hydrophobic drugs. Self-micro emulsifying drug delivery systems (SMEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water micro (SMEDDS) and nano (SNEDDS)-emulsions, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the GIT.<sup>3</sup> SMEDDS, however, have a smaller lipid droplet size (<100 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs.<sup>4</sup>

Cefuroxime Axetil is the 1- acetyloxy ethyl ester of cefuroxime, coming under second-generation cephalosporins. During absorption, this acid-stable, lipophilic, oral prodrug derivative of cefuroxime is hydrolysed to cefuroxime by intestinal and/or plasma enzymes.

The axetil ester owing to its poor solubility provides an oral bioavailability of only 35% to 50% of cefuroxime.

Depending on conditions, its plasma half-life ranges between 60 and 90 minutes. So, it belongs to BCS Class II and it requires improvement in its solubility profile.

Generally, SMEDDS are administered either as liquid dosage forms or filled in soft gelatine capsules. As they are bound to several disadvantages like leakage from capsule, incompatibility with the capsule shell, low stability etc, solid intermediates of these liquid SMEDDS have been prepared in order to overcome these problems.

### MATERIAL AND METHODS

#### Materials

Cefuroxime axetil (CA) was received from Indoco Remedies, Mumbai, Surfactants and Co surfactants were received from Gattefosse and Aerosil 200 from Evonik. Water used was double distilled procured from Indian Chemical Co. (ICC), Bangalore, India. All other chemicals and reagents used were of A.R. grade, procured commercially and used as received.

#### Methods

##### Saturation Solubility Studies

An excess amount of Cefuroxime axetil (approximately 500mg) was added to 2mL of each of vehicle in screw-capped glass vials under continuous stirring for 72 hrs. The equilibrated sample was centrifuged at 4,500 rpm for 10 min to remove the un dissolved drug. Aliquots of supernatant were filtered and diluted with methanol and the concentration of the drug was quantified using a UV spectrometer at  $\lambda_{max}$  281 nm.<sup>5,6</sup>

##### Construction of pseudoternary phase diagram

Water titration method was employed to construct the phase diagram. Briefly a mixture of labrasol and lutrol

E400 in different ratios (Smix ratio 1:1, 1:2, 2:1) were prepared in order to identify the micro emulsion region. Then Smix and capryol 90 were added in different ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 4:6, 3:7, 2:8, 1:9 in screw capped vials. Then, the mixture of oil phase and Smix was titrated with water and its phase clarity and flow ability was examined visually. Appearance of turbidity was considered as end point of titration. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% intervals. The calculation for the addition of aqueous phase was done by calculating the percentage of each component of the micro emulsion present at each 5% addition using a micropipette.<sup>7,8</sup>

### Preparation of Liquid Smedds

A series of SMEDDS formulations were prepared using Labrasol and Lutrol E400 as the Smix combination and Capryol 90 as oil. Accurately weighed Cefuroxime Axetil (126.15 mg) was placed in a beaker and the surfactant mixture was added and solubilised. Then the oil was added and the components were thoroughly mixed by gentle stirring and sonicated for 15 minutes to form homogenous mixture. The mixture was stored in suitable container and the evaluation parameters were carried out.

**Table 1:** Formulation of liquid SMEDDS

Formulation code	Oil (% v/v)	Smix (% v/v)	% Labrasol in Smix	% Lutrol E400 in Smix
F-1	10	90	60	30
F-2	15	85	56.66	28.33
F-3	20	80	53.33	26.66
F-4	25	75	50	25
F-5	30	70	46.66	23.33

### Evaluation of liquid SMEDDS

#### Clarity<sup>9</sup>

Percentage transmittance was checked against distilled water using UV spectrophotometer using dilution and transparency using visible spectrophotometer at 650 nm by dilution with distilled water (100 times).

#### Drug Loading Capacity

In this study, an excess amount of Cefuroxime axetil (approximately 500mg) was added to 2mL of each of vehicle in screw- capped glass vials under continuous stirring for 72 hrs. The equilibrated sample was centrifuged at 4,500 rpm for 10 min. Aliquots of supernatant were filtered and diluted with methanol and the concentration of the drug was quantified using an UV spectrometer at  $\lambda_{max}$  281 nm.<sup>5,6</sup>

#### Dispersibility Test<sup>10</sup>

The efficiency of the formulation was assessed using a standard USP dissolution apparatus II. 1 mL of each

formulation was added to 500 mL of water at  $37 \pm 0.5^\circ\text{C}$ . A standard stainless steel dissolution paddle rotating at 50 rpm providing gentle agitation. The *in vitro* performance of the formulation was visually assessed using the prescribed grading system:

### *In vitro* release Study

*In vitro* release study for all F1-F4 formulations were done by filling the liquid SMEDDS to hard gelatine capsules and introduced into USP dissolution apparatus II. The dissolution media 0.07 N HCl, rpm 100 were selected based on the standard procedures that available in USP and sample were taken every 5-15 min up to one hour. The absorbance was measured by UV spectrometer at  $\lambda_{max}$  of 281 nm.

### Globule Size of analysis and zeta potential<sup>6,11</sup>

Liquid SMEDDS were diluted 250 times with 0.1 N HCl / distilled water under gentle stirring. After achieving equilibrium, the emulsions were analysed by using a globule size apparatus (Malvern zetasizer nano ZS 170 version 7.02). The zeta potential of the SMEDDS formulation was assessed to obtain the charge on oil droplets using zetasizer nano.

### Preparation of solid SMEDDS

The optimized liquid SMEDDS formulation was converted into free flowing powder by adsorption of liquid SMEDDS onto Aerosil 200 in 1:0.5 ratio.<sup>11</sup> S-SMEDDS was prepared by mixing liquid SMEDDS containing Cefuroxime Axetil with Aerosil 200. In brief liquid SMEDDS was added drop wise over Aerosil 200 contained in broad porcelain dish. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation. Resultant damp mass was passed through sieve no. 100 and dried at ambient temperature or using desiccator and stored until further use.<sup>12,13</sup> The resulting powder may then be directly filled into capsules.

### Stability Studies<sup>14</sup>

Stability studies were performed for the determination of shelf life. The SMEDDS formulations were kept in rubber stoppered vials at two different temperatures ( $20 \pm 0.5^\circ\text{C}$  and  $40 \pm 0.5^\circ\text{C}$ ) and ambient humidity conditions for a period of two months. The samples were withdrawn after specified time intervals (0, 15, 30, 45, 60 days) and the drug content was measured using UV spectrophotometer.

### Evaluation of S-SMEDDS

#### Droplet Size and zeta potential of Emulsion

The S-SMEDDS formulation was reconstituted 250 times with distilled water under gentle stirring and the globule size, size distribution and zeta potential were analysed by zeta sizer nano.

#### Morphological Analysis of Solid SMEDDS (SEM)

The outer macroscopic structure of the solid SMEDDS was investigated by S-4100 scanning electron microscope (Hitachi, Japan). The SEM images were analyzed with an

image analysis system (Image inside Version 2.32) for particle size analysis.

### Solid State Characterization of Solid SMEDDS (DSC & XRD)

Physical state of cefuroxime axetil in S-SMEDDS was characterized using differential scanning calorimeter. Thermograms of cefuroxime axetil and S-SMEDDS were obtained using differential scanning calorimeter (TA Instruments, USA). Furthermore, X-ray powder scattering measurements (X-RD) were carried out with an X'Pert PRO diffractometer (PAN analytical, The Netherlands)

### In vitro drug release Study<sup>6,14</sup>

Drug release studies from solid SMEDDS were performed using USP dissolution apparatus II with 900 mL of 0.07 N HCl as a medium at  $37 \pm 0.5^{\circ}\text{C}$ . The speed of the paddle was adjusted to 100 rpm. Cefuroxime axetil - loaded solid SMEDDS (equivalent to 125 mg of Cefuroxime) and 125 mg of pure Cefuroxime axetil, Marketed product of the Cefuroxime (tablet) were placed in a dissolution apparatus and at predetermined time intervals 5, 10, 15, 30, 45 and 60 min; an aliquot (3 mL) of the sample was collected, filtered and analyzed for the content of Cefuroxime axetil by UV Spectroscopy.

## RESULTS AND DISCUSSION

### Preparation and evaluation of liquid SMEDDS

The results of solubility studies of cefuroxime Axetil in various oils, surfactants and co surfactans are depicted in table 2. Based on the solubility studies, capryol 90 was selected as oil, labrasol as surfactant and lutrol E400 as co surfactant.

### Construction of pseudoternary phase diagram

For developing a suitable formulation of micro emulsions, the classical pseudo ternary phase diagram technique was followed by employing aqueous titration method. Briefly, oil was mixed with surfactant and co surfactant and titrated with water till a turbid emulsion was reached. Phase diagram was subsequently constructed from the data generated by plotting % of oil (capryol 90), water and total surfactant/co surfactant mixture (Smix): Labrasol-Lutrol E400, at different ratios as three vertices of a triangle as shown in figure 1. The various Smix were tried such as; 1:1; 1:2 and 2:1. Among these ratios, Smix 2:1 was found to be the best combination with broader micro emulsion area and the emulsion formed was clear/less turbid and was spontaneous in formation.

### Drug loading capacity, %drug content and clarity

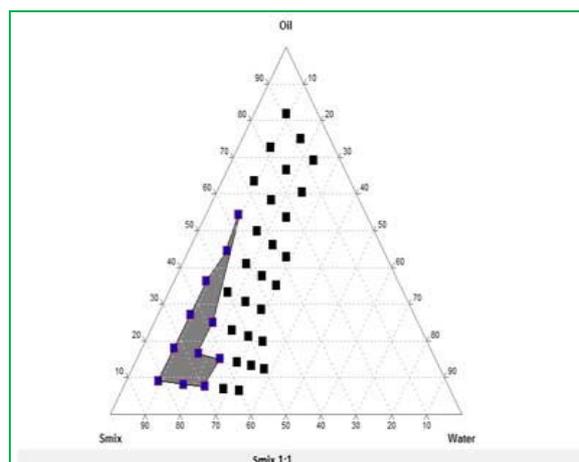
The drug loading studies were conducted for all the formulations to determine the maximum drug that can be loaded in the SMEDDS. The drug was found to precipitate as the concentration of oil was increased. The results present clear evidence as depicted in table 3.

The % transmittance was more than 80% for all the formulations except F-1 (63.09 %). The best results have

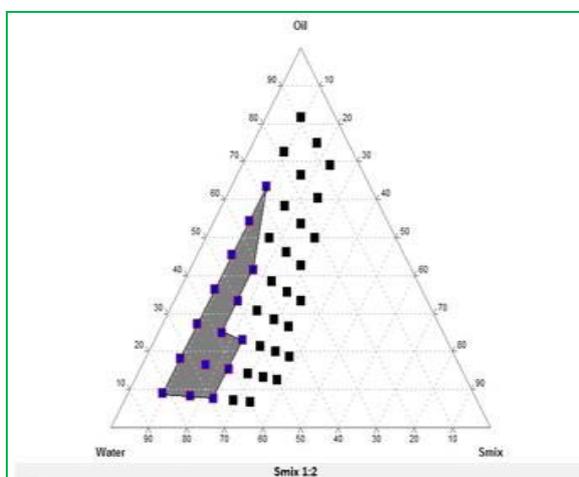
been reported for F-3 (95.94 %). This is due to the adjustment time required for the surfactant and co surfactant molecules orienting at the interface and for attaining the required curvature for the thermodynamic stability which was less.

Table 2: Saturation Solubility studies

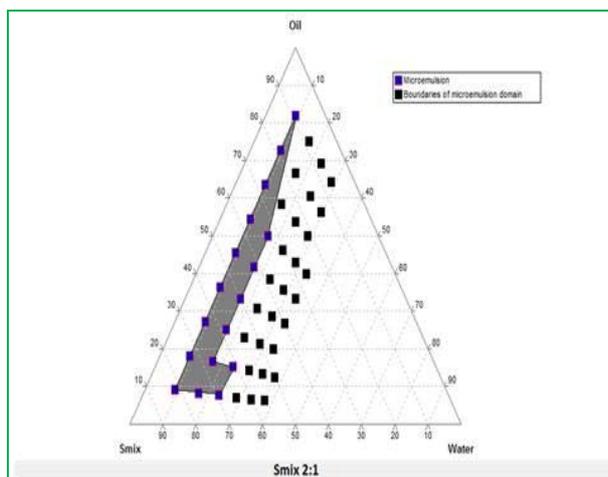
Category	Components	Concentration (mg/mL)
Oil	Capryol 90	8.205
	Labrafil	5.1
	Oleic acid	0.771
	Cottonseed oil	0.708
	Sesame oil	1.128
	Castor oil	0.961
Surfactants	Labrasol	44
	Plurol Oleique	4.5
	Tween 80	2.03
	Span 80	1.85
Co-surfactants	Transcutol 90	90
	Lutrol E400	152
	Propylene glycol	30.1
Distilled water		0.69



(a)



(b)



(c)

**Figure 1:** Pseudoternary Phase diagrams for the Smix ratios (a) 1:1, (b) 1:2 and (c) 2:1 respectively. Phase diagram of Smix 2:1 Capryol 90/ Labrasol/ Lutrol E400 micro emulsion system.

### Dispersibility test

The emulsification was spontaneous with a transparent bluish white appearance conforming to the official standards followed Grades A, B and C type of micro emulsion o/w. This suggests that the formulation will remain as micro emulsion when dispersed in GIT.

**Table 3:** Drug loading, %drug content and clarity of SMEDDS formulation.

Formulation Code	Drug Loading (mg/ml)	% Drug content	% Transmittance at 650 nm
F 1	166.66	99.20 ± 0.217	63.09
F2	135.89	98.45 ± 0.159	89.1
F3	126.15	99.30 ± 0.081	95.94
F4	66.15	98.82 ± 0.449	89.12
F5	29.74	84.63 ± 0.677	83.17

### Droplet Size, Zeta Potential and Poly Dispersity Index (PDI)

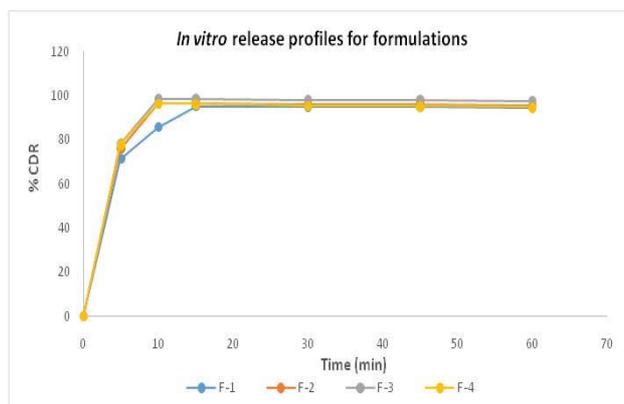
The formulations exhibited small particle size (93.85nm) and the value of poly dispersity index (PDI) of samples was found to be 0.139, suggesting a fairly mono disperse emulsion formed upon dilution with gastric fluid in body, also that the optimized SMEDDS formulation would remain stable.

The zeta potential of the SMEDDS formulation was found to be -0.467 mV with a conductivity of 0.0663 mS/cm. The charge on the droplets is negative due to the presence of free fatty acids.

### In Vitro Release Studies:

The % drug release studies were carried using 0.07 N HCl as dissolution medium (as prescribed in USP) and the formulations showed maximum % of drug release within 10 minutes. The formulation F-3 showed 98.61% release after 10 minutes, which is considered as the optimized formulation as compared to drug release from the rest of all formulations.

Micellar solubilization and/or enhanced contact surface might be responsible for the increase in drug release from surfactant solutions. This establishes that self emulsifying drug delivery systems can effectively increase the drug dissolution rate of poorly water soluble drugs and can be formulated as an immediate release dosage form for poorly water soluble drugs like Cefuroxime Axetil.



**Figure 2:** *In vitro* drug release profiles for formulations (F1-F4).

### Formulation and Evaluation of Solid SMEDDS

#### Selection of Solid Adsorbent/Carrier:

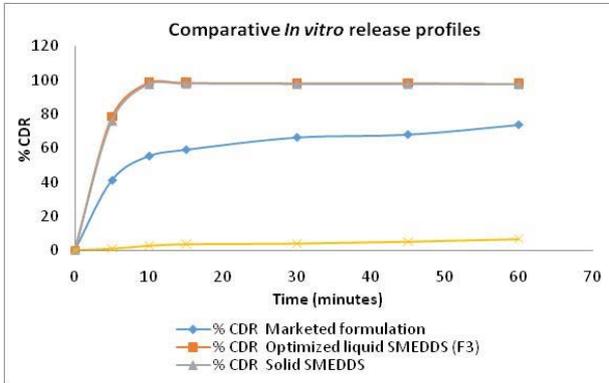
Different types of adsorbents were employed like Aerosil 200, Maltodextrin (Glucidex) and Lactose in different ratios. Compared to maltodextrin and lactose, Aerosil 200 gave good adsorption efficiency in ratio of 1:0.5. Solid SMEDDS with maltodextrin were not free flowing in either ratios 1:1 and 1:2. Solid SMEDDS with Lactose gave free flowing powder but showed improper mixing ability.

Aerosil 200 showed best adsorption efficiency with good mixing ability and free flowing powder was obtained. This was evident from the % drug content results where the % drug content of solid SMEDDS with Aerosil showed better result (93.22 %) than with lactose (77.62 %) The optimized formulation (F-3) was selected for conversion to solid SMEDDS and stored for evaluated.

#### Comparative *in vitro* release profile of pure drug, marketed formulation (tablet) and Optimized formulation.

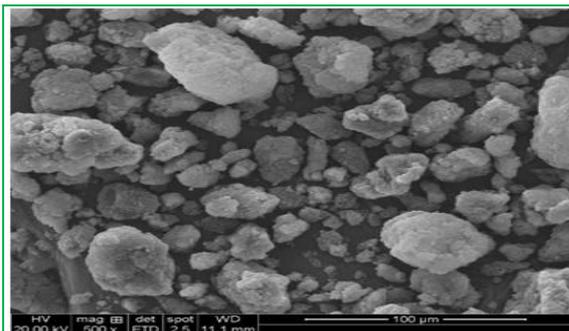
The % cumulative drug release of optimized solid SMEDDS formulation was found to be 97.56 % after 15 minutes which was similar to the release shown with liquid SMEDDS which was better compared to pure drug (6.58 %) and marketed formulation (73.85 %).

Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, can bypass first pass metabolism. Thus SMEDDS reduce the pre systemic clearance in the GI mucosa and hepatic first-pass metabolism. As cefuroxime Axetil is a BCS class II (poor soluble, high permeable), by improving the solubility of drug, the bioavailability of the drug can be increased.

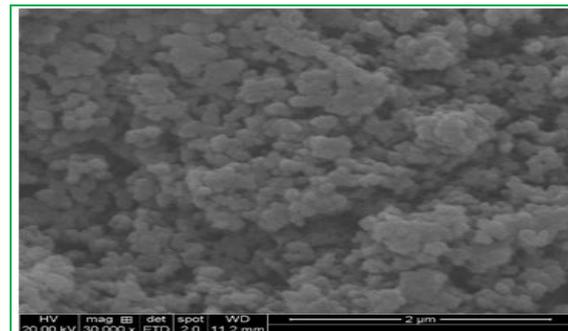


**Figure 3:** Comparative *in vitro* profile of Pure drug, optimized formulation (SMEDDS), Solid SMEDDS and market formulation of Cefuroxime Axetil.

**Solid state characterization of solid SMEDDS**

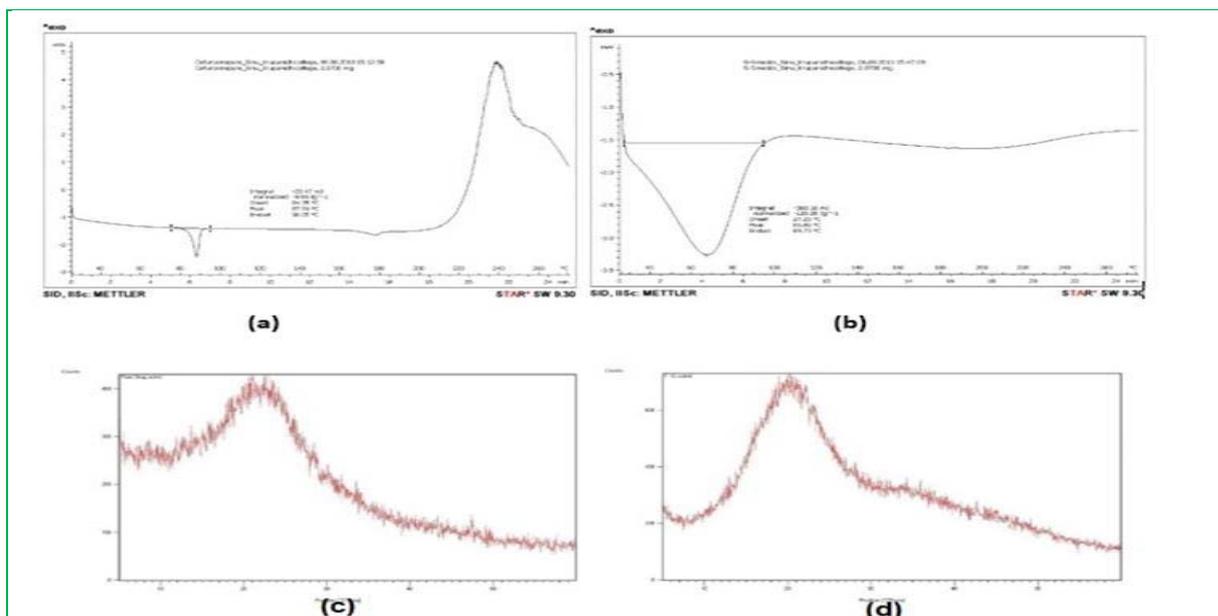


(a)



(b)

**Figure 4:** SEM images of solid SMEDDS of Cefuroxime Axetil in different magnifications i.e. 500 and 30,000x respectively.



**Figure 5:** DSC and X-RD characterization of pure drug (a and c) as well as S-SMEDDS (b and d) respectively.

### Stability Studies

From the stability studies, it was concluded that the SMEDDS formulation was stable under the specified temperature and humidity conditions. There was no considerable change found in the % drug content, Dispersibility and *in vitro* release of the optimized formula after 60 days at  $20 \pm 0.5^\circ\text{C}$  and at  $40 \pm 0.5^\circ\text{C}$  respectively.

No precipitation of the drug was observed after 60 days of storage and the drug was in solubilized form within the SMEDDS. Also, no interaction was found between SMEDDS and the capsule shell ascertaining the stability of formulation in hard gelatin capsule. This was confirmed by the % drug content studies. The self-dispersion of the formulation was rapid within 1 minute giving a fine dispersion.

### CONCLUSION

From the present investigation, it can be concluded that the prepared SMEDDS formulations, consisting of labrasol and lutrol E400 as surfactant components and capryol 90 as oil component, are stable with good emulsification efficiency and droplet size, thus ascertaining the stability of formulation *in vivo* ensuring formation of fine dispersion on dilution in GI fluids. Moreover, it can also be concluded that the S-SMEDDS of cefuroxime Axetil can be obtained by employing adsorption technique using Aerosil 200 as solid carrier with good flow properties, drug content and release profiles. The liquid SMEDDS and solid SMEDDS showed better *in vitro* release profiles than pure drug and marketed formulation. Thus the present study confirmed that the SMEDDS provide promising potential for enhancing dissolution rate and thereby bioavailability of cefuroxime Axetil.

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