

# Formulation and Evaluation of Self-emulsifying Drug Delivery System of Carbamazepine.

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## ABSTRACT

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The aim of this research work was to formulate SMEDDS of carbamazepine. Carbamazepine is an anti-epileptic drug used from a long time in treatment of epilepsy but it has poor bioavailability when used as a conventional dosage form. The SMEDDS of carbamazepine was prepared to enhance its bioavailability and its release rate was evaluated by its *in-vitro* release. The solubility of carbamazepine was determined in various oils, surfactants and co-surfactants. Pseudoternary phase diagrams were used to determine the microemulsion area of formulation. SMEDDS of carbamazepine was evaluated for globule size, zeta potential, clarity, effect of centrifugation, assay, dilutability, refractive index, transmittance, and stability. Formulation development and screening was done based on Pseudoternary phase diagram and results were obtained from the evaluation tests mentioned above. The optimized formulation was further evaluated for its *in-vitro* release having formula containing surfactant Cremophore RH-40(25%), co-surfactant PEG-400 (25%), and oil Labrafill M 1944 CS (21.30 %). It was observed that the SMEDDS formulation showed 85.63% release within 25 m. while conventional dosage form show only 27.95% release.

**Keywords:** Carbamazepine, SMEDDS, Cremophore RH-40, PEG-400, Labrafill M-1944 CS.

## INTRODUCTION

Carbamazepine is a drug widely used as an antiepileptic agent in therapy of psychomotor seizures and trigeminal neuralgia. It is traditionally given by oral route of administration but due to its poor water solubility it shows slow and irregular absorption from gastrointestinal tract. Furthermore this drug is characterised by a considerable hepatic first pass effect owing to the enzymatic auto-induction of its metabolism. Peak plasma concentration in plasma is usually attained 4-8 h after oral ingestion but may be delayed by as much as 24h. Reportedly it has oral bioavailability of less than 50 %. The efficacy of drug can be theoretically evaluated by its concentration at active target site as well as its blood level.

Oral absorption of several poorly water soluble drugs was enhanced by SMEDDS. SMEDDS is the mixture of oil, surfactant and co-surfactant having poorly water soluble drug. It forms the fine dispersion of oil in water in the range of 10-100 nm when comes in contact with the water in stomach. Among the lipid based drug delivery system the SMEDDS is the promising technology to improve the rate and extent of absorption of poorly water soluble drugs. The commercial available SMEDDS formulation containing ritonavir and saquinavir gives the good clinical evidence of enhanced oral bioavailability and absorbance from the gastrointestinal tract by oral route of administration<sup>1</sup>.

In this study the SMEDDS of carbamazepine containing the oil, surfactant, and co-surfactant were developed and physicochemical characteristics were evaluated and release profile was determined by *in-vitro*. The solubility of carbamazepine in various oils, surfactants and co-surfactants were determined. To determine the composition of these vehicles and microemulsion formulation area, the pseudoternary phase diagrams were constructed. The formulated SMEDDS of carbamazepine were characterized for Zeta potential, Particle size analysis, Dilutability, Assay, Refractive index, Thermodynamic stability were investigated in detail<sup>2</sup>. The release profile of carbamazepine SMEDDS from capsules were evaluated using USP dissolution apparatus I in 0.1 N HCl and the release of carbamazepine SMEDDS compared with the release of carbamazepine from conventional tablet<sup>3</sup>. The oral bioavailability of carbamazepine from SMEDDS is higher than the release of carbamazepine from conventional tablet. Our study indicates that the SMEDDS formulation consisting of Labrafill M 1944 CS, PEG-400, and Cremophore-RH 40 shows oral bioavailability of carbamazepine.

## MATERIAL AND METHODS

### Drug and chemicals:

Carbamazepine was obtained as gift sample from Sun Pharmaceuticals, Mumbai. Cremophore RH-40 (Polyoxyl 35 hydrogenated castor oil) was obtained from BASF (India). Labrasol (caprylocaproyl macrogol-8 glycerides), Labrafil M1944 (oleoyl macrogol glycerides), Labrafac CC (linoleoyl macrogol glycerides), Capryol 90 (propylene glycol monocaprylate), Transcutol P (diethylene glycol monoethyl ether) were obtained from Gattefosse (Mumbai, India).

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Soyabean oil, corn oil, castor oil, olive oil, iso-propyl myristate were obtained from Loba Chem. Acrysol K-150 was obtained as gift sample from coral pharma chem (Ahmadabad, Gujrat). All other analytical grade chemicals and solvents were of analytical grade.

### Solubility analysis

Preformulation solubility analysis was done to select the vehicle in which drug is more soluble and suitable for formulation of SMEDS. The solubility of carbamazepine in various oils, surfactants and co-surfactants was determined by adding excess amount of carbamazepine into 2 ml of each vehicle in a centrifuge tube, followed by mixing (250 rpm) in an orbital shaker (Electrolab, Mumbai) at 25°C for 24 h<sup>4</sup>. The samples were centrifuged at 1200 rpm for 30 m to remove the excess carbamazepine after which the concentration of carbamazepine in the supernatant was measured by UV method (Jasco; V 630 Plus) after appropriate dilution with methanol and 0.1 NHCL.

### Construction of Phase Diagram

On the basis of the solubility data presented in Table 1, Labrafill M 1944 CS was selected as oil, Cremophore RH-40 as surfactant and PEG-400 as co-surfactant. Pseudoternary phase diagrams of oil, surfactant/ cosurfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a dropwise manner. For each phase diagram at a specific ratio of S/CoS (i.e. 1:1, 2:1, 3:1 v/v), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 minutes. Then each mixture was titrated with water and visually observed for phase clarity and flowability<sup>5</sup>. The concentration of water at which turbidity-to-

transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addition on the microemulsion boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component<sup>6</sup>. Phase diagrams were then constructed using CHEMIX software.

### Preparation of SMEDS of Carbamazepine

A series of SMEDS formulation were carried out by using Cremophore RH 40 and PEG-400 as S/CoS combination and Labrafill M 1944 CS as oil. In all formulations the level of carbamazepine was kept constant (i.e.100mg) and the varying ratio of oil, surfactant and co-surfactant were added. Then the components were mixed by gentle stirring and sonication and were heated at 40°C on a magnetic stirrer until carbamazepine was perfectly dissolved<sup>7</sup>. The mixture was stored at room temperature until further use. The various formulation ratios are given in Table 2.

### Characterization and Evaluation:

#### Freeze Thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at - 4°C for 24 hours followed by thawing at 40°C for 24 h<sup>8</sup>. Centrifugation was performed at 3000 rpm for 5 m. The formulations were then observed for phase separation<sup>9</sup>. Only formulations that were stable to phase separation were selected for further studies.

#### Determination of Particle Size and Polydispersive index

Globule size and polydispersive index of the carbamazepine SMEDS were determined by light scattering spectroscopy using He Ne-laser as a source of light. The SMEDS were transferred to standard quartz cuvette, and the droplet size was determined by He Ne-laser (10 mV) light scattering at 90° at 25°C<sup>10</sup>. Data analysis was conducted using software package (windox5) provided by manufacturer.

Table 1: Solubility of carbamazepine in various vehicles

Sr.No.	Ingredients	Solubility in mg/ml
<b>Oils</b>		
1	Acrysol K-150	58.7
2	Castor Oil	23.02
3	IPM	34.5
4	Labrafill M 1944 CS	60.3
5	Capryol 90	55.4
6	Seasame oil	38.2
<b>Surfactant</b>		
1	Tween 80	44.4
2	Labrasol	40.2
3	Capryol 90	38.7
4	Cremophore RH 40	46.8
<b>Co-surfactant</b>		
1	Transcutol- HP	101.2
2	PEG-400	120.3
3	Propylene glycol	98.3

Table 2: Composition of optimized formulations of carbamazepine SMEDS

Formulation	S/cos ratio	Oil (% V/V)	Surfactant (% V/V)	Co-surfactant (%V/V)
<b>F1</b>	1:1	6.41	28.84	28.84
<b>F2</b>	1:1	21.30	25	25
<b>F3</b>	1:1	77.59	11.72	11.72
<b>F4</b>	2:1	18.07	28.11	14.05
<b>F5</b>	2:1	46.67	13.33	6.66
<b>F6</b>	3:1	57.69	4.80	1.60

### Self-Emulsification and Precipitation Assessment

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessed using the grading system given in Table. 3. In brief, different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by dropwise addition of the carbamazepine (SMEDDS) into 250 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 h<sup>12</sup>.

### Zeta Potential

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SMEDDS formulation was measured using a (Malvern Nano Zetasizer instrument). The SMEDDS were diluted with a ratio of 1:20 v/v with distilled water and mixed for 1 m using a magnetic stirrer.

### Refractive Index

Refractive index of the placebo SMEDS and drug-loaded SMEDS was determined with an Abbe-type thermo stated refractometer<sup>12</sup>.

### Transmittance

Transmittance of the carbamazepine SMEDS were measured against distilled water with a UV-visible Spectrophotometer at 630 nm<sup>12</sup>.

### In-vitro drug release studies

The In-vitro dissolution studies were carried out by using paddle type USP dissolution apparatus II. Dissolution tests were done separately for Marketed drug Tablet and SMEDS capsules containing the equivalent drug to 100 mg of pure drug were used for dissolution studies. Dissolution was carried out in 900 ml 0.1 N HCl at 50rpm at temperature of 37°C<sup>13</sup>. Sample aliquots (10 ml) of dissolution medium were withdrawn at different time intervals, filtered and replaced with fresh medium. The samples were assayed spectrometrically at 285 nm.

### Stability Studies

The SMEDDS formulations were put into empty hard gelatin capsules (size 0) and subjected to stability studies at 40°C/75% RH. They were withdrawn at specified intervals for analysis over a period of 3 months<sup>14</sup>. Drug content of the capsules was analyzed using UV spectrometric method. The SMEDS formulations were evaluated for particle size, clarity of microemulsion, polydispersive index, and zeta potential. The sampling was done on a 0,30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> day.

## RESULTS

### Solubility studies

One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen *in vivo*. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in Table No.1. As seen from the Table No.1, Labrafill M 1944 CS showed the highest solubilization capacity for carbamazepine, followed by Cremophore RH-40 and PEG 400. Thus, for our study we selected Labrafill M 1944 CS as oils and Cremophore RH -40 and PEG 400 as surfactant and cosurfactant, respectively.

### Pseudoternary phase diagrams

Pseudo-ternary phase diagrams were constructed to identify self-micro emulsifying region and to select suitable concentration of oil (Labrafill M 1944 CS), surfactant (Cremophore RH-40) and co-surfactant (PEG-400) for the formulation of SMEDS. In present study, Labrafill M 1944 CS was tested for phase behaviour studies with Cremophore RH 40 and PEG-400. As seen from the ternary plot (Fig. 1) the microemulsion existing area increases as the s/cos ratio increases. However it was observed that increasing the surfactant ratio resulted in the loss of flowability. Thus an s/cos ratio of 1:1 was selected for formulation.

### Effect of drug on the phase diagram

The effect of the drug on the phase diagram was studied using pseudoternary phase diagram. The oil (Labrafill M1944 CS) was tested with s/cos in various ratios like 1:1, 2:1 and 3:1. In

Table 3: Visual Assessment of Efficiency of Self-Microemulsification

Grade	Dispersibility	Time of self microemulsification (m)
A	Rapid forming microemulsion Which is clear or slightly bluish in appearance	<1
B	Rapid forming, slightly less clear emulsion which has a bluish white appearance	<2
C	Bright white emulsion (similar to milk in appearance)	<3
D	Dull, greyish white emulsion with a slightly oily appearance that is slow to emulsify	>3
E	Poor or minimal emulsification with large oil droplets present on the surface	>3

the present study it was found that the drug incorporation in the SMEDS had no significant difference in microemulsion existing area when compared with corresponding formulation without carbamazepine.

### Characterization and Evaluation of SMEDS:

#### Freeze thawing

Freeze thawing was carried out to evaluate the stability of formulation. It was observed that in formulations F3, F5, F6 there was separation of two layers; hence these formulations were excluded for further studies.

#### Particle size determination

The droplet size distribution of various formulations is given in Table No.4. It was observed that formulation F 1 .having highest proportion of surfactant ( 6.41 %) and co-surfactant (28.84 %) and oil ( 28.84 %) shows the lowest mean particle diameter, where formulation F 3 having lowest proportion of surfactants shows highest mean particle size. Thus an increase in the oil phase resulted in proportional increase in particle size because of simultaneous decrease in the s/cos proportion. Addition of surfactants to the microemulsion system causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand.

#### Self-Emulsification and Precipitation Studies

The results of self-emulsification and precipitation studies are given in Table 4. It was seen that an increase in the proportion of Labrafill M 1944 CS in the composition resulted in decreasing self-emulsification time. The decrease in self-emulsification time can be assumed to be due the relative decrease in surfactant concentration, leading to decreased viscosity of the formulation. The S/CoS ratio of 2:1 was kept

constant for the initial formulation study. However, it was found that the resultant dispersion showed precipitation and thus was not stable, because of the presence of PEG 400. PEG 400 can be assumed to act as a cosolvent for carbamazepine (as seen from solubility studies), and thus it increases the solubilization capacity of the vehicle (Labrafill M 1944 CS). However, when the concentrate (SMEDDS) is dispersed in water, PEG 400, being water-soluble, is anticipated to enter the water phase and redistribute mainly between the water phase and the emulsion-water interface, resulting in a loss of solvent capacity of the vehicle. Thus, the problem of precipitation was solved by increasing the surfactant proportion (S/CoS 1:1) in the system.

#### Zeta potential, Refractive index and Drug content (%)

The values of *Zeta potential, Refractive index and Drug content (%)* of formulations are shown in Table 5. Formulation (F2) has zeta potential -0.57 mv. The negative zeta potential indicates that a droplet of microemulsion having no charge on particles, so no flocculation of particles and thus the microemulsion was stable. The refractive index of formulation was 1.37 shows the isotropic nature of formulation. The drug content of formulations was determined by UV spectrophotometrically.

#### In-vitro drug release:

The In-vitro drug release studies were performed and the % drug release graph was plotted against time. A comparison of in-vitro drug release profile of marketed formulation and SMEDDS formulation are given in Fig. 2. Based on drug release comparison studies, it was observed that the drug release from SMEDDS was found to be significantly higher when compared with conventional marketed formulation. There was 96.1% release of drug from formulation F 2 in

Table 4: Particle size, polydispersive index, and dispersion time of SMEDDS formulation

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Particle size	8nm	15.3nm	225nm	13.5nm	84.6nm	215nm
Polydispersive index	0.24	0.3	01.2	0.6	0.5	0.7
Dispersion time	<1	<1	>3	<1	>3	>3

Table 5: Zeta potential, Refractive index and Drug content values of Carbamazepine SMEDDS

Parameter	SMEDDS Formulations		
	F1	F2	F3
Zeta Potential	-21.2 mv	-0.57 mv	-1.63 mv
Refractive index	1.380	1.375	1.379
Drug content (%)	98.84	99.1	99.2

Table 6: Stability assement of carbamazepine SMEDS formulation

	Storage (Temp. 40°C and Humidity 75 %)											
	F 1				F 2				F 3			
	0days	30days	60days	90days	0days	30days	60days	90days	0days	30days	60days	90days
Particle size (nm)	8	9.2	8.9	8.2	15.3	14.8	15.7	16.1	13.5	14.8	14.2	14.8
Polydispersive index (mv)	0.24	0.18	0.64	0.88	0.30	0.44	0.59	0.66	0.71	0.66	0.86	0.70
Drug content (%)	98.84	98.16	98.21	98.10	99.1	98.2	99.4	97	99.2	98.9	98.4	99.1
Dispersion Time (m)	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1



Fig. 1: Pseudo-ternary phase diagrams of various ratios of oil to s/cos A (1:1), B (1:2), C (1:3)

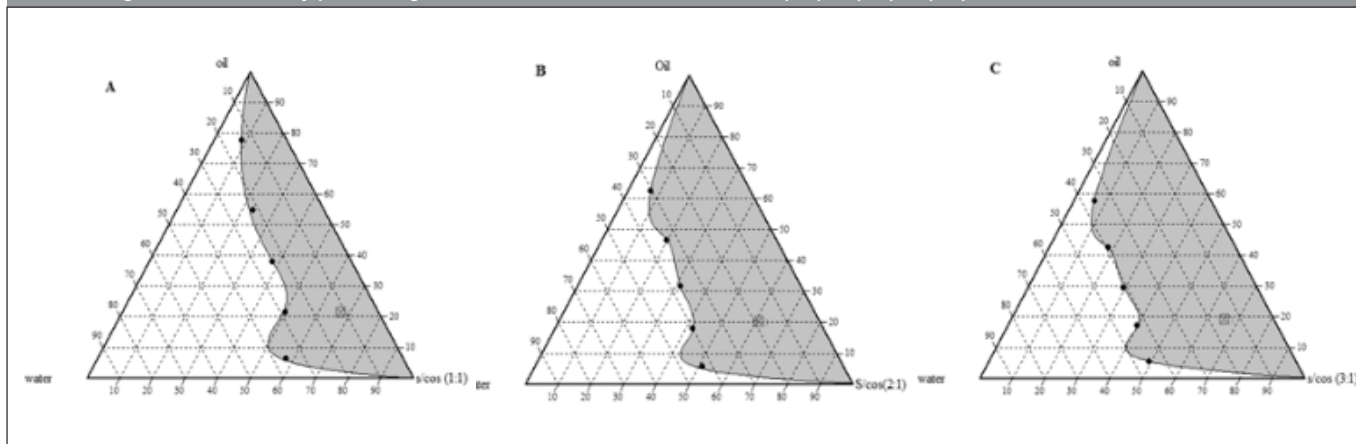
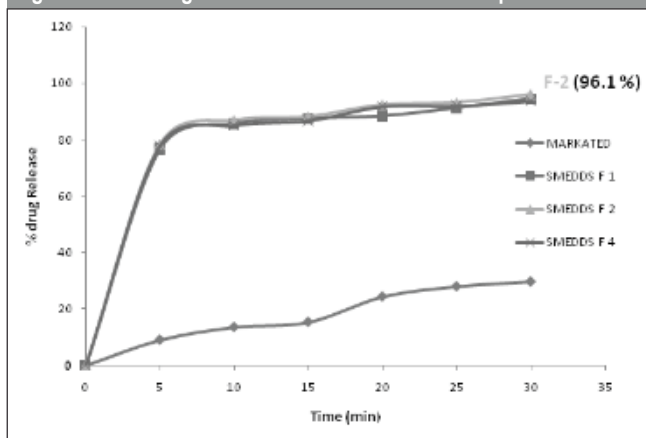


Fig. 2: In-vitro drug release from various carbamazepine SMEDDS



30 m. It was suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with small droplet size which permitted a faster rate of drug release into the aqueous phase, much faster than conventional marketed carbamazepine formulation. Thus, this greater availability of dissolved carbamazepine from the SMEDDS formulation could lead to higher absorption and oral bioavailability.

#### Stability assessment of SMEDS formulations

Generally, SMEDDS formulations are put into hard gelatin capsules as the final dosage form. However, liquid-filled hard gelatin capsules are susceptible to leakage, and the entire system has a very limited shelf life owing to its liquid characteristics and the possibility of precipitation of the drug from the system. Thus, the developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. Table 6 gives the results of the evaluation test conducted on stability samples. The formulation was found to be stable for 3 months. There was no significant change in the drug content, or particle size of the

resultant emulsion. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. Furthermore, the formulation was found to show no phase separation, drug precipitation, or capsule leaks. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules.

#### DISCUSSION

Poor water solubility and less absorption is a major limitation with many drugs despite their good therapeutic efficacy. SMEDDS provides an opportunity for the improvement in the *in vitro* and *in vivo* performance of poorly water soluble drugs and thus serve as an ideal carrier for the delivery of drugs belonging to BCS classes II and IV. The current study was performed to define the role of self emulsifying formulations to enhance the bioavailability of carbamazepine. SMEDDS represent a possible alternative to the more traditional oral formulations for lipophilic compounds. It has isotropic mixture of oil, surfactants, and co-surfactants. This mixture should be clear, monophasic liquid at ambient room temperature. SMEDDS self-emulsifies rapidly in the aqueous contents of the stomach under gentle digestive motility in the gastrointestinal tract to present the drug in solution in small droplets of oil (<100 nm). It is considered that the excipients in SMEDDS increase the dissolution and permeability of drug by significantly decreasing droplet size. The use of SMEDDS for the delivery of carbamazepine could improve its solubility and permeability through the mucous membranes significantly.

In the present work, we have prepared the carbamazepine SMEDDS formulations and assessed the droplet size, zeta potential, robustness to dilution, and dissolution *in vitro*. Tablets of carbamazepine in traditional form were used as a control in the present study. The choice of excipients to prepare SMEDDS depends on its drug dissolving capacity.

Carbamazepine possesses the highest solubility in Labrafill M 1944 CS (60.3 mg/ml); hence, we selected Labrafill M 1944 CS as oil phase for carbamazepine SMEDDS formulation. The selection of surfactant and cosurfactant in this study was governed by their emulsification efficiency rather than their ability to solubilize drug. The efficiency of self-microemulsification is much more related to the hydrophilic–lipophilic balance (HLB) value of the surfactant. Surfactants with HLB value >10 are greatly superior at providing fine, uniform microemulsion droplets. Safety is the main determining factor in choosing a surfactant. Non-ionic surfactants are less toxic and less affected by pH and ionic strength than ionic surfactants. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsion. SMEDDS shows the 96.1% release in 30 m as compared with marketed formulation which shows a limited dissolution rate. Thus the study confirmed that SMEDDS formulation can be used as possible alternative to traditional oral formulation of carbamazepine to improve its solubility and oral bioavailability.

#### CONCLUSION

An optimized carbamazepine loaded formulation consisting of Labrafill M 1944 CS (21.30% w/w), Cremophore RH 40 (25%), PEG 400 (25%) offers the advantage of good clarity systems at high oil content and thus should offer good solubilization of carbamazepine. Thus our studies conformed that SMEDDS can be used as a possible alternative to conventional oral formulation of carbamazepine. Results further conclude that SMEDDS can be explored as a potential drug carrier for dissolution enhancement of carbamazepine and other lipophilic drug.

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