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FORMULATION AND EVALUATION OF SELF-MICRO EMULSIFYINGDRUG DELIVERY SYSTEM OF ELTROMBOPAG OLAMINE FOR ORAL ADMINISTRATION

Ankitkumar Bhagora[1]*, Tora Shah[2] and Jaini Patel[3]

Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur.

***Corresponding Author: Ankitkumar Bhagora**
Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur.

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ABSTRACT
The present work is to formulated and evaluated a self-micro emulsifying drug delivery system (SMEDDS) containing Eltrambopag Olamine (ELT) and also explored the ability of porous Neusilin® US2 capsule as a solid carrier for SMEDDS. SMEDDS formulations of varying proportions of clove oil, tween 80 and PEG 400 were selected and subjected to in-vitro evaluation, including dispersibility studies, droplet size, zeta potential measurement and release studies. The results indicated that the drug release profile of ELT from SMEDDS formulations was statistically significantly higher (p-value < 0.05) than the plain ELT powder. Thermodynamic stability studies also confirmed the stability of the prepared SMEDDS formulations. The optimized formulation, which consists of 12% of clove oil, 44% of tween 80 20% of PEG 400 was loaded into directly filled liquid loadable capsule of Neusilin® US2 by simple adsorption method. The droplet size of the microemulsion formed by the optimized formulation was 245.7 ± 1.6 nm, and the droplets were spherical in shape. The % transmittance, zetapotential and viscosity of optimized formulation is 99.22%, -26.34 mv and 12.33 cps respectively. SMEDDS adsorbed powder also evaluated for DSC, FTIR and XRD and compare with pure drug. In vitro release studies performed in comparison topure drug and it reveals that the SMEDDS loaded with ELT capsule showed about 3 folds improvement in release of drug. Overall, incorporation of ELT in SMEDDS, either liquid or solid, resulted in improved solubility and dissolution rate compared to pure ELT. This study indicates that a liquid and solid SMEDDS is a strategy for solubility enhancement in the future development of orally delivered dosage forms.

KEYWORDS: SMEDDS, Eltrambopag Olamine (ELT), Neusilin® US2, XRD, FTIR.

INTRODUCTION TO DRUG DELIVERY SYSTEM

Self-micro emulsifying systems (SMEDDS): Among the lipid-based systems, Self-emulsifying drug delivery systems (SEDDS) is a promising strategy to improve the bioavailability of poorly water- soluble compounds. SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. The size of the droplet formed is between 100 and 300 nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro-emulsions with a droplet size of less than 50 nm.[1,2]

Mechanism which increases drug absorption by SMEDDS include: in vivo solubilization of drug, increase in gastric residence time of drug, Promotion of intestinal lymphatic transport of drug, Affecting intestinal permeability.[3]

Advantages of SMEDDS are: Increase bioavailability by decrease in dose, decrease in foodeffects, prolong release of medicament, can be for both liquid and solid dosage forms, overcome of the irritation caused by the contact between drug and the wall of GIT, Low energy consumption, Easy manufacturing process, less time required, Hydrophobic drugs can be absorbed by stable plasma-time profile, Drugs which can be degraded by GIT can be used.

SMEDDS are composed of lipids, surfactants, co solvents and co surfactants and drug candidate.[3] The evaluation technique of SMEDDS include assay, globule size analysis, Zeta Potential Measurement, Visual evaluation, %Transmittance, *In-vitro* Dissolution Time OR Dispersibility Test, Dilution studies, Refractive index, Stability study.

Introduction to Eltrambopag Olamine (ELT)[4-6]

Eltrambopag Olamine is a red powder. It is a Thrombopoietin Receptor Agonists used to treat low platelet levels in people who have a certain blood disorder called chronic immune (idiopathic) thrombocytopenia purpura (ITP) or who have chronic hepatitis C. It may also be used to treat people with a

certain blood disorder (aplastic anemia). It possesses molecular weight of 564.643g/mol. It binds and stimulates the platelet thrombopoietin receptor (TPO-R or CD110)-a member of the hematopoietin receptor super family. Activation of TPO-R leads to the proliferation and differentiation of megakaryocytes, thereby increasing platelets. TPO-R Agent also Stimulate platelet production in the bone marrow. It is poorly soluble in water, methanol and ethanol. Peak absorption of ETO occurs around 2-6 hour following oral administration, and the total oral absorption of drug-related material following a 75 mg dose was estimated to be at least 52%. It is eliminated primarily via the feces (59%) along with 31% being renally excreted.

MATERIALS AND METHODS

Materials: The active drug Eltrambopag Olamine was obtained from Nicholas Piramal Pharmaceutical. Oils (Oleic acid, Transcutol, Coconut oil, Captex 300, Capmul, Castor oils, IPM, Labrafac, Selected Edible oils) were procured from Gattefosse, Surfactants (Tween 80, Tween 60, Span 60, Span 80, Cremophore RL40, SLS), Co Surfactants (IPA, PG, PEG 400, PEG 600) were procured from Starcoin chemicals and Aerosil, Cab-O-Sil, Neusilin, etc. were procured from Torrent research center.

Methods

Standard calibration curve of ELT in methanol: Eltrambopag Olamine (10 mg) was dissolved in 100 ml of methanol to obtain a solution (100µg/ml)

Preparation of stock solution: The standard solution of ELT was subsequently diluted with methanol to obtain a series of dilutions containing 5, 10, 15, 20, 25 and 30 µg/ml concentrations. The absorbance of each solution was measured at 468 nm against methanol as a blank.

Standard calibration curve of ELT in PBS 6.8+2% SLS: Preparation of phosphate buffer pH 6.8: Potassium dihydrogen phosphate (11.45 gm) and sodium hydrogen phosphate (28.80 gm) were dissolved in sufficient water to produce 1000 ml and pH was adjusted.

Preparation of standard stock solution: The stock solution of ELT (5µg/ml) was prepared in the phosphate buffer solution (pH 6.8+2% SLS) and prepared solution was scanned for absorbance between 400-800 nm. The spectrum was found out using spectrophotometer (shimadzu UV-1800). The standard stock solution of ELT was subsequently diluted with buffer 6.8 to obtain a series of dilutions containing 2,4,6,8,10,12,14 and 16 µg/ml of ELT. The absorbance of each solution was measured at 468 nm against PBS 6.8 +2% SLS solution as a blank.

Drug excipients compatibility study: A 10mg of ELT was mixed with 3ml of oil, surfactant, co- surfactant. The mixture was stored in vials for 1 month at room temperature and was evaluated for transparency and drug content for one month.

Pre-Compression Parameters: Angle of repose

To find out the flow properties of prepared powder, funnel method was used. In this method height of funnel was fixed at distance of 2 cm from the bottom of the surface. ELT powder was allowed to flow through the orifice of funnel to form a heap. A circle was drawn and diameter (D) and radius (D/2) of the pile was measured and the angle of repose was calculated.

The angle of repose was calculated using the following equation.

$$\tan \theta = H / R$$

Where, θ = Angle of repose, H = Height of the tip from surface, R = Radius of the heap (D/2)

Bulk Density: Accurately weighed powder was poured in measuring cylinder. The volume was noted which called as bulk volume (Vo). Bulk density was calculated by using the following formula. From this, bulk density was calculated using the following formulae.

$$\eta b = M / Vo$$

Where, ηb = Bulk Density, M = Weight of powder (gm), Vo = Initial volume of powder in cm^3

Tapped Density: Known quantity of powder (M) was filled in the measuring cylinder and the powder was tapped for 100 taps using Tapped density apparatus. The volume of powder noted as (Vt), tapped density was calculated using the following formula

$$\eta t = M / Vt$$

Where, ηt = Tapped Density, Vt = Final tapped volume of powder in cm^3Porosity of powder was calculated from bulk density and tapped density.

Primary screening of Components for L-SMEDDS: Solubility of ELT was checked in various oils (olive oil, Sunflower oil, Clove oil, Oleic acid, Capmul MCM), various surfactants (Tween 80, Tween 20, labrasol, Cremphor RH 40), and different co-surfactants (PEG 400, Propylene glycol, captex 200, peceol). A 3ml of each was taken in stopped vials of 5 ml and excess amount of drug was added to eachvial. Vials were placed on magnetic stirrer for 72 hours followed by centrifugation at 10000 RPM. The supernatant was filtered through 0.45 µm and then absorbance was measured in UV spectrophotometer at 468nm. Adequately diluted sample of oil, surfactant, and co-surfactant were taken as blank. The components in which drug showed highest solubility were selected and used for further study.

Construction of Pseudo Ternary Phase Diagram: Chemix software was employed to select maximum area of mono phase. Pseudo ternary phase diagrams were constructed to obtain microemulsion existence area. The

pseudo ternary phase diagrams were constructed by oil, Smix and water using water titration method at room temperature. The procedure consists of preparing solutions containing different ratio of Smix by weight such as 1:1, 2:1, 3:1, etc. Each of these solutions used for preparing a mixture containing oil and Smix in the ratios by weight: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4,7:3, 8:2, 9:1. After each addition of water, the mixture was observed for its appearance (turbid or clear). Turbidity of the samples indicates formation of a coarse emulsion. A clear isotropic solution indicates the formation of a micro emulsion. The formation of micro emulsion regions was monitored visuallyfor turbidity–transparency–turbidity.

Preparation of ELT L-SMEDDS: The ratio of surfactant to co-surfactant was optimized from the phase diagram with maximum area. Surfactant and co-surfactant were weighed accurately and vortexed for 5-10 minutes. Smix was placed in an oven at 50°C for 1 hour. The amount of oil was added at different ratio with respect to Smix. The mixture was mixed by vortex shaker for 5-10 minutes. Place inoven at 50°C for 1 hour to form an isotropic mixture. Add drug to these isotropic formulations and mix by vortex shaker until a clear solution is obtained.

The developed ELT L-SMEDDS was evaluated for organoleptic parameter, transmittance, refractive index, pH, type of emulsion, viscosity, droplet size, size distribution, zeta potential measurement.

Formulation and characterization of ELT S-SMEDDS: The optimized ELT L-SMEDDS formulation was transformed into free-flowing powder by adsorption of it onto solid carriers. The solid carrier was optimized based on free-flowing property and good compressibility. Various solid carriers including Neusilin US2, Aerosil and Lactose were used as an adsorbent. The conversion process involved addition of L-SMEDDS onto carriers under continuous mixing in a blender. The powder was dried and kept aside for further trials. The composition of S-SMEDDS is shown in Table.

Fourier Transform Infrared (FTIR) spectroscopy: FTIR spectroscopy of drug was carried out on FTIR spectrophotometer (Jasco FTIR-4700, Japan) for identification. One to two mg sample was mixedwith one hundred mg of KBr powder. This mixture was grounded for 2-3 minutes using mortar and pestle. The mixture was taken in the sample holder and measured the IR spectra in the range between 4000 cm-1 - 400 cm-1.

Differential Scanning calorimetry: A DSC technique is used to confirm the structural changes indrug. The DSC thermograms of bulk drug powder and S-SMEDDS was performed. Pure drug TBZ and developed TBZ S-SMEDDS were placed in sealed aluminium pan. An empty pan served as a reference. The sample were heated between 50-300˚C on a DSC. Heating Rate of 10˚C/min with nitrogen supply. **X-ray Diffraction (XRD):** X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. X-ray Diffraction is based on constructive interference of monochromatic X-rays and acrystalline sample. These X-rays generated by a cathode ray tube are filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interference obtained is evaluated using bragg's law to determine various characteristics of the crystal orpolycrystalline material. X ray study was performed for Pure drug TBZ and developed TBZ S-SMEDDS.

Density and filling of S-SMEDDS into capsules: The final batch of ELT S-SMEDDS was submitted for checking bulk density and finally packed into HGC (size 0) using manual capsule filling machine.

Weight variation: Capsules (10) containing SMESDDS were weighed and the content was removed. The capsule body and cap were singly weighed and weight variation was found.

Lock length: The lock length was found using digital Vernier calipers and average of 10 capsules was noted.

Drug Content: Ten capsules were individually weighed and crushed. A quantity of powder equivalent to the mass of one capsule was extracted in buffer (PBS 6.8). The solution was filtered through 0.45 □m membrane. The drug content was determined by UV spectrophotometer at a wavelength of 468 nm after a suitable dilution against blank.

***In vitro* drug release study:** In vitro release studies of different formulations were performed according to USP apparatus II, paddle method. Paddle speed was maintained at 50 rpm. The dissolutionmedia was PBS 6.8 + 2% SLS (900 mL). Samples (10mL) were collected at predetermined time intervals (2, 4, 6, 8, 10, 15, 20 minutes) and replaced with equal volume of fresh medium, filtered through a 0.45 µm filter and analyzed with a UV-Visible spectrophotometer at 468 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved.

Stability study: The optimized batch of S-SMEDDS loaded capsule was submitted to stability chambers (Model-TH 90 S, Thermolab, India) for short term stability study as per ICH guidelines (40 ± 2°C and 75 ± 5% RH; 1 month). The capsules were packed in flint vials and sealed hermetically with rubber plugs and aluminum caps. Samples were taken out at 7th day, 14th day and 28th day and checked for different performance and physicochemical parameters.

RESULT AND DISCUSSION

The reported melting point values for was in the range of 242°C-244°C which was in agreement with literature.

The λmax showing maximum absorbance was found to be 468nm. Calibration curve of ELT was taken in methanol. Calibration data of ELT in methanol is shown in Table. The linearity ranges (5-30 µg/ml), regression Equation (y=0.0269x+0.0114) were described in Figure. The regressioncoefficient (0.997) indicated suitability of the method.

The observation of physical mixture of ELT+excipients is shown in Table. The results indicate stable characters of ELT with proposed excipients. For selecting the appropriate ME components, solubility of ELT was estimated in various oils, surfactants and co-surfactants. They were selected on the basis of higher solubility. The highest solubility of ELT was found in Clove oil (68.41mg / 3 mL) ascompared to other oils. So, Clove oil was used for the preparation of SMEDDS. The highest solubility of ELT was found in Tween 80 (54.52 mg /3 mL) as compared to other surfactants. So, Tween 80 was used for the preparation of SMEDDS. The highest solubility of ELT was found in PEG 400 (80.27 mg/3 mL) as compared to other co- surfactants. So, PEG 400 was used for the preparation of SMEDDS.

In order to obtain an appropriate concentration range of the components of microemulsion, pseudo ternary phase diagram was constructed for different Smix ratio viz.1:1, 1:2, 1:3, 2:1, 2:3, 3:1 and 3:2 as in shown in following Tables. The Smix ratio which provided stable and clearer microemulsion was selected for further study. With the help of phase diagram, relationship between the phase behavior of its mixture and components could be explained.

The results of various parameters of ELT L-SMEDDS are shown in Table. The average globule size of ELT L-SMEDDS was found to be 245.62 nm. The globule size distribution graph of formulation is shown in figure. The satisfactory globule size helps in dissolution and it is also suitable for better absorption. The polydispersity index (PDI) value of final L-SMEDDS was found to be 0.164 respectively. Polydispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of polydispersity, the lower is the uniformity of the droplet size in the formulation. Zeta potential was found to be -26.34 mv. This confirms physical stability and no agglomeration.

Out of tried solid carriers, Batch E1 having Neusilin US2 as a carrier showed acceptable flowability (Angle of Repose: 27.34°Rad). So, in further trials, solid SMEDDS comprised of CSD was used.

Studies of infrared spectra of pure drug, raw materials were conducted with an IR spectrophotometer (Jasco FT-IR 4700) using the KBr disc method. The samples were diluted with KBr. The characteristics FTIR peaks of ELT was found at 3025 cm-1 (O-H group), 1502.76 cm-1 (N-O group) and 681.713 cm-1 (C-Br) corresponding to its core chemical groups in figure 16. Similar peaks were retained in FTIR spectrum of ELT S-SMEDDS indicating no chemical modification of drug and confirming chemical stability. The peak appeared at 250-256°C corresponds to drug's melting point, which was found to be disappeared in S-SMEDDs. This confirms that drug is converted into amorphous form. The intense peak due to drug's crystalline nature is shown figure, which is lost in next figure. This supports the existence of amorphous form of drug in S-SMEDDS.

The bulk density of S SMEDDS was 0.571 gm/cm^3. There was no significant weight variation and all capsules were passed through the test of weight variation. The lock length value of size 0 Capsule was 20.4 mm. The average drug content was 99.56% for develop capsule. In vitro drug release showed that pure drug was not soluble in pH 6.8 phosphate buffer, but when drug is inserted in Liquid SMEDDS it was dissolved easily and giving higher dissolution rate in LSMEDDS than pure drug.

The results of stability study are shown in Table. The data indicate that the formulation is stable in subjected conditions of temperature and humidity.

Table 1: Selection of solid carriers for S-SMEDDS formulation.

Ingredients	E1	E2	E3
Neusilin US2	12 gm	-	-
Aerosil	-	12 gm	-
Lactose	-	-	12 gm
L-SMEDDS	30 mL		

Table 2: Absorbance data of ELT in methanol.

CONCENTRATIONS (µg/ml)	ABSORBANCE (Mean ±SD)
0	0
5	0.165±0.0041
10	0.286±0.0037
15	0.416±0.0040
20	0.529±0.0035
25	0.682±0.0037
30	0.838±0.0060

Table 3: Absorbance data of ELT in pH 6.8+2%SLS.

CONCENTRATION (µg/ml)	ABSORBANCE (Mean ±SD)
0	0
2	0.192 ±0.0052
4	0.344 ±0.0037
6	0.485 ±0.0035
8	0.608 ±0.0043
10	0.767 ±0.0030
12	0.891 ±0.0047

Table 4: Results of Pre-formulation characterization of drug.

Properties	Parameter	Observation
Organoleptic properties	Colour	Red fine powder
	Odour	No characteristic odour
	Taste	Bitter taste
Solubility	Aqueous solubility	Insoluble in water (0.00729 mg/ml
	Non-Aqueous solubility	Soluble in methanol, dichloromethane (20 mg/ml), acetone, ethanol (20 mg/ml)
Physical properties	Melting point (ºC)	242-244 ºC (Determined by capillary method)
Derived properties	Bulk density (gm/ml)	0.321
	Tapped density (gm/ml)	0.587
	Flow property	41.50º
	Porosity	54.68%
	Hausner's ratio	1.30
Assay	Percentage drug content	99.55%

Table 5: Results of drug excipients compatibility study.

Parameter	Beforestorage	Observation after 1 month storage at		
		Room temperature	Controlled room temperature (25^0C and 60 ± 5%RH)	Higher temperature (45^0C and 75 ±5%RH)
Colour	White	No change	No change	No change
Odour	Characteristic	No change	No change	No change
Degradation products (visual)	No	No	No	No
Physical state	Solid	Solid	Solid	Solid
Drug content	98.94%	98.56.%	99.36.%	98.86%
Any other sign of instability	No	No	No	No

Table 6: Solubility of ELT in various oil, surfactant and co-surfactant.

FORMULATION COMPONENTS		SOLUBILTY (mg/3ml)
Oils	Olive Oil	10.4
	Sunflower Oil	12.1
	Clove Oil	68.41
	Oleic Acid	41.32
	Capmul MCM	10.17
Surfactants	Tween 80	54.52
	Tween 20	40.23
	Labrasol	63.61
	Cremophor RH 40	47.05
Co-surfactant	PEG 400	80.27
	PG	71.26
	Captex 200	10.24
	Peceol	17.37

Table 7: Components for Pseudo Ternary Phase Diagram at Smix ratio 1:1.

Formulation code	Oil:Smix	OIL	Smix	Water
F1	1:9	12.16	66.84	21.00
F2	2:8	18.74	60.16	21.10

F3	3:7	28.79	57.50	16.71
F4	4:6	36.72	52.52	10.76
F5	5:5	45.10	43.11	11.73
F6	6:4	50.48	37.70	11.82
F7	7:3	61.61	29.35	9.04
F8	8:2	70.24	22.04	7.72
F9	9:1	81.66	15.10	3.24

Table 8: Components for Pseudo Ternary Phase Diagram at Smix ratio 1:2.

Formulation code	Oil: Smix	Oil	Smix	Water
F10	1:9	14.62	79.125	6.25
F11	2:8	25.20	71.60	3.20
F12	3:7	33.27	63.51	3.22
F13	4:6	40.07	53.68	6.25
F14	5:5	45.88	47.87	6.25
F15	6:4	52.04	38.87	9.09
F16	7:3	66.53	30.25	3.22
F17	8:2	70.59	26.19	3.22
F18	9:1	79.65	17.13	3.22

Table 9: Components for Pseudo Ternary Phase Diagrammatic Smix ratio 1:3.

Formulation code	Oil: Smix	Oil	Smix	Water
F19	1:9	17.12	79.65	3.23
F20	2:8	25.06	71.70	3.24
F21	3:7	31.20	62.55	6.25
F22	4:6	38.88	52.00	9.12
F23	5:5	43.14	45.10	11.76
F24	6:4	50.48	37.76	11.76
F25	7:3	60.61	30.3	9.09
F26	8:2	69.19	21.72	9.09
F27	9:1	79.12	14.60	6.28

Table 10: Components for Pseudo Ternary Phase Diagramat Smix ratio 2:1.

Formulation code	Oil: Smix	Oil	Smix	Water
F28	1:9	9.40	48.20	42.4
F29	2:8	16.86	54.60	28.54
F30	3:7	30.60	57.64	11.76
F31	4:6	36.88	57.00	9.12
F32	5:5	44.46	46.45	9.09
F33	6:4	53.69	40.06	6.25
F34	7:3	61.5	32.25	6.25
F35	8:2	73.59	25.19	3.22
F36	9:1	81.65	15.13	3.22

Table 11: Components for Pseudo Ternary Phase Diagram at Smix ratio 2:3.

Formulation code	Oil: Smix	Oil	Smix	Water
F37	1:9	15.12	81.65	3.23
F38	2:8	21.71	69.2	9.09
F39	3:7	30.5	60.5	9.0
F40	4:6	35.77	52.47	11.76
F41	5:5	45.12	43.12	11.76
F42	6:4	54.01	36.9	9.09
F43	7:3	62.00	31.75	6.25
F44	8:2	71.31	22.40	6.29
F45	9:1	81.64	15.13	3.23

Table 12: Components for Pseudo Ternary Phase Diagram at Smix ratio 3:1.

Formulation code	Oil: Smix	Oil	Smix	Water
F46	1:9	12.9	70.44	16.66
F47	2:8	21.07	67.17	11.76
F48	3:7	31.31	59.6	9.09
F49	4:6	38.88	52.03	9.09
F50	5:5	47.88	45.87	6.25
F51	6:4	55.69	38.06	6.25
F52	7:3	63.5	30.25	6.25
F53	8:2	71.58	25.19	3.23
F54	9:1	81.65	15.12	3.23

Table 13: Components for Pseudo Ternary Phase Diagram at Smix ratio 3:2Table 13.2: ANOVA for Quadratic model (Sphericity).

Formulation code	Oil: Smix	Oil	Smix	Water
F55	1:9	14.15	76.76	9.09
F56	2:8	23.5	67.41	9.09
F57	3:7	31.3	59.61	9.09
F58	4:6	38.05	53.7	6.25
F59	5:5	47.85	45.9	6.25
F60	6:4	53.69	40.06	6.25
F61	7:3	63.5	30.25	6.25
F62	8:2	71.58	25.19	3.23
F63	9:1	81.64	15.13	3.23

Table 14: Results of TBZ L-SMEDDS.

No.	Parameter	Value
1.	Organoleptic parameter	Blue tint
2	Transmittance	99.22%
3	Refractive Index	1.16
4	pH	6.8
5	Type of Emulsion	W/O
6	Viscosity	12.33 cps
7	Zeta potential	-26.34 mv

Table 15: In vitro drug release in PBS 6.8 of (ELT and Capsule).

Time(minutes)	% Of drug release in PBS 6.8	
	Pure drug	Capsule
0	0	0
2	12.54	38.14
4	29.46	79.63
6	30.74	83.41
8	32.14	90.31
10	30.74	98.41

Table 16: Results of stability study.

Parameters	Capsule			
	Initial	7^{th} Day month	14^{th} Day	28^{th} Day
Assay (%)	99.14±0.072	98.96±0.023	99.63±0.047	99.27±0.031
Physical degradation	No	No	No	No
%Q10	98.41	99.24	98.23	99.14

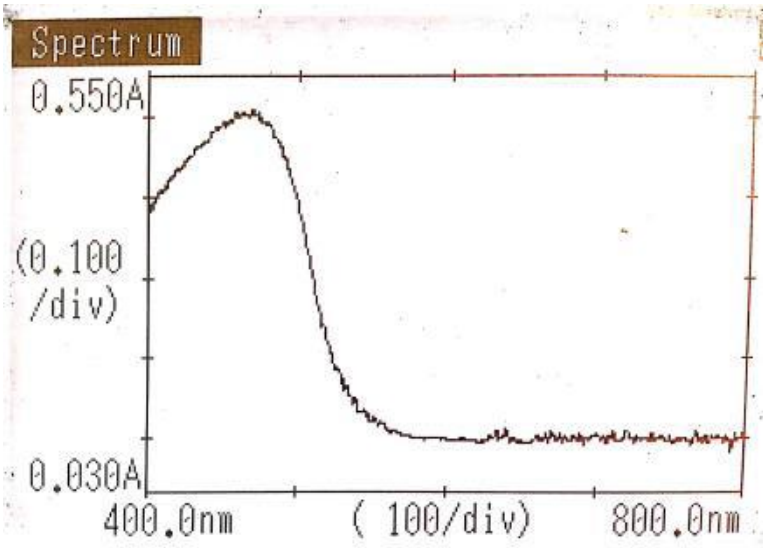

Figure 1: UV Absorption spectra of Eltrambopag Olamine.

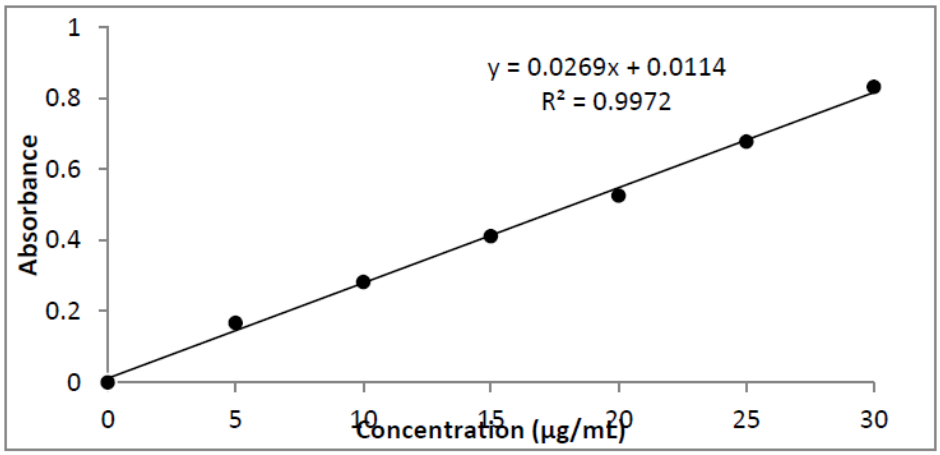

Figure 2: Calibration Curve of ELT in methanol.

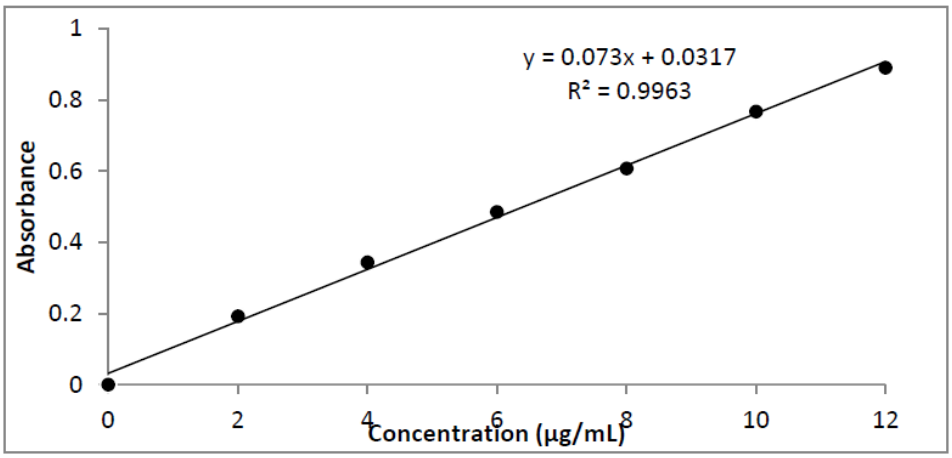

Figure 3: Calibration curve of ELT in PBS pH 6.8 + 2% SLS.

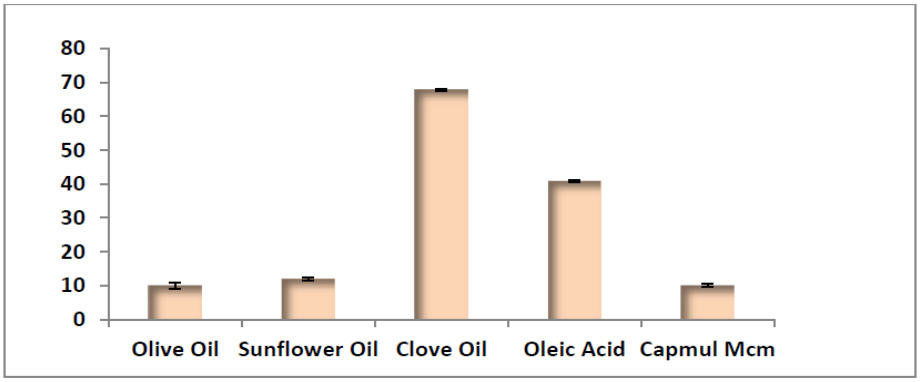

Figure 4: Solubility of ELT in oils.

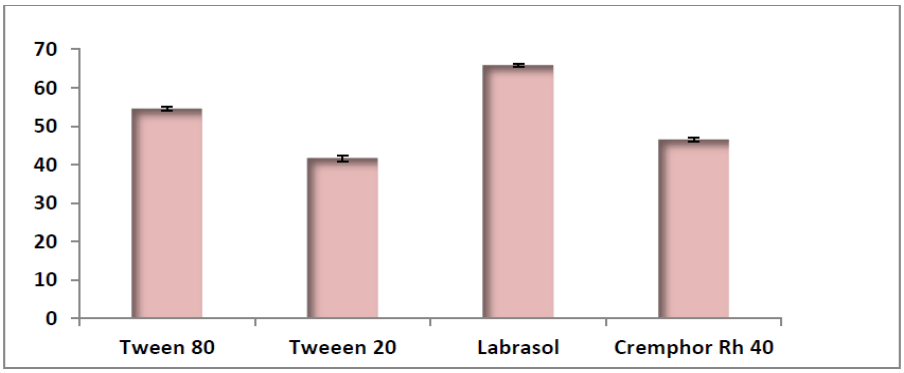

Figure 5: Solubility of ELT in Surfactants.

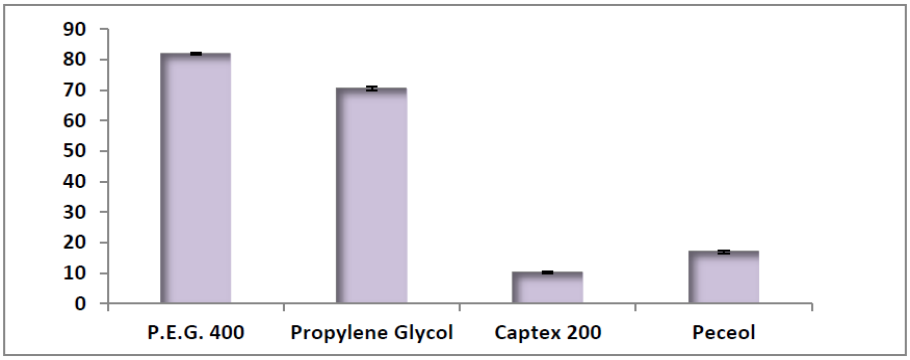

Figure 6: Solubility of ELT in Co Surfactants.

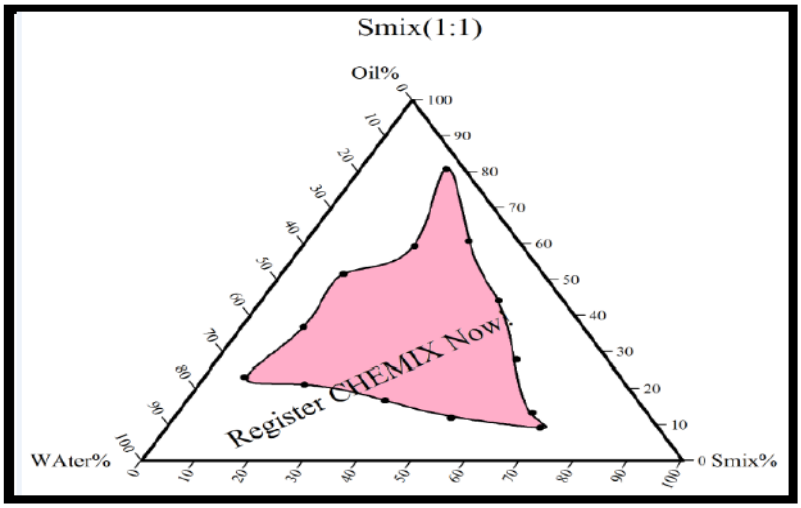

Figure 7: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 1:1 Oil:Smix ratios.

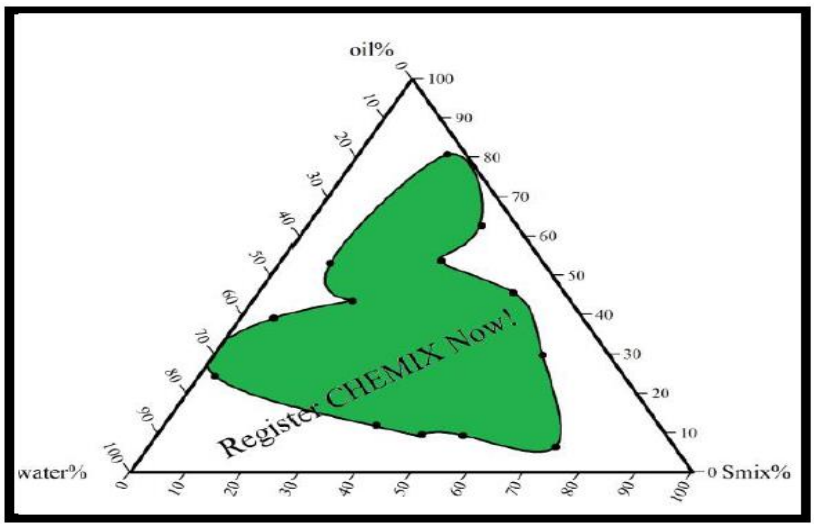

Figure 8: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 1:2 Oil:Smix ratio.

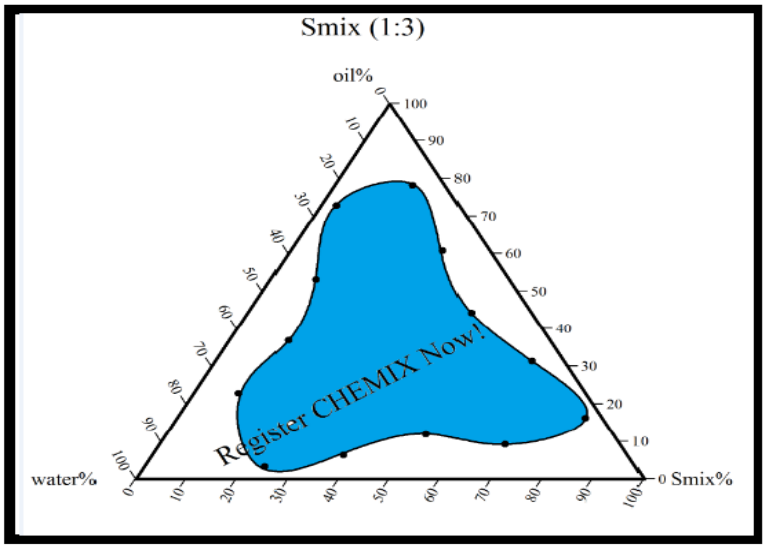

Figure 9: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 1:3 Oil:Smix ratio.

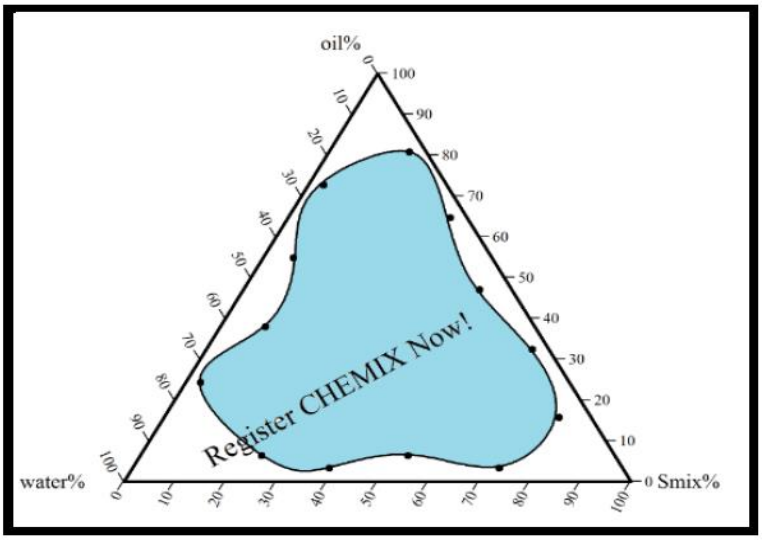

Figure 10: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 2:1 Oil: Smix ratio.

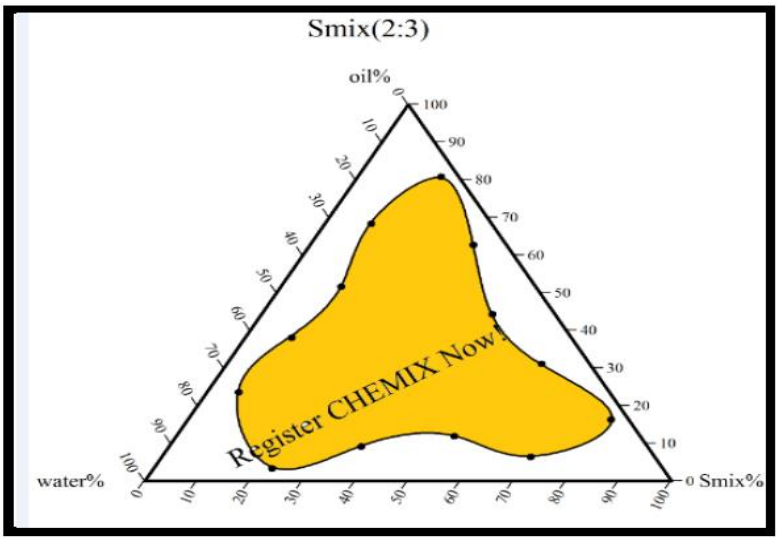

Figure 11: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 2:3 Oil:Smix ratios.

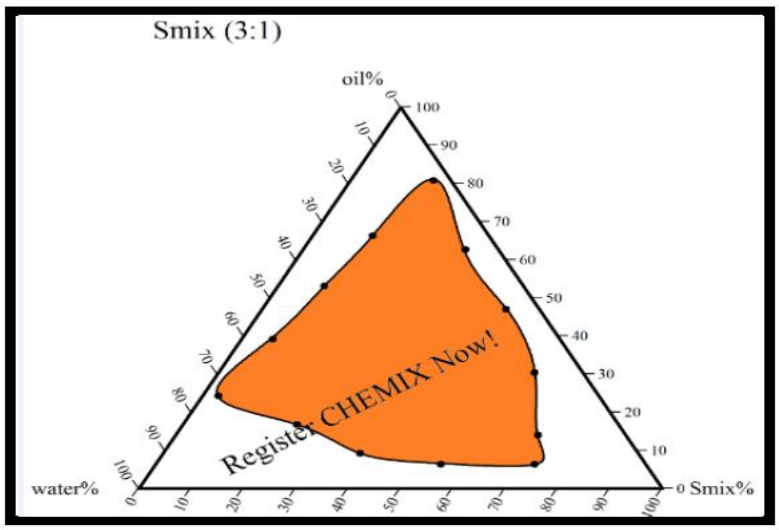

Figure 12: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 3:1 Oil: Smix ratio.

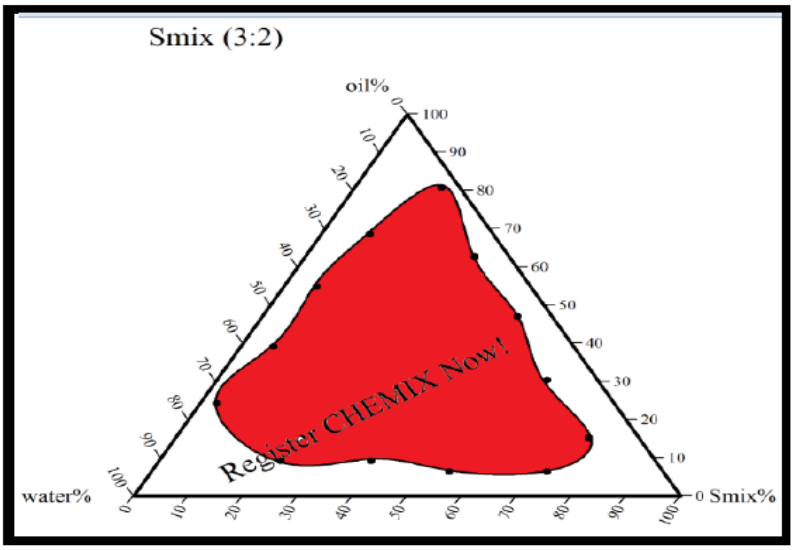

Figure 13: Pseudo-ternary phase diagrams of ELT loaded MEs composed of Oil, Smix and waterat 3:2 Oil:Smix ratio.

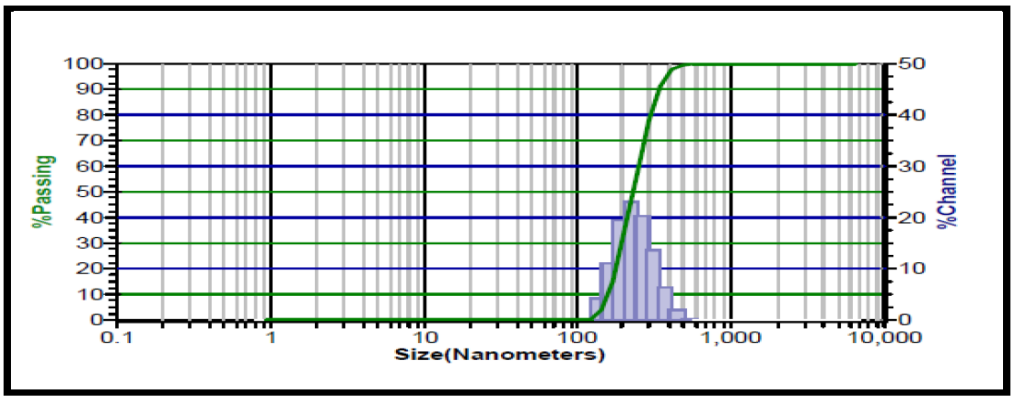

Figure 14: Globule size graph of batch F35.

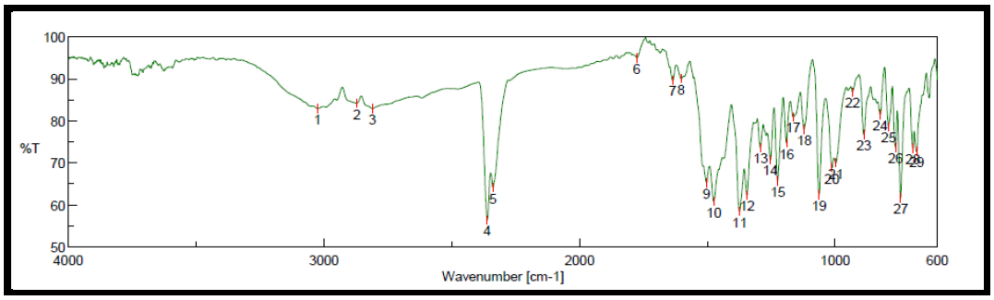

Figure 15: FTIR Spectra of ELT.

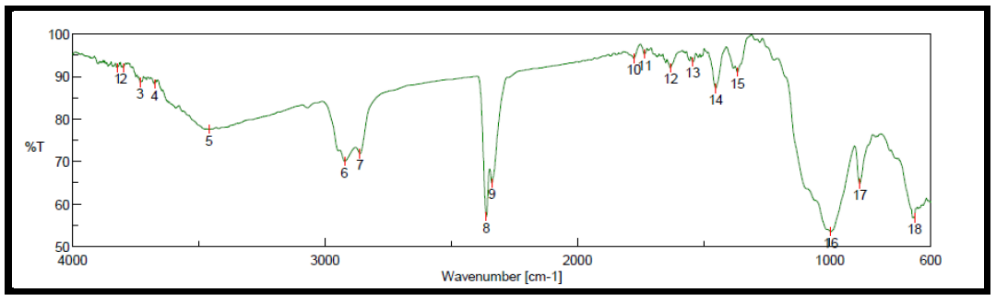

Figure 16: FTIR Spectra of ELT S-SMEDDS.

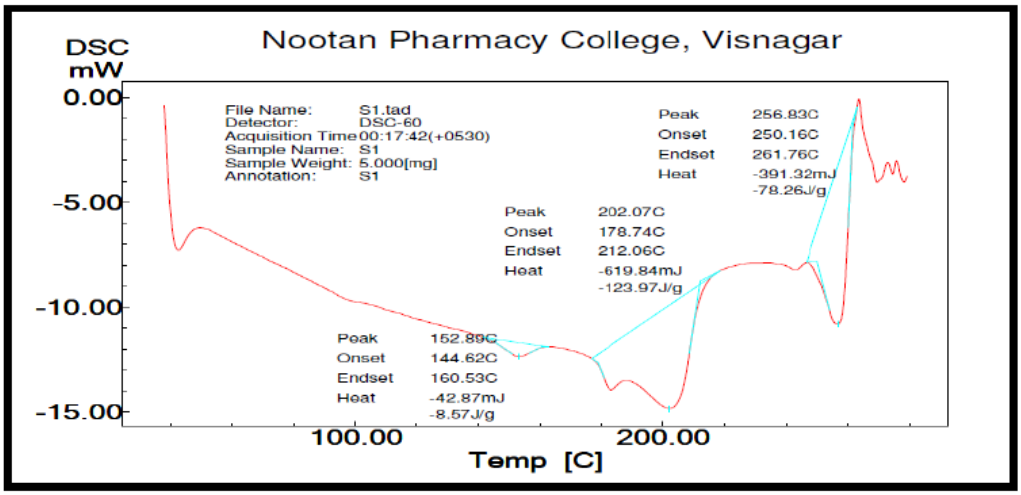

Figure 17: DSC graph-1 of pure drug.

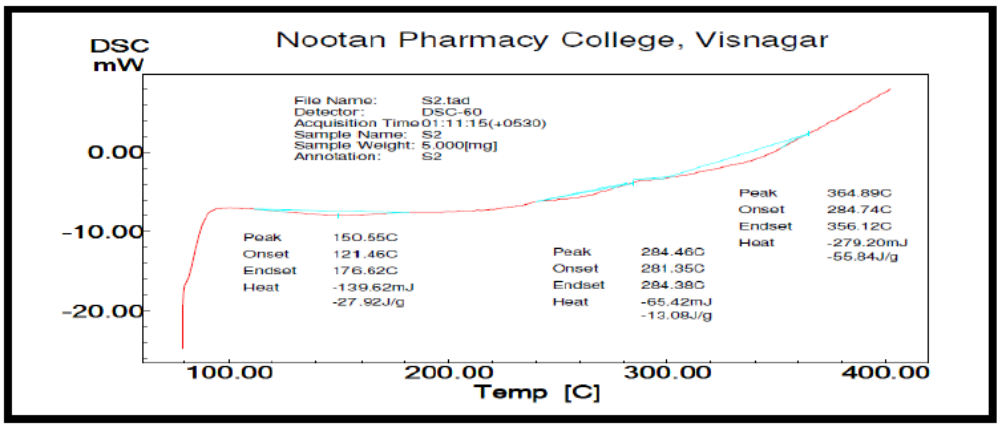

Figure 18: DSC graph-2 of S-SMEDDS.

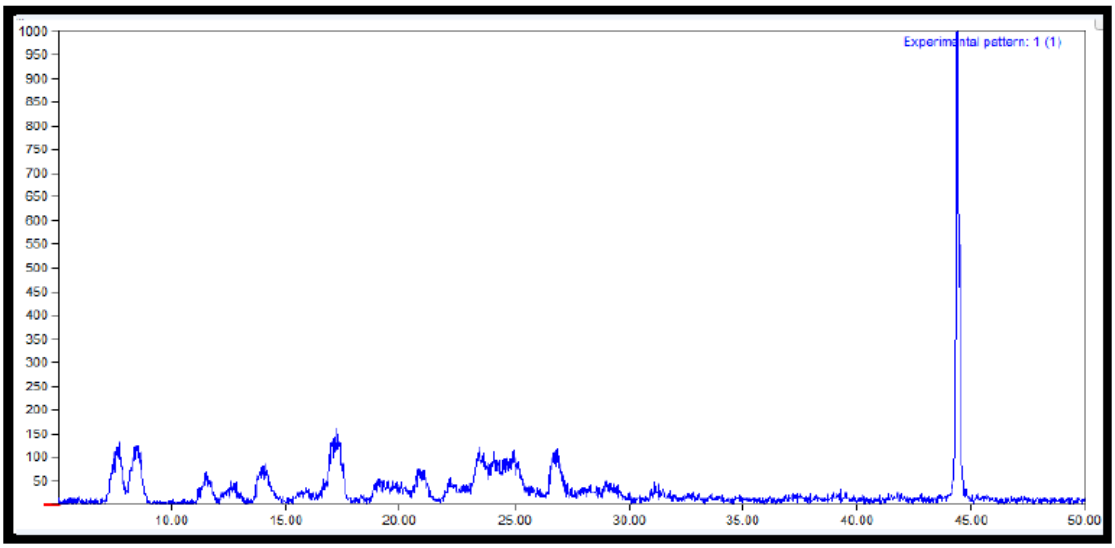

Figure 19: XRD of pure drug.

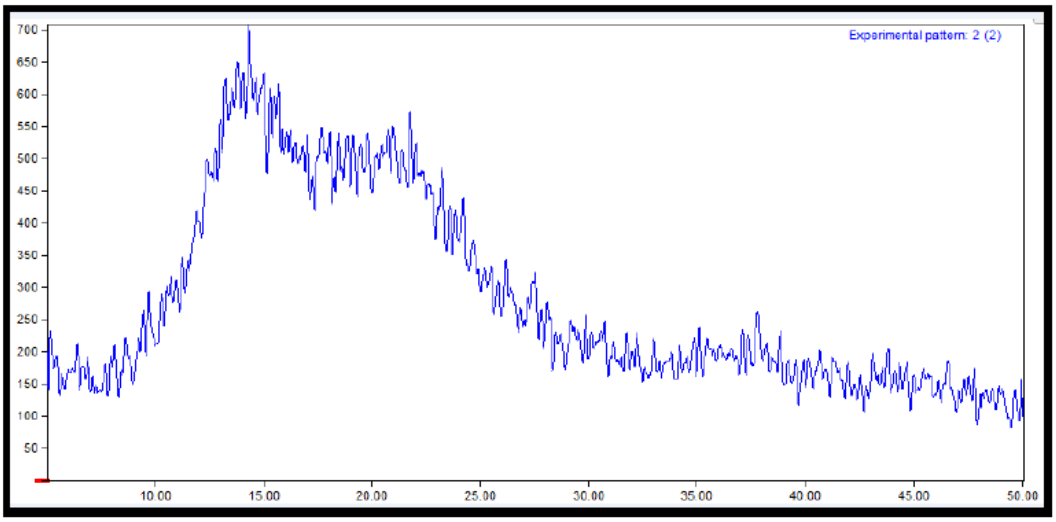

Figure 20: XRD of Solid SMEDDS.

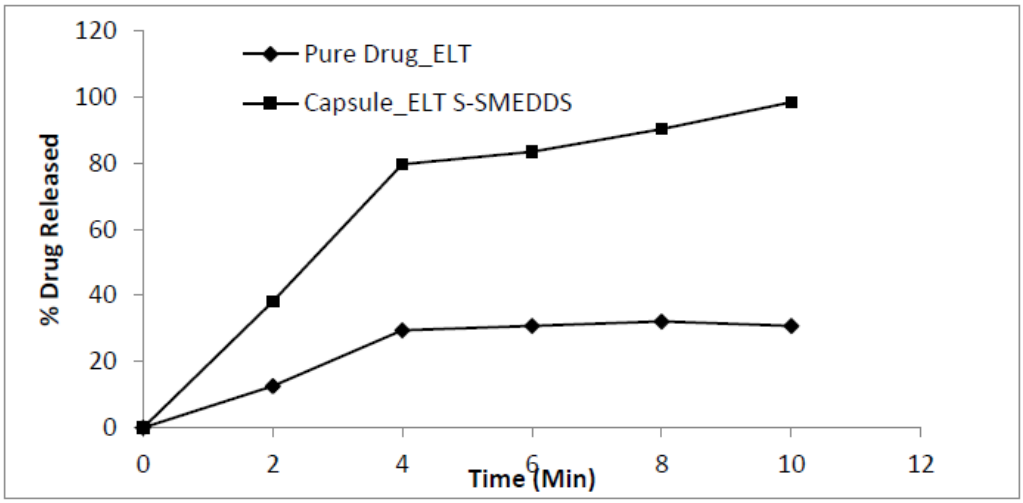

Figure 21: %Drug release in phosphate buffer pH 6.8.

CONCLUSIONS

It is always a challenging task for formulation scientist to develop suitable formulation for poorly water-soluble drug. In the proposed work, ELT was formulated into L SMEDDS and then adsorbed onto carriers to form S SMEDDS. Selection of Smix was found to be critical in preparation of L MSEDDS. The adsorbent (Neusilin US2) had shown acceptable property for S-SMEDDS. Chemix software had assisted in optimization of Smix ratio and composition of oil and water. FTIR, DSC and X ray studies supported the result and confirmed the amorphous nature of drug in S SMEDDS. The drug had shown improved dissolution when incorporated into capsule. The results of short-term stability study had proven stable characters of proposed formulation.

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