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Development and evaluation of L-SEDDS Delivery system for treatment of epilepsy

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Abstract:

The biopharmaceutical classification system (BCS), which is based on estimates of the contribution of solubility, permeability, and dissolution to oral drug absorption from dosage forms. First described in 1995, the BCS and its principles have been used in guidelines issued by the Food and Drug Administration. Solubility is the property of a solid, liquid, or gaseous hemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, costeffectiveness, least sterility constraints, and flexibility in the design of dosage form. objective of present work is to formulate Solid SMEDDS to enhance solubility, dissolution rate which may improve therapeutic performance and drug loading capacity so as to develop alternative to traditional oral formulations to improve bioavailability. Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-microemulsifying drug delivery systems (SeEDDS) to improve the oral bioavailability of lipophilic drugs.

Introduction: Oral bioavailability of such drugs, being primarily a function of their solubility and dissolution, tends to exhibit inadequate magnitude with high intra- and inter subject variability. Further, oral bioavailability also depends upon a multitude of other drug factors such as stability in GI fluids, intestinal permeability, and resistance to metabolism by cytochrome P450 family of enzymes present in gut enterocytes and liver hepatocytes, and interactions with efflux transporter systems such as P-glycoprotein (P-gp). Several approaches have been employed to improve the oral bioavailability of diverse

drugs during formulation. Among these, oral lipid-based drug-delivery systems have shown immense potential in improving the poor and inconsistent drug absorption of many poorly water-soluble drugs, especially following their administration after meals. These approaches include various types of lipid suspensions, solutions, and emulsions. With applications in specific domains, lipidic formulations have therefore gained a significant niche in oral drug delivery systems **[1].**

Various strategies have been widely investigated to enhance the bioavailability of poorly absorbed drugs in order to increase their clinical efficacy when administered orally. It is estimated that between 40% and 70% of all new chemical entities identified in drug discovery programs are insufficiently soluble in aqueous media1. Poorly absorbed drugs pose a challenge to the formulation scientists to develop suitable dosage form which can enhance their bioavailability. Broadly, poorly soluble drugs can be formulated in three different forms to overcome the challenge of poor absorption crystalline solid formulations, amorphous formulations, and lipid formulations [2].

Solubility is the most important physicochemical property used in drug discovery and development and thus a good understanding of the concept and methods to predict or determine solubility are significant for the pharmaceutical scientist. The number of poorly water-soluble drug candidates, found in drug discovery and development, it cause increasing problems with poor and changeable bioavailability **[3].**

Self-emulsifying drug delivery systems (SEDDS) are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs. According to the Biopharmaceutics Classification System (BCS), a compound is inadequately soluble if the highest dose strength cannot be dissolved in 250 ml in the pH range between 1 and 7. Such compounds are categorized as class II drugs. If drugs are both poorly soluble and poorly permeable through the membranes of the gastrointestinal (GI) tract, then they are classified as class IV. Formulation scientists were pushed to come up with strategies to develop such difficult compounds into orally bioavailable and therapeutic efficient drugs. The solubility of a poorly soluble drug can be modified in many ways, such as salt formation, cosolvents, crystal engineering, cyclodextrin, nanoparticles etc. A guaranteed approach to beat low bioavailability and systemic toxicity is the use of drug-loaded nanosized drug carriers, such as polymeric nanoparticles (NPs), liposomes, dendrimers, emulsions and micelles **[4].** Lipid emulsions are attractive systems for enhancing drug solubility of poorly soluble or practically insoluble drugs due to their capacity to integrate lipophilic drugs. According to the literature data, there is a rising interest in the lipid and surfactant based systems, for example, lipid solution, surfactant dispersion emulsion, liposomes, microemulsion, dry emulsion and self microemulsifying formulations **[5].**

Material and methods:

Solubility Studies for selection of oils, surfactants and cosurfactants: The solubility of lamotrigene in various oils, surfactants, and co-surfactants were measured through the shake flask method for selection of oils, surfactants and cosurfactants for the formulation. Lamotrigene was mixed with 2 ml of selected oil (Sunflower oil) / surfactant (Tween 80) / cosurfactant (Glycerol) in glass vial and heated to 60 °C for 2 min in a water-bath. Then mixtures were equilibrated at 25°C for 48 h in a water bath and then centrifuge at 3000 rpm for 15 min followed by filtration. Now 0.5 mL supernatant was and the lamotrigene content was determined by UV-Visible double beam spectrophotometer at 268 nm after dilution with methanol **[6-7].**

Construction of phase diagram: Pseudoternary phase diagrams were constructed to examine the formation of oil in water microemulsions using three axes of the triangle represent oil, Smix, and water. A water titration method is used for the building of a pseudo ternary plot of water, oil, co-surfactant and, surfactant, with drug candidates at a suitable temperature. The levels of oil, co-surfactant and, surfactant, were taken at the range of 10 % - 60 % (w/w), 0 % - 30 % (w/w) and 40% - 90 % (w/w) respectively. The prepared mixtures kept on a magnetic stirrer for 2-3 minutes till equilibrium. Once the equilibrium was obtained the type of emulsion micro or coarse were identified by Organoleptic Characters. A clear or slightly bluish sample was taken as a microemulsion. The changes from transparent to turbid were noticed. CHEMIX ternary plot software was used for the preparation of phase diagram **[8].**

Table 1: Based on the solubility study, the oil, surfactant and cosurfactant were selected.

Drug	**Oil**	**Surfactant**	**Cosurfactant**
Lamotrigene	Olive Oil	Tween 80	Glycerol

Slow titration with aqueous phase was carried out to each weight ratio of oil and Smix, through the visual observation the following categories were assigned.

- Transparent and easily flowable: oil/water nanoemulsions
- Transparent gel: nanoemulsion gel
- Milky or cloudy: emulsion
- Milky gel: emulgel

In the phase diagrams, only microemulsion (ME) points were plotted (shaded area), so that there is no overcrowding of the phases in the diagram, as for formulation development, only the microemulsion region is of interest **[6].**

Dilution Process:

Prepared SEDDS formulation contains 50 mg quantity of lamotrigene. Phosphate buffer (pH 6.8), 0.1 N HCl, and Distilled water was used for the dilution of 1 part SEDDS of each solution. Thus, prepared different three types of formulations for this study.

Experimental Design: This experimental work involves a three-component system: the oil X1 (Olive oil), the surfactant X2 (Tween 80), and the co-surfactant X3 (Glycerol). For the optimization of the SEDDS box, Behenken factorial design was employed by varying its components/factor. For the designing of this experimental work Design expert version, 12 software was used. For the optimization and selection of suitable formulation, twenty experimental runs were applied one by one, as well as three central points, were assumed, and according to experimental procedure surfactant, co-surfactant and oil were mixed in a different ratio. Two variables were selected as responses, such as droplet size (Y1) and turbidity (Y2), Optimized formulation was screened based on the positive and negative results of these responses. The goal of this process optimization was set and it was focused to minimize Y1 (<50 nm) and Y2 (<20 NTU). It was important to convert the parts by weight of X1, X2, and X3 to the percentage by weight using Design-Expert version 12 before the results review. After an experimental run, an effective quadratic equation for each response was obtained. . The average droplet size (Y1) and turbidity (Y2) were used as the answers. Behenken factorial architecture was then used for SEDDS box optimization by varying its components/factor. The experimental plan was developed using version 12 of Design-Expert Software.

Twenty experimental runs with three central points have been designed by combining separate portions of oil, surfactant, and co-surfactant, as recommended by the experimental plan. To explain and better understand the relationships between the independent and dependent variables, ANOVA, 2D, and 3D plots were developed with the help of software. Based on the point prediction method, the optimized formulation was chosen.

Table 2: Experimental design for the study

Formulation Code	**X_1**	**X_2**	**X_3**
	Olive Oil (w/w)	**Tween 80 (w/w)**	**Glycerol (w/w)**

LSEF1	38	37	25
LSEF2	39	38	23
LSEF3	40	40	20
LSEF4	20	60	10
LSEF5	40	40	20
LSEF6	6.36	40	20
LSEF7	40	40	3.18
LSEF8	40	6.36	20
LSEF9	60	60	10
LSEF10	40	40	20
LSEF11	40	40	20
LSEF12	40	40	20
LSEF13	60	20	30
LSEF14	40	73.63	20
LSEF15	40	40	20
LSEF16	20	20	10
LSEF17	60	20	10
LSEF18	20	60	30
LSEF19	60	60	30
LSEF20	73.63	40	20
LSEF21	40	40	20
LSEF22	40	40	36.81
LSEF23	20	20	30

Evaluation L-SEDDS:

Thermodynamic stability tests: Selected formulations were subjected to different thermodynamic stability tests (Centrifugation, Heating cooling cycle and Freeze thaw cycle), to overcome selecting metastable formulation.

Centrifugation: Selected formulations from phase diagrams were centrifuged at 3500 rpm for 30 min and observed for phase separation, creaming and cracking. Formulations that are stable were taken for heating cooling cycle.

Heating cooling cycle (H/C cycle): Stability of emulsions on variation of temperature was studied by H/C cycle. Six cycles between refrigerator temperature 4°C and 45°C with storage at each temperature for not less than 48 h. Formulations, that are stable at these temperatures, were subjected to Freeze thaw cycle.

Freeze thaw cycle: Three freeze thaw cycles between -21°C and +25°C with storage at each temperature for not less than 48 h was carried out for the formulations. Formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility tests for assessing the efficiency of self emulsification **[9].**

Dispersibility tests [10]: The efficiency of dispersibility was assessed using a USP XXII dissolution apparatus II. Each formulation (0.5ml) was added to 500 ml distilled water maintained at 37±0.5 C, with paddle rotating at 50rpm for gentle agitation. The in vitro performance of the formulations was visually assessed using the grading system as shown below.

Grade A: Rapidly forming (within 1 min) emulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

The Formulations that passed the thermodynamic stability and dispersibility tests in Grade A and B were selected for further studies.

Effect of pH and robustness to dilution: Formulations were subjected to 50, 100, 1000 and 3000 fold dilution with distilled water, 0.1M HCl and simulated intestinal fluid (pH 6.8). The resultant diluted emulsions were checked manually for any physical changes such as (coalescence of droplets, precipitation or phase separation) after 24 h storage **[11].**

Globule size measurement: The mean globule size and polydispersity index of the resulting emulsions were determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer 3000 (Malvern Instruments Worcestershire, UK) Light scattering was monitored at 25ºC at a 90ºangle120°Ɵ.

Droplet Size determination: For the proper analysis of the droplet size of SEDDS, Its 1 ml quantity was taken in a beaker and kept on a magnetic stirrer then the solution was diluted 10 to 100 times with 0.1 N HCL and water **[12-13]**. To achieve equilibrium, the formed emulsion was retained for 1 h, and then the particle size analyzer was used to determine droplet size.

Phase Separation Study: A 5 ml distilled water glass tube was taken and 1 ml of SEDDS was added, then this mixture was held at 25°C. For successful mixing, a Vortex mixer was used for 1 minute. For phase separation analysis, the resulting mixer was kept aside for 2 hours **[6]**.

Determination of self emulsification time: Optimized SEDDS of lamotrigene self emulsification time was determined by using the USP type II dissolution apparatus. To provide gentle agitation 1 ml optimized lamotrigene SEDDS dropwise mixed with 250 ml filtered water by maintained 60 rpm paddle rotation speed at 37 °C. During the process rate of micro emulsification and color produced was observed visually **[10].**

Transmittance and turbidity measurement: The percentage transmittance and turbidity of the optimized microemulsion were measured with the help of UV–Visible spectrophotometer and Nephelometer respectively.

Zeta potential determination: The zeta potential indicates the physical stability of the colloidal structures by calculating the presence of an electric charge on the surface of the particles. The microemulsion stability is directly associated with the magnitude of the surface charge present of the colloidal particles. The Zeta potential has been calculated by Zeta-Sizer. Experiments were replicated three times at 25 °C (Malvern instrument, Worcestershire, UK) 120 **[14].**

Viscosity: Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc, Middleboro, MA, spindle # CPE40) was used to determine the viscosity of different formulations at 25±1.0°C 65.

Refractive index and percent transmittance: The refractive index of the system was measured using Abbe's refractometer. The percent transmittance of the system was measured using UV spectrophotometer at 268 nm (Shimadzu, Japan) keeping distilled water as blank [**15].**

Drug content estimation: Prepared SEDDS containing drug equivalent to one dose was added in 50 mL volumetric flask containing methanol and mixed it well. The extracted solution was suitably diluted and analysed for drug content using UV-spectrophotometer **[16]**.

Result and discussion:

Solubility Study: Lipophilicity of a drug in the oil phase is important because less amount of oil is needed for the formation of the micro emulsion, due to the high solubility of the drug in the oily phase. Based on the solubility of lamotrigene in different vehicles shown in **(Table 3)** sunflower oil was elected as the oil and glycerol as co-surfactant for improved drug loading.

Table 3: Solubility profile in vehicles

Vehicles	**Solubility in mg/ml ± SD**	**Selected vehicles for microemulsion formulation**
OIL		
Nut meg Oil	4.87± 0.01	
Soya bean oil	0.47± 0.01	
Labrafil oil	0.65± 0.07	
Castor oil	0.99± 0.05	
Olive Oil	5.43± 0.01	√
Sunflower oil	4.17± 0.02	
SURFACTANT		
Capryol 90 (nonionic water-insoluble)	0.43± 0.01	
Labrasol	0.49 ± 0.02	
Span 80	6.31± 0.02	
Tween 80	94.21± 0.06	√

Tween 60	83.21± 0.01	
CO-SURFACTANT		
Transcutol	4.16± 0.02	
Propylene Glycol	3.99± 0.03	
Glycerol	127.1± 0.12	√
PEG	2.34± 0.02	

Dilution Study: Study of dilution was done for the examination of the emulsification and recrystallization of the drug. The dilution analysis on preconcentrates of SEDDS has been conducted to access the impact of dilution. To create stable micro emulsion, an accurate mixture of emulsifiers is required for the production of SEDDS formulation, one part SEDDS formulation was diluted with 10 parts of distilled water, 0.1N Hcl, and phosphate buffer 7.4 pH, shown in **(Table 4.12)**. The study suggests that the formulation **LSEF3** was more stable since no precipitation or crystallization of the drug occurred.

Table 4: Observation of Dilution Study

Vehicles	**LSEF1**	**LSEF2**	**LSEF3**
Distilled water	Cloud nature appearing within 4-5 h	Cloud nature appearing within 4-5 h	No cloud nature appearing upto 6 h
0.1 N HCL (pH 1.2)	Cloud nature appearing within 3-4 h	Cloud nature appearing within 4-5 h	No cloud nature appearing upto 6 h
Phosphate Buffer pH 7.4	Cloud nature appearing within 4-5 h	Cloud nature appearing within 4-5 h	Cloud nature appearing within 4-5 h

Selection of formulations from Phase diagrams: From each phase diagram constructed, different formulations were selected from ME region so that drug could be incorporated into it on the following basis.

Table 5: Lamotrigene SEDDS Components

Components select for SEDDS	Utilization
Olive oil	Chosen as Oil
Tween 80	Chosen as Surfactant
Glycerol	Chosen as Co- surfactant

Pseudo ternary phase diagram study: As SEDDS come in contact with water with constant agitation, it turns into o/w emulsion. The system's phase behavior was analyzed using multiple surfactants to co-surfactant ratios. In each category, surfactants and co-surfactants (Smix) were mixed in the ratios like 1:0.5, 1:1 and 1:1.5 (w/w). The self-emulsifying properties of the prepared SMEDDS series were visually examined. A pseudo-ternary phase diagram was utilized for the screening of surfactants and identification of the self emulsification region.

After performing the solubility analysis and phase diagram review, components for SEDDS formulation were selected. This was highlighted in **(Table 5 and Figure 1 – 3)**

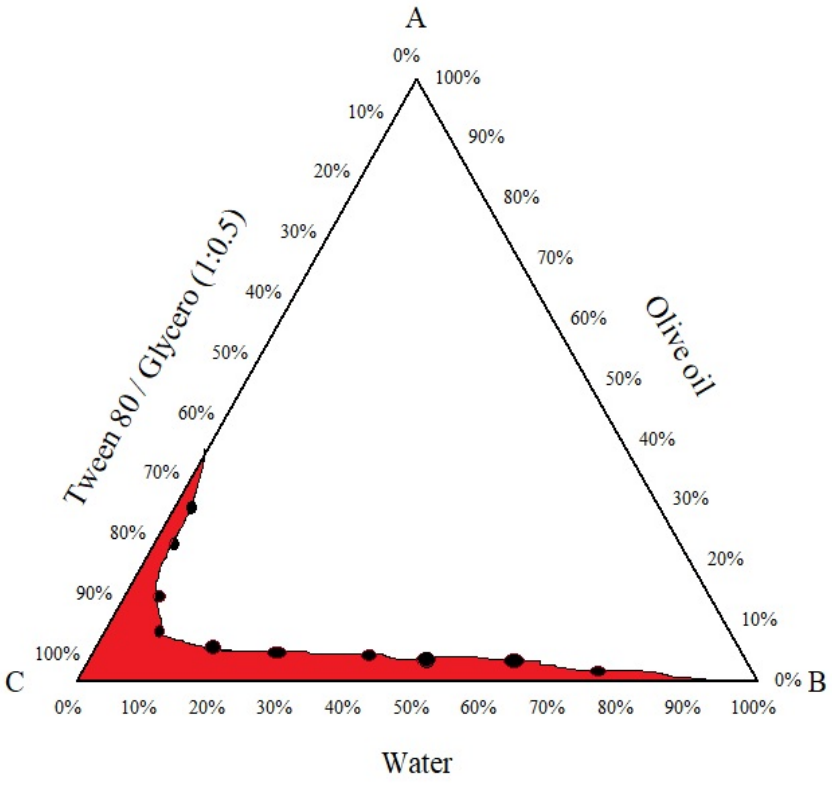

Figure 1: Pseudo ternary phase diagram Shows region of Self emulsification (T80 / Gly; 1:0.5): W

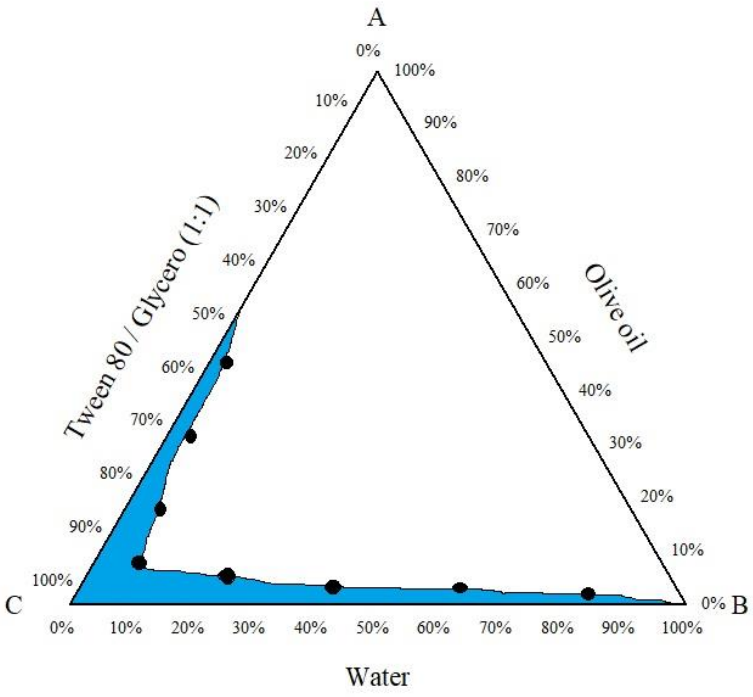

Figure 2: Pseudo ternary phase diagram Shows region of Self emulsification (T80 / Gly; 1:1): W

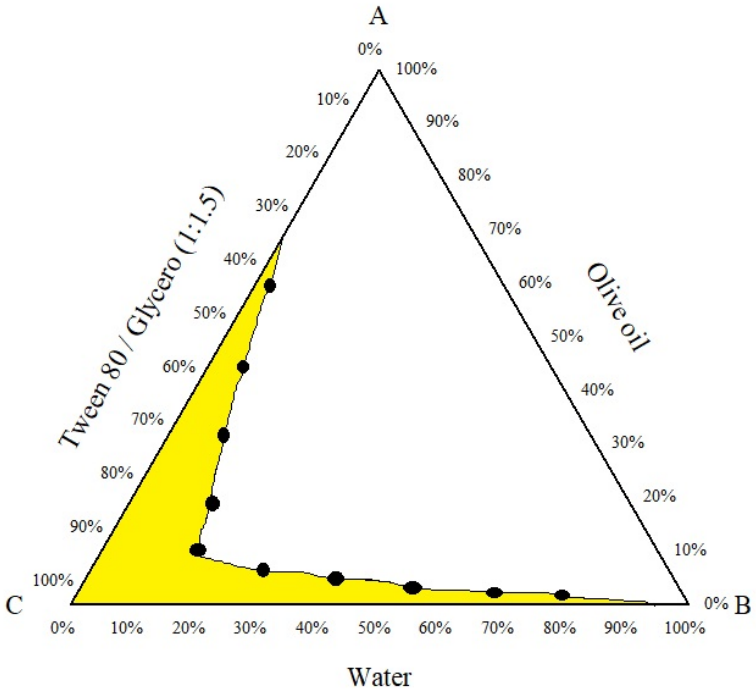

Figure 3: Pseudo ternary phase diagram Shows region of Self emulsification (T80 / Gly; 1:1.5): W

Thermodynamic stability tests: For the elimination of the metastable formulations in minimum possible time from final selection, thermodynamic stability tests were performed. The results of thermodynamic

stability test were given in the **Table 6**. The prepared emulsions were thermodynamically stable systems which are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking.

Table 6: Thermodynamic stability test and dispersion test

Formulation code	Centrifuge	H/C cycle	Freeze Thaw	Disperse Grade	Inference
LSEF1	Pass	Pass	Pass	D	Fail
LSEF2	Pass	Pass	Fail	A	Fail
LSEF3	Pass	Pass	Pass	A	Pass

Dispersibility tests: Dispersibility tests were carried to find the formation of emulsions from the prepared L-SEDDS after oral administration. The results of dispersibility tests are given in the. Majority of the formulations emulsify as soon as they come in contact with dissolution media. The formulations containing surfactants fewer amounts could take longer time to emulsify, because of absence of cosurfactant, formation of interfacial film is rarely achieved. The similar results were observed with higher oil concentration, due to lack of availability of cosurfactant in the formation of interfacial film.

Effect of pH and robustness to dilution: The optimized oil and Smix concentrations are robust to all dilutions with various dissolution media. Robustness to dilution, with excess of water, 0.1M HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4 showed no precipitation or phase separation. There was no significant effect of pH on the optimized formulations LSEF3, was observed, as non-ionic surfactants are less affected by changes in pH and ionic strength compared to ionic surfactants. It confirms the preparations were robust to high dilution and variations in pH.

Experimentation on Globule size: The smallest Globule size observed is 32.32 ± 0.58 nm (LSEF1), while the largest Globule size was obtained for 214.18 ± 2.91nm (LSEF14. Based on globule size, the following quadratic equation will describe the effect of the independent variables:

$$\mathbf{Y_1 = 60.4464 + 29.738\ X_1 - 32.3991\ X_2 - 11.6357\ X_3 - 19.4875\ X1\ X_2 - 22.1125\ X_1\ X_3 + 8.0125\ X_2\ X_3 7.35421\ X_{12} + 18.2967\ X_{22} + 9.47377\ X_{32}}$$

Where Y_1 **is** Globule size **(nm),** X1 is (Sunflower oil), X2 is (Tween 60), X3 is (Glycerol) Results after tests show that Sunflower oil has a positive influence on the size of the globule while the presence of

Tween 60 and Glycerol has a negative effect, so the size of the globule increases with Sunflower oil while it decreases with Tween 60 and Glycerol.

The **180.75 F-value** of the model indicates that the model is appropriate. **P-values** are found to be **0.0001** as P-values less than 0.05 suggest that the model is important.

Fit Statistics: The 0.9616 **Predicted R^2** is in excellent agreement with the 0.9884 **Adjusted R^2** that is, less than 0.2 is the difference. The signal to noise ratio is specified by Adeq Precision.

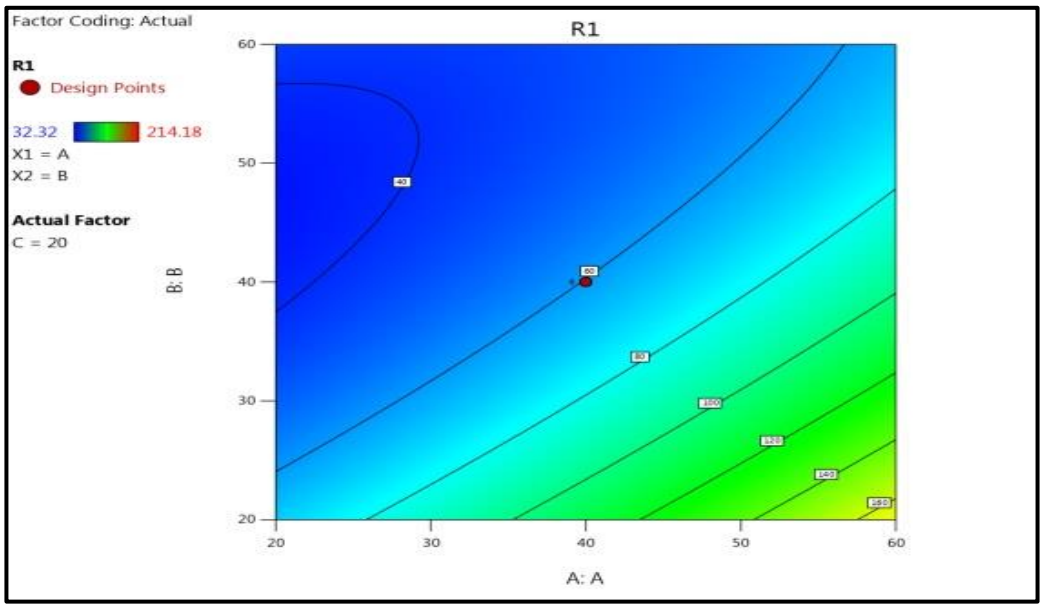

Figure 4.12: Graphs of globule size (nm) Contour plot

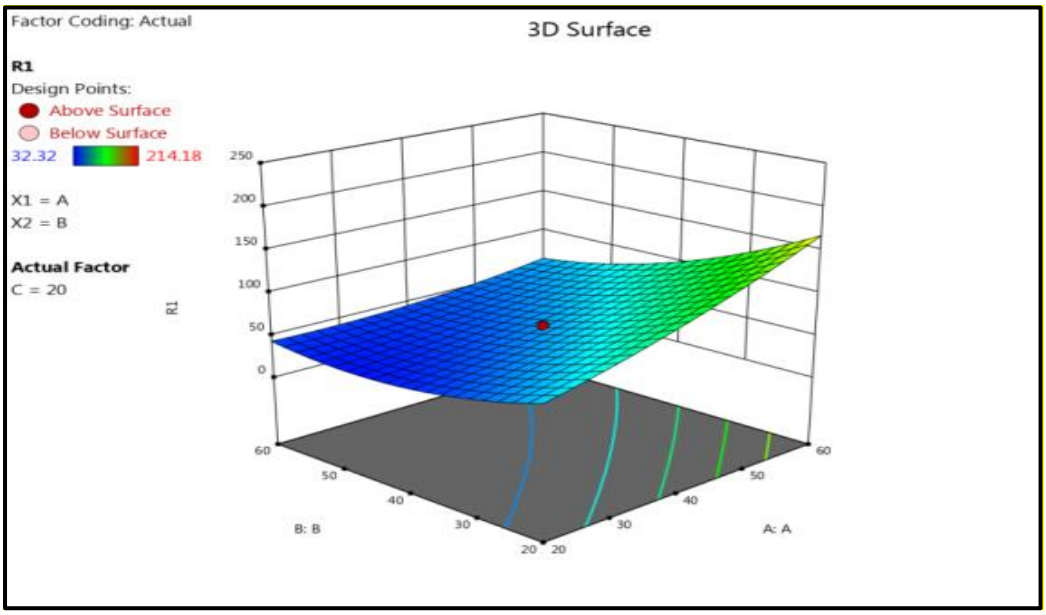

Figure 4.13: Graphs of globule size (nm) 3D Surface Contour plot

Experimentation on Turbidity:

The least turbidity is observed in 17.14±0.23 NTU (LSEF4), while the highest turbidity is observed for 279.13±1.11 NTU (LSEF17). The influence of the independent variables on turbidity will be explained by the following quadratic equation:

$$\mathbf{Y_2 = 32.2875 + 51.2946\ X_1 - 53.5682\ X_2 - 18.7626\ X_3 - 21.8 X_1\ X_2 - 38.075\ X1\ X_3 - 8.875\ X_2\ X_3 + 22.5717\ X_{12} + + 26.0188\ X_{22} + 3.2965\ X_{32}}$$

Where Y_2 **is** Turbidity (NTU) X1 is (Olive oil), X2 is (Tween 80), and X3 is (Glycerol)

Results after experimentation show that Olive oil has a positive effect on the turbidity while Tween 80 and Glycerol presence has a negative effect, for this reason, turbidity increases with Olive oil whereas it decreases with Tween 80 and Glycerol.

The 38.91 F-value model shows that model is important. **P-values are found to be 0.0001** as P-values less than 0.05 suggest that the model is important.

Fit Statistics: The 0.35612 Projected $\mathbf{r^2}$ is in fair agreement with the 0.9723 Modified $\mathbf{r^2}$ the difference is lesser than 0.2. The surface graphs of the 3D response and their corresponding 2D- contour graphs show the effect of independent variables

Optimized formula: The confirmation technique of point prediction is applied for the optimization of lamotrigene formulation. The optimized formula is 40 percent w/w of oil X1 (Olive oil), 40 percent w/w of surfactant X2 (Tween 80), and 20 percent w/w of co-surfactant X3 (Glycerol), which shows a globule size of 76.16 nm and turbidity of 32.28 NTU.

Droplet Size Analysis: 72.34 nm mean droplet size was found, which was very small. After dilution with water, the L-SEDDS were found to be transparent and the preparation was stable for more than one week.

Phase Separation Study: Phase separation analysis indicates that for the subsequent study, during a 2-hour phase a mixture of lamotrigene, glycerol, Olive oil, and Tween 80 has insignificant phase separation.

Self-emulsification time: The assessment of self emulsification property of any L-SEDDS was based on its rate of emulsification, As the L-SEDDS system comes in contact with water, with mild agitation it is completely and quickly dispersed into the medium. The result of the experiment shows that the rate of self emulsification depends on the individual formulation composition and the ratio of surfactant, oil, and co surfactant it consists. Higher the percentage of surfactant system greater the spontaneity of emulsification,

due to excess diffusion of aqueous phase into oil phase causing significant interfacial disruption and discharge of droplet into the bulk aqueous phase. The L-SEDDS self-emulsifying time was 32.15 ± 1.43s.

Determination of turbidity: The turbidity and transmittance of prepared SEDDS were found to 32.28 NTU.

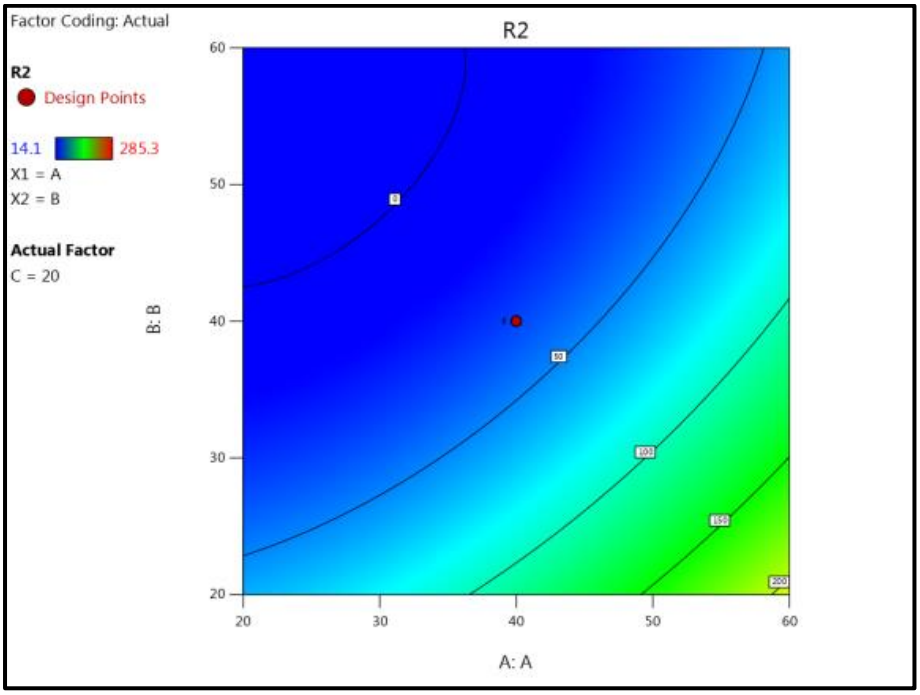

Figure 4.14: Graphs of Turbidity (NTU) Contour plot

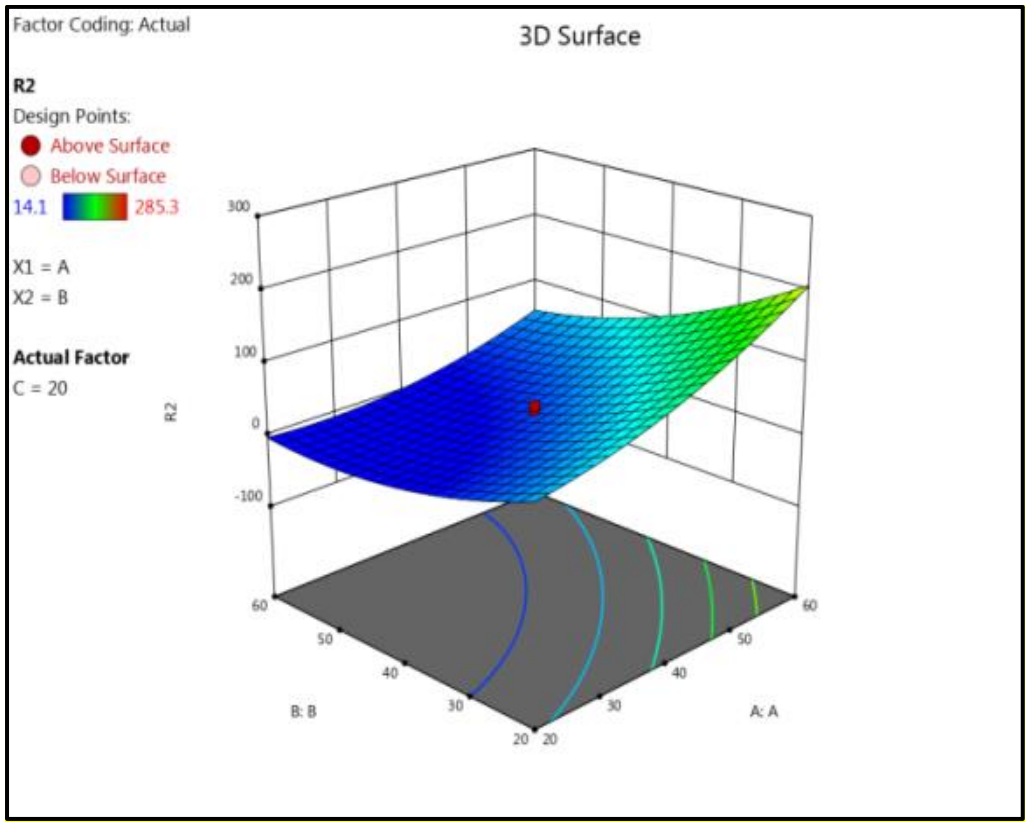

Figure 4.15: Graphs of Turbidity (NTU) 3D Surface Contour plot

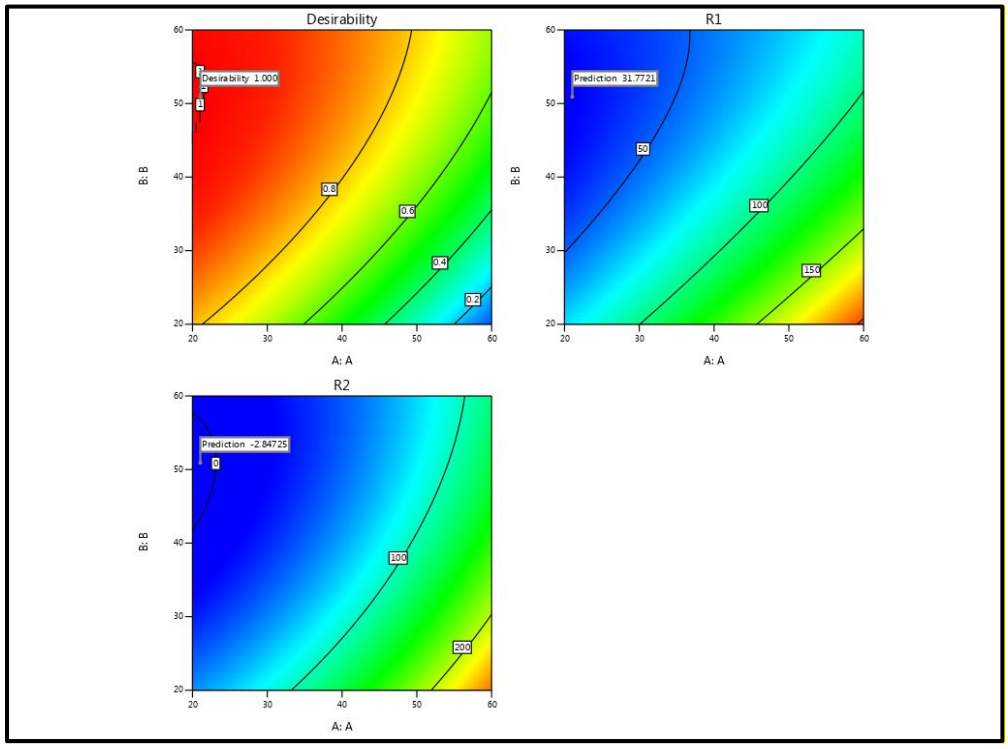

Figure 4.16: Graphs of Desirability

Zeta-Potential Determination: The zeta potential value of the L-SEDDS was found to be - 32.81 mV (LSEF3). This Negative zeta potential value of optimized formulations indicated that the formulation was negatively charged and sufficient repulsive force between emulsion globules was present, due to that an un-coagulated stable system was formed .

Viscosity: The sequence of viscosity of prepared SNEDDS batches are in decreasing order of LSEF3. The viscosity of all the formulations was found in the range of 20.4-28.6 cps and shows Newtonian type of flow characteristics. Results also revealed that the viscosity is directly function of concentration of oils and surfactants used in the formulation.

Refractive index and percent transmittance: The refractive index of the prepared formulation was similar to the refractive index of the water (1.333). In addition, the formulation showed more than 96% percent transmittance. The refractive index and percent transmittance data indicate the formulations were transparent.

Summary and conclusion:

The SEDDS (Self emulsifying drug delivery system) studied solubility in the oil phase is important because less amount of oil is needed for the formation of the micro emulsion, due to the high solubility of the drug in the oily phase. As SEDDS come in contact with water with constant agitation, it turns into o/w emulsion. The system's phase behavior was analyzed using multiple surfactants to co-surfactant ratios. In each category, surfactants and co-surfactants (Smix) were mixed in the ratios like 1:1,1:0.5 and 1:2 (w/w). The self-emulsifying properties of the prepared SMEDDS series were visually examined. A pseudo-ternary phase diagram was utilized for the screening of surfactants and identification of the self emulsification region. Study of dilution was done for the examination of the emulsification and recrystallization of the drug.

The prepared various combination of L-SEDDS formulatons from LSEF1 – LSEF23 and evaluated for various parameters. The experimentation designed on 3^2 factorial methods and the x1, x2, x3 were the formulation variables i.e. oil, surfactant and co-surfactant. These variables reflect the variation on different parameters studied for optimization best formulation. The dilution analysis on preconcentrates of SEDDS has been conducted to access the impact of dilution. The formulation **LSEF3** was more stable since no precipitation or crystallization of the drug occurred. From each phase diagram constructed, different formulations were selected from ME region so that drug could be incorporated into it on the following basis. The prepared emulsions were thermodynamically stable systems which are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking.

Dispersibility tests suggested that majority of the formulations emulsify as soon as they come in contact with dissolution media. The formulations containing surfactants fewer amounts could take longer time to emulsify, because of absence of cosurfactant, formation of interfacial film is rarely achieved. The similar results were observed with higher oil concentration, due to lack of availability of cosurfactant in the formation of interfacial film. There was no significant effect of pH on the optimized formulations **LSEF3**, was observed, as non-ionic surfactants are less affected by changes in pH and ionic strength compared to ionic surfactants. It confirms the preparations were robust to high dilution and variations in pH.

The Y_1 **is** Globule size **(nm),** X1 is (Sunflower oil), X2 is (Tween 60), X3 is (Glycerol) Results after tests show that Sunflower oil has a positive influence on the size of the globule while the presence of Tween 60 and Glycerol has a negative effect, so the size of the globule increases with Sunflower oil while it decreases with Tween 60 and Glycerol. Results after experimentation show that Olive oil has a positive effect on the turbidity while Tween 80 and Glycerol presence has a negative effect, for this reason, turbidity increases with Olive oil whereas it decreases with Tween 80 and Glycerol. The confirmation technique of point prediction is applied for the optimization of lamotrigene formulation. The optimized formula is 40 percent w/w of oil X1 (Olive oil), 40 percent w/w of surfactant X2 (Tween 80), and 20 percent w/w of co-surfactant X3 (Glycerol), which shows a globule size of 76.16 nm and turbidity of 32.28 NTU. After dilution with water, the SEDDS were found to be transparent and the preparation was stable for more than one week. Phase separation analysis indicates that for the subsequent study, during a 2-hour phase a mixture of lamotrigene, glycerol, Olive oil, and Tween 80 has insignificant phase separation. The result of the self emulsification property showed that the rate of self emulsification depends on the individual formulation composition and the ratio of surfactant, oil, and co surfactant it consists. Higher the percentage of surfactant system greater the spontaneity of emulsification, due to excess diffusion of aqueous phase into oil phase causing significant interfacial disruption and discharge of droplet into the bulk aqueous phase. The L-SEDDS self-emulsifying time was 32.15 ± 1.43s. The zeta potential value of the L-SEDDS was found to be - 32.81 mV (LSEF3). This Negative zeta potential value of optimized formulations indicated that the formulation was negatively charged and sufficient repulsive force between emulsion globules was present, due to that an un-coagulated stable system was formed. The viscosity of all the formulations was found in the range of 20.4-28.6 cps and shows Newtonian type of flow characteristics. Results also revealed that the viscosity is directly function of concentration of oils and surfactants used in the formulation. The formulation showed more than 96% percent transmittance and indicated the formulations were transparent in nature.

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