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Original Research Article

Formulation and Evaluation of Self-Micro Emulsifying Drug Delivery System (SMEDDS) of Ticagrelor

Ratna Sree Vadapalli[1*], Sunitha Reddy, M[2]

[1]Centre for Pharmaceutical Sciences, IS, JNTUH, Kukatpally, Hyderabad, Telangana-500085, India
[2]Associate Professor & Head of the Department, Centre for Pharmaceutical Sciences, IST, JNTUH, Kukatpally, Hyderabad, Telangana-500085, India

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***Corresponding author:** Ratna Sree Vadapalli
Centre for Pharmaceutical Sciences, IS, JNTUH, Kukatpally, Hyderabad, Telangana-500085, India

Abstract

The present work mainly emphasized on the enhancement of solubility of Ticagrelor by developing Self- Micro emulsifying drug delivery system. Ticagrelor is a BCS class IV drug with poor aqueous solubility and permeability. The saturated solubility of Ticagrelor in various oils, surfactants and co-surfactants was determined by using UV-spectroscopy. The excipients were selected based on their maximum solubility and compatibility for Ticagrelor. SMEDDS formulations od Ticagrelor were developed using different oils, surfactants and co-surfactant combinations (4:1 and 3:1). Pseudo ternary phase diagrams were constructed and based on pseudo ternary phase diagrams, Nano emulsification area was evaluated .Formulations were designed based on the pseudo ternary phase diagram using various proportions of oil (Capmul MCM E8 EP), surfactant (Labrasol), co-surfactant (PEG-400). The prepared formulations were selected among them F1 was optimized and carried out for further evaluations like dispersibility test, self-emulsification time ,phase separation and stability test, thermodynamic stability studies, droplet size and zeta potential, invitro drug release studies. The results of present study demonstrate that Ticagrelor SMEDDS can be used as a potential means for improving the solubility of Ticagrelor.

Keywords: Ticagrelor, Isotropic mixture, SEDDS, pseudo ternary phase diagram, surfactants.

1. INTRODUCTION

An increasing number of recently discovered drug substances exhibit poor water solubility and hence low absorption after oral administration. Approximately 35-40% of all new chemical entities discovered suffer from poor aqueous solubility. The properties of new chemical entities (NCE) shifted towards higher molecular weight and increasing lipophilicity, resulting in decreased aqueous solubility. Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potentialpharmacodynamic activity. Further, poorly water soluble drugs are administered at much higher individual doses than actually desired to achieve necessary plasma levels [1, 2].

The therapeutic efficacy and bioavailability of any drug depends upon the solubility of drug. Solubility of drug is one of the important parameter to attain the desired concentration of drug in systemic circulation for the pharmacological response. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation.Various solubility enhancement techniques are investigated such as particle size reduction, pH adjustment, co-solvency, complexation, solid dispersions, SMEDDSetc. However each technique has its own advantages and limits. Among all these techniques SMEDDS appear to be potential method for the solubility enhancement due to its ease of formulation and evaluation [3, 4].

SMEDDS are well known for their potential to enhance the solubility of hydrophobic drugs and consists of isotropic mixtures of an oily vehicle, surfactants, co-surfactants and thickening agents. SMEDDSrequire very less energy to emulsify, and so theyundergo spontaneous emulsification in the lumen of gut up on dilution in aqueous phase under the gentle agitation provided by the gastrointestinal motility. The microemulsions so formed are easily absorbed from the

gastrointestinal tract through the villi as chylomicrons [5, 6].

Ticagrelor (TCG), a cyclopentyl-triazolo-pyrimidine, belongs to a class of chemically noncompetitive and reversible antagonists of the platelet P2Y12 ADP receptor [1-4]. TCG was approved for use in patients with acute coronary syndrome based on a phase III study (Platelet Inhibition and Patient Outcomes), which showed a significant benefit compared with clopidogrel [5, 6]. However, TCG exhibits very low solubility (,10 µg/mL) at all pH values. It also has low intestinal membrane permeability corresponding to Biopharmaceutical Classification System (BCS) class IV. Because of these properties of TCG, the absolute bioavailability of TCG after oral administration is ~36% [7]. Although formulations to enhancethe bioavailability and antiplatelet activity of TCG, such as solid dispersion8 and cocrystallization [9], have recently been reported, few studies have been performed.

2. MATERIALS AND METHODS

2.1 Materials

Tween 20 (polyoxyethylenesorbitan monolaurate), Tween 80 (polyoxyethylenesorbitan monooleate), Span 80 (sorbitan monooleate), and polyethylene glycol 400 (PEG 400), Labrafac CC (medium-chain triglycerides), Lauroglycol FCC (propylene glycol monolauratetype I), Lauroglycol 90 (propylene glycol monolauratetype II), Labrafac Lipophile WL 1349 (medium-chain triglycerides), Capryol PGMC (propylene glycol monocaprylate, type I), Capryol 90 (propylene glycol monocaprylate, type II), Labrasol (caprylocaproyl macrogol-8 glycerides), and Transcutol P (diethylene glycol monoethyl) were kindly provided by Gattefossé. Capmul MCM (glyceryl caprylate/caprate), Capmul MCM C8 EP and Distilled water was used throughout the experiments.

2.2 Uv- Spectroscopic Analysis of Ticagrelor

Preparation of Standard Stock Solution Using Methanol

The standard stock solution of Ticagrelor sample was prepared by taking 20 mg of drug into 10ml volumetric flask and make up to the volume by using methanol, the solution was sonicated for 2-3 min to dissolve drug.

Preparation of Working Standard Solution

To prepare working standard solution pipette out 0.1ml of stock solution into 10ml volumetric flask and dilute upto the mark with methanol [7, 8].

2.2.1 Determination of absorption maxima (λmax) of Ticagrelor in methanol

From the working standard solution, a range of concentrations of 1,2,3,4,5 µg/ml were preparedand scanned in double beam spectrophotometer against respective blank by using spectrophotometric method.

The absorption maxima of Ticagrelor in methanol were deliberate in range of 700-200nm.

2.2.2 Calibration Curve of Ticagrelor In Methanol

The calibration curve of ticagrelor was plotted by using methanol as a solvent.20 mg of drug was weighed and diluted with methanol in 10ml volumetric flask to give a concentration of 2000µg/ml. From this reserve solution, 0.1ml was taken and diluted to 10ml to give a concentration of 20µg/ml. From the above solution, a range of concentrations of 1,2,3,4,5µg/ml were prepared and the absorbance was measured at 255nm against a blank using uv-spectrophotometer.

2.3 Solubility Studies

An excess amount of Ticagrelor was added to various oils, surfactants and co-surfactants and mixed by using cyclo-mixer. The mixture was kept at ambient temperature for 72 hours to attain equilibrium. The equilibriated sample was centrifused at 100rpm for 10 min to remove the insoluble drug. An aliquot of the supernatant was diluted with methanol and Ticagrelor was quantified by using uv spectrophotometer.

2.4 Pseudo ternary Phase Diagram

From the solubility studies components used for the construction of the phase diagram are Capmul MCM C8 EP (oil), Labrasol (surfactant), PEG-400(co-surfactant). Pseudo ternary phase diagram were constructed using water titration method at room temperature to identify self emulsifying regions and to select suitable concentrations of oils, surfactants and co-surfactants for formulation of SEDDS .The ratio of surfactant to co-surfactant (S mix) in each group were mixed in weight ratio (1:3,3:1,4:1). Oil and specific S mix ratios are mixed thoroughly in different weight ratios such as 9:1,8:2,7:3,6:4,5:5,4:6,3:7,2:8 and 1:9. Each mixture was titrated with water and vortexed for 2 mins and allowed to equilibrate. The change in the physical state from transparent to turbid were visually observed and marked on the three component ternary phase diagram were each axis represents oil, S mix and water .phase diagram were plotted [9, 10].

2.5 Formulation of Liquid SMEDDS of Ticagrelor

Different proportions of oil, surfactant and co-surfactant were selected based on ternary phase diagram.A series of SEDDS formulations were prepared by taking different ratios of selected excipients Capmul MCM C8 EP, Labrasol, PEG-400. S mix was prepared separately by mixing desired amount of surfactant and co- surfactant. The amount of drug (Ticagrelor) was kept constant in all the formulations (90mg). Ticagrelor was added to the oily phase in small amounts with continuous stirring until a clear solution was obtained. Ticagrelor containing oil phase was added to the S mix this mixture was continuously stirred until a homogenous mixture is formed .Finally

the formulations obtained were kept at room temperature.

3. Evaluation of Ticagrelor SMEDDS Formulation

3.1 Globule Size and Zeta Potential

The prepared liquid SEDDS of Ticagrelor formulations are diluted with distilled water in ratio of (1:100) are stirred on the cyclo mixer for 1min and left aside for 1 hour .The globule size and zeta potential of resultant formulation are determined by DLS spectroscopy at 90 angle using a Zeta sizer ZS 90 (Malvern instruments). Zeta potential of the diluted solution of the prepared liquid SEDDS formulation was analysed using electrophoretic cell .Size of the liquid SEDDS formulation of Ticagrelor was analysed by placing the diluted solution on the disposable cuvets at 25^{O} c.

3.2 Self Emulsification Time [11]

Emulsification time: The time taken for the pre-concentration of the formulation to from a homogenous mixture upon dilution is called emulsification time.

Pre-concentration of the emulsion liquid SEDDS Ticagrelor formulation was added drop wise to the beaker containing distilled water and allowed for continuous stirring on the magnetic stirrer at 100rpm and visually assed for time taken for the self emulsification.

Tendency to form emulsion was determined as:
Good: If emulsification occurs within <1min with clear bluish transparent appearance.
Bad: If emulsion is not clear.

3.3 Dispersibility test [12]

The dispersibility test of SEDDS is carried out to assess its capability to dispense intoemulsion and categorize the size of resulting globules.0.1 ml of preconcentrate of SEDDS was added into 250 ml of distilled water and the contents were stirred using magnetic stirrer at ~ 100 rpm and the time required for the formation of emulsion is noted.On titration with water the SEDDS formulation forms a mixture which is of different types depending upon which the Invitro performance of formulation can be assessed using grading system.
GRADE A: Rapidly forming(less than 1min), having a clear or bluish appearance.
GRADE B: Rapidly forming, slightly less clear emulsion having bluish white appearance.
GRADE C: Fine milky emulsion that formed within 2mins.
GRADE D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2mins).
GRADE E: Formulations exhibiting poor or minimal emulsification with large oil globules present on the surface

3.4 Phase separation and stability test:

20ml distilled water is taken in a beaker its temperature is maintained at 37°C. To this distilled water formulation of ticagrelor liquid SEDDS 1ml was added and diluted by agitation this was kept aside for 24hrs. Then the formulation is visually assed for any phase separation.

3.5 Effect of Dilution [13]

Formulations were diluted with excess of water, 0.1 N HCl and phosphate buffer (pH 6.8) and was stored for 24 hours. No precipitation or phase separation was found which indicate that all the formulations were stable on dilution.

3.6 Centrifugation

Distilled water and formulation of Ticagrelor SEDDS are mixed together in the ratio of (1:10) then the formulations are subjected to centrifugation at 3500rpm for 30min and observed for any physical changes like precipitation or phase separation the formulations which were stable after centrifugation were selected for future evaluation.

3.7 Thermal Stability Studies

Due to the possibility of drug precipitation in an excipient matrix, the formulation's physical stability is crucial to its effectiveness. Poor formulation physical stability can cause excipient phase separation, which can have an impact on both therapeutic efficacy and excipient bioavailability. Additionally, incompatibilities between the formulation and the capsule's gelatin shell may result in brittleness, softness, delayed disintegration, or insufficient drug release. These studies go through the following cycles:

3.7.1. Freeze Thaw Stress Cycle

Formulation of Ticagrelor SMEDDS and Distilled water mixed in the ratio (1:10) then these formulations were subjected to three cycles of freeze-thaw between 21 and 25 °C with storage at each temperature for not less than 48 h. Phase separation, cracking, or creaming are not present in formulations that pass this test, which indicates strong stability. The formulations that pass this test are 9subsequently subjected to a dispersibility test to estimate their ability to produce emulsions on their own.

3.7.2. Heating and Cooling Cycle

The formulation of Ticagrelor SMEDDS and distilled water are mixed in the ratio of (1:50) and the subjected to six cooling and heating cycles between the refrigerator temperature (4°C) and the higher temperature (45°C) are carried out, with exposure to each temperature lasting no longer than 48 hours.

Centrifugation testing is then performed on those formulations that pass the stability test.

3.8 pH: pH of the Ticagrelor SEDDS formulation is measured by using ph meter.

3.9 Drug loading efficiency [16]

Drug content in formulation was determined UVSpectrophotometrically. 50mg of each formulation was accurately weighed and dilute to 100mL with methanol. Resultant solutions were analyzed spectroscopically following suitable dilution. Drug loading efficiency was calculated by equation:

$$\text{Drug loading efficiency} = \frac{Amount\ of\ Drug\ in\ known\ amount\ of\ foarmulation}{Initial\ Drug\ load} \times 100$$

FT-IR studies

FT-IR Spectrum of pure drug, solid SMEDDS and Liquid SMEDDS formulation were obtained by FT-IR Spectrophotometer. The spectrums were taken with the accumulation 24 scans and a resolution of 4cm-1 over the range of 400-4000 cm-1. The spectrum of formulation so obtained was compared with spectrum of pure drug for any interactions.

3.10: In-vitro drug release studies

The In-vitro drug release studies are done using USP II dissolution test apparatus. The capsules containing liquid and solid SEDDS formulation of Ticagrelor are placed in the 900ml of buffer medium that is 0.1NHCL .conditions maintained are temperature 37+5 c, PH 1.2, 5RPM 50.At regular intervals that is 5 ,10,15,30,45,60,90,120min the samples (5ml) are withdrawn and filtered using 0.45um filter mad analysed using UV spectrophotometer. The drug release is calculated from the calibration curve.

4. Formulation of Solid – SMEDDS

From the evaluation studies done on different Ticagrelor SEDDS, formulationTCL3P1 with good stability, good self nano emulsification property and showed less particle size and less PDI was selected to formulate as solid SEDDS. S-SEDDS was prepared by mixing liquid SEDDS containing Ticagrelor with nuselinas carrier in ratio 1:2. Liquid SEDDS was added in drop wise manner over nuselin contained in porcelain dish. After each addition, contents were mixed using glass rod for uniform distribution of formulation. Resultant damp mass was passed through sieve no.120 and dried at room T oC and stored until further use.

5. Characterization of S-SMEDDS

Flow properties of S-SMEDDS [17, 18]

Angle of repose

The angle of repose of S-SNEDDS was determined by funnel method. Height of funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of powder. Accurately weighed sample was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the equation:

$\tan \theta = h/r$

Where h and r are height and radius of powder cone.

Bulk density and tapped density

A quantity of 2gm of S-SEDDS was introduced into 10mL measuring cylinder. Initial volume was noted and cylinder was allowed to fall under its own weight into a hard surface from a height of 2.5 cm at 2 second intervals. Tapping was continued until no further change in volumewas noted. Bulk density and Tapped density were:

Calculated using the following equations:

$$\text{Bulk density (BD)} = \frac{weight\ of\ powder\ blend}{volume\ of\ the\ packing}$$

$$\text{Tapped density (TD)} = \frac{Weight\ of\ the\ powder\ blend}{Tapped\ volume\ of\ the\ packing}$$

Compressibility index

The compressibility index of the blend was determined by Carr's compressibility index given by the equation.

$$\text{Carr's compressibility index (\%)} = \frac{(TD-BD)}{TD} \times 100$$

Hausner's Ratio

Hausner's Ratio is a number that is correlated to theflowability of a powder (or) granular material. Hausner's ratio can be calculated by the equation:

$$\text{Hausner's Ratio} = \frac{Tapped\ Density}{Bulk\ Density}$$

Drug content [19]

S-SMEDDS of Ticagrelor was accurately weighed equivalent to 10mg and dissolved in sufficient quantity of methanol. The solution was sonicated for 10min in order to extract the drug in methanol and filtered. The absorbance of filtrate was measured at 255 nm using UV-Visible Spectrophotometer.

RESULTS AND DISCUSSION

Determination OF **λ**max of Ticagrelor

Observation: The spectrum of Ticagrelor showed maximum absorption at wavelength 255nm in methanol.

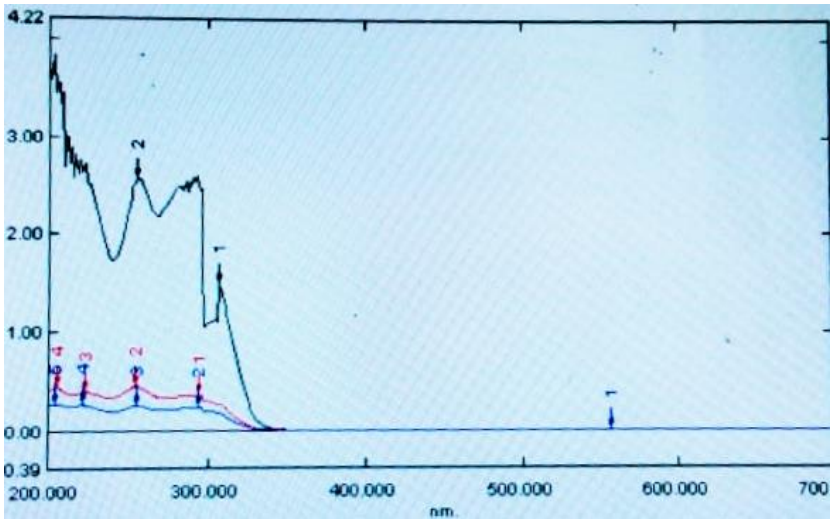

Fig 1: UV spectrum of Ticagrelor in methanol

CALIBRATION CURVE OF TICAGRELOR IN METHANOL

OBSERVATION

The standard graph was plotted using the values shown in table Standard plot of Ticagrelor in methanol was plotted by taking absorbance on x-axis and concentration on y-axis ,the plot is shown in .The regression coefficient R^2 was found to be 0.9909.

Table 1: Standard graph values of Ticagrelor in methanol

CONCENTRATION (µg/ml)	Absorbance
1	0.086
2	0.097
3	0.142
4	0.182
5	0.210

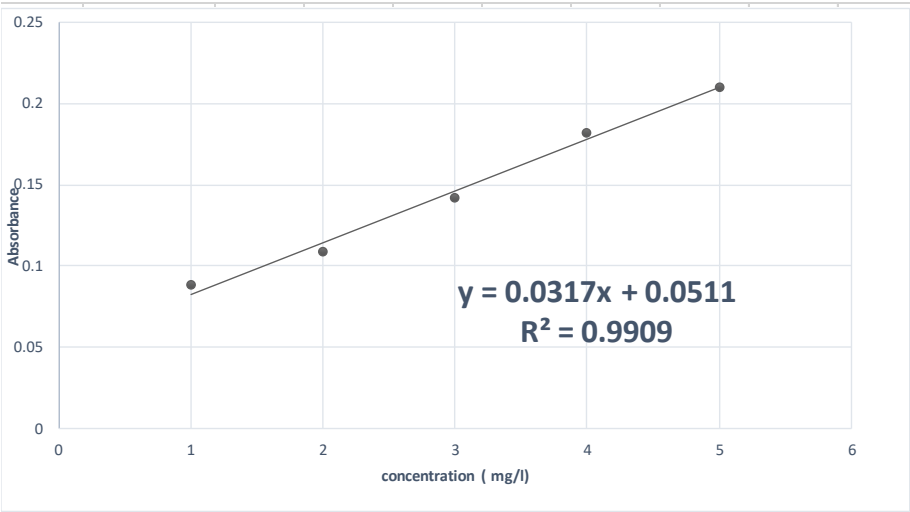

Fig 2: Calibration curve of Ticagrelor in methanol

SOLUBILITY STUDIES

The excipients used in the SEDDS should show maximum solubility for the drug to ensure maximum solubilization of the drug and to prevent precipitation of the drug in gut lumen. The solubility results of the Ticagrelor in various lipid vehicles, surfactants and cosurfactants are reported in thefigures 1, 2 and 3. The maximum solubility of Ticagrelor in oils was found to be maximum in Capmul MCM C8 EPin surfactants the highest solubility was found in Labrasol and in co-surfactants the highest solubility was in PEG 400.

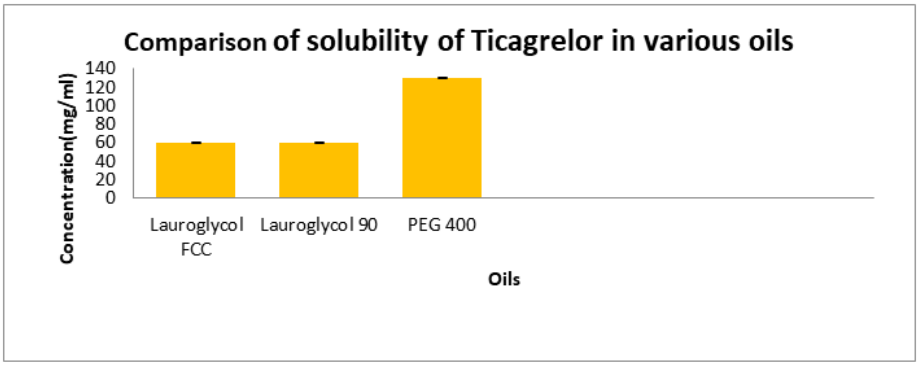

Fig 3: Comparison of solubility of Ticagrelor in various oils

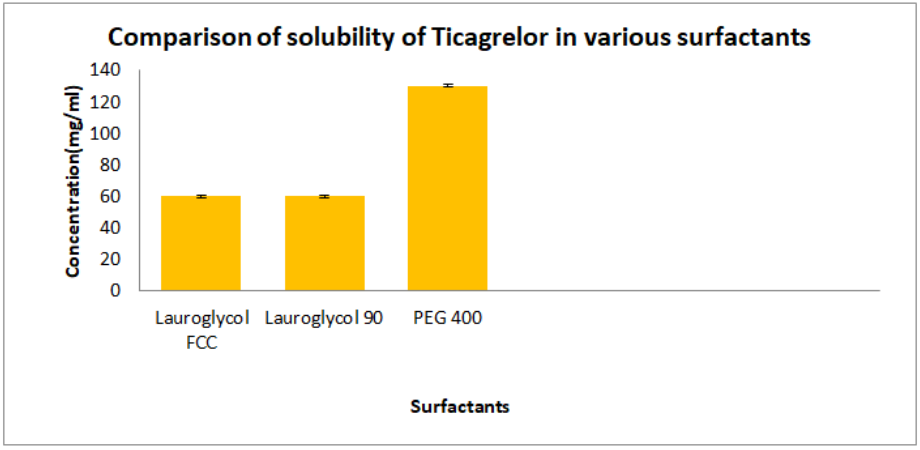

Fig 4: Comparison of solubility of Ticagrelor in various surfactants

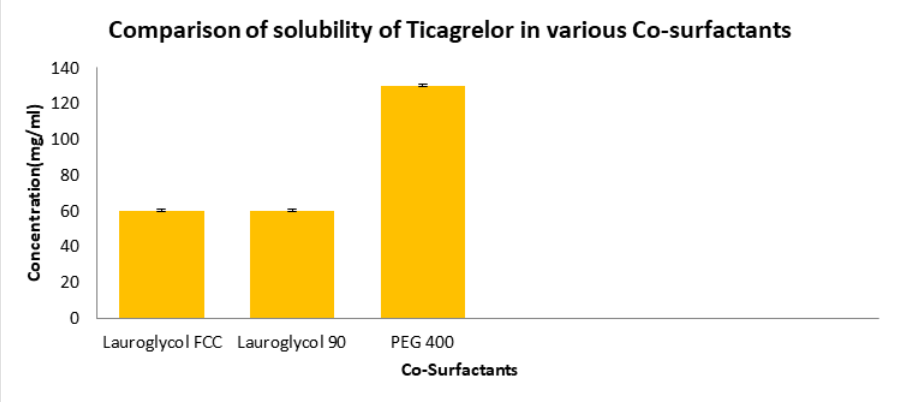

Fig 5: Comparison of solubility of ticagrelor in various Co-surfactants

Table 2: Composition of Ticagrelor liquid SEDDS formulation

S. No	Formulation	API(mg)	CapmulMCMC8EP (mg)	S mix (mg)	Total (mg)
1	TCL3P1(1:8)F1	900	500	4500	5900
2	TCL4P1(1:9) F2	900	500	4500	5900

PSEUDOTERNARY PHASE DIAGRAM

In the present study pseudo ternary phase diagrams were constructed against oil, water and surfactant/ co-surfactant using water titration methods. The results are shown in the Figures 5 and 6.

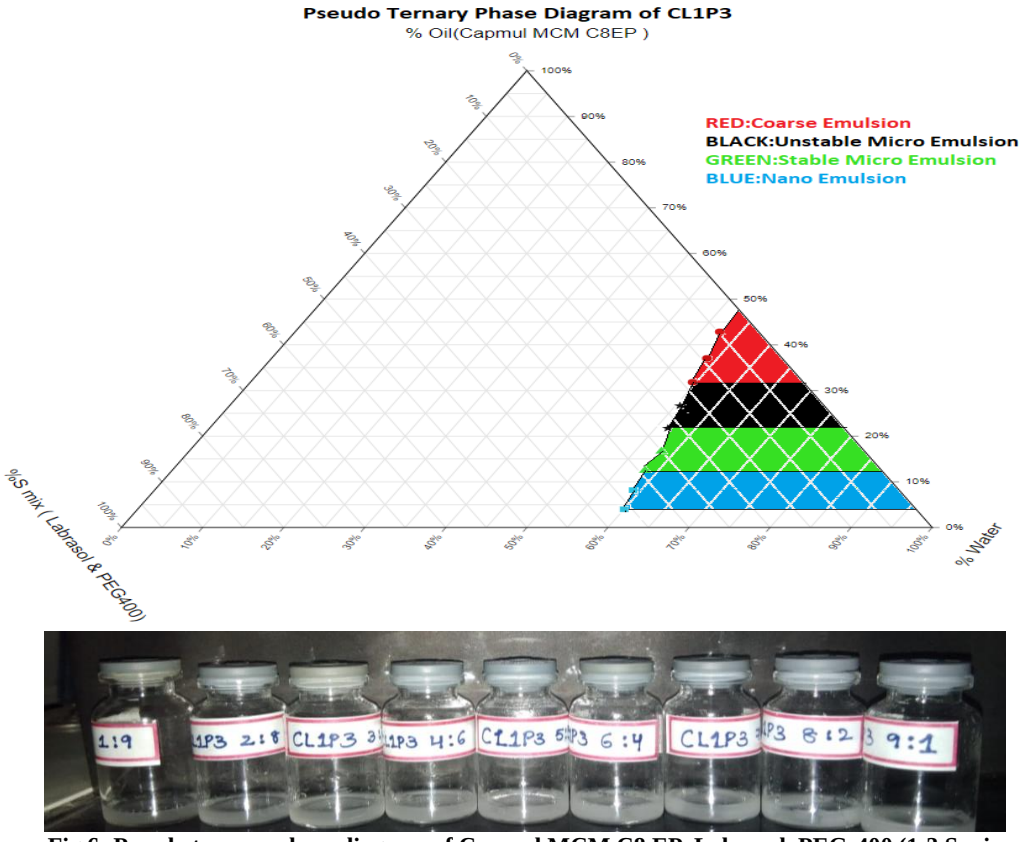

Fig 6: Pseudo ternary phase diagram of Capmul MCM C8 EP, Labrasol, PEG-400 (1:3 S mix

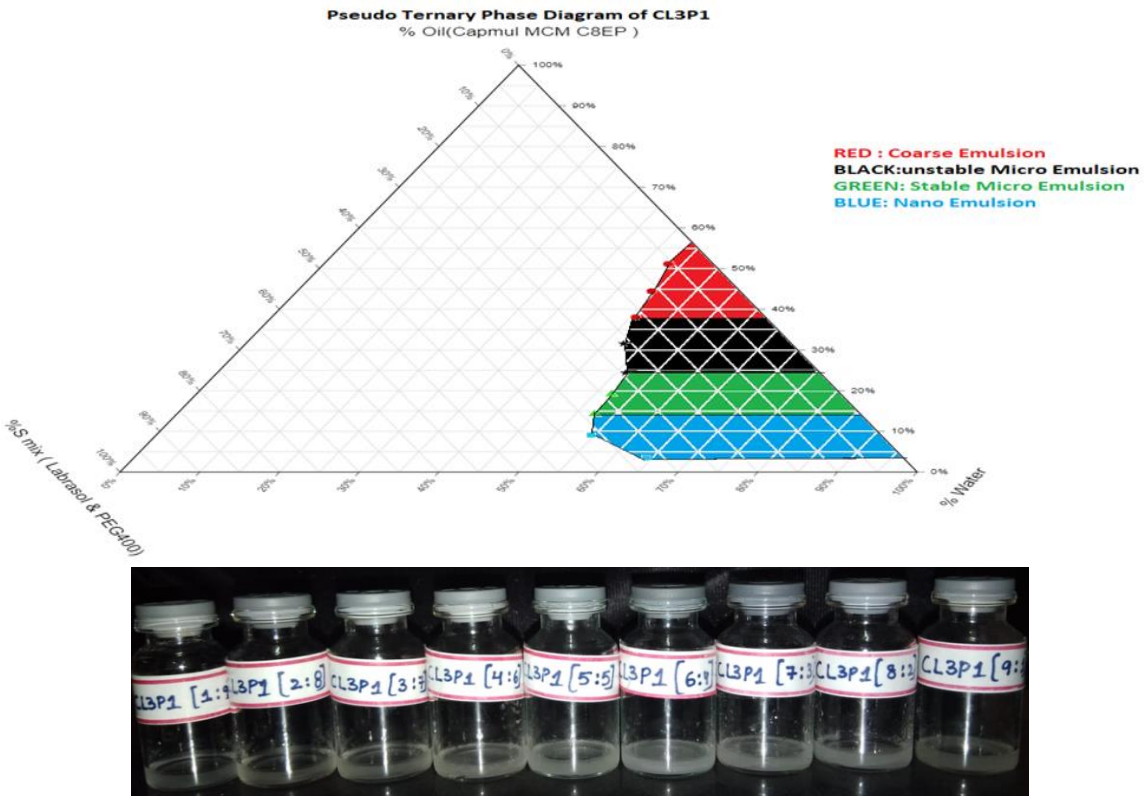

Figure 7: Pseudo ternary phase diagram of Capmul MCM C8 EP, Labrasol, PEG-400 (3:1 S mix)

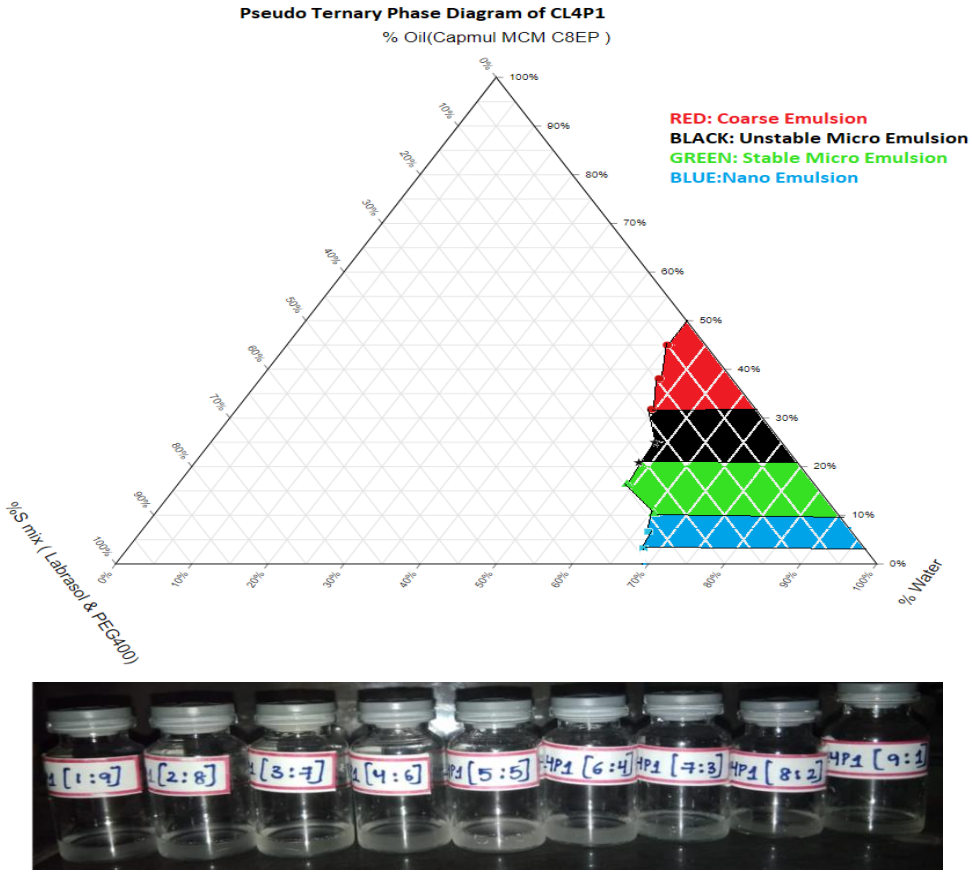

Figure 8: Pseudo ternary phase diagram of Capmul MCM C8 EP, Labrasol, PEG-400 (4:1 S mix)

Droplet size and Zeta potential determination:

Droplet size, PDI and Zeta potential of the prepared formulations were determined. Droplet size was found to be in between 49.52 to 51.86 nm and PDI of all formulations was found to be below 0.5 i.e. there is distribution of uniform size particles. Zeta potential was found to be in between -38.1 to -22.7 mV. The results are given in Table and Figures. From the results it was found that formulation TCL3P1 showed less droplet size than other formulations.

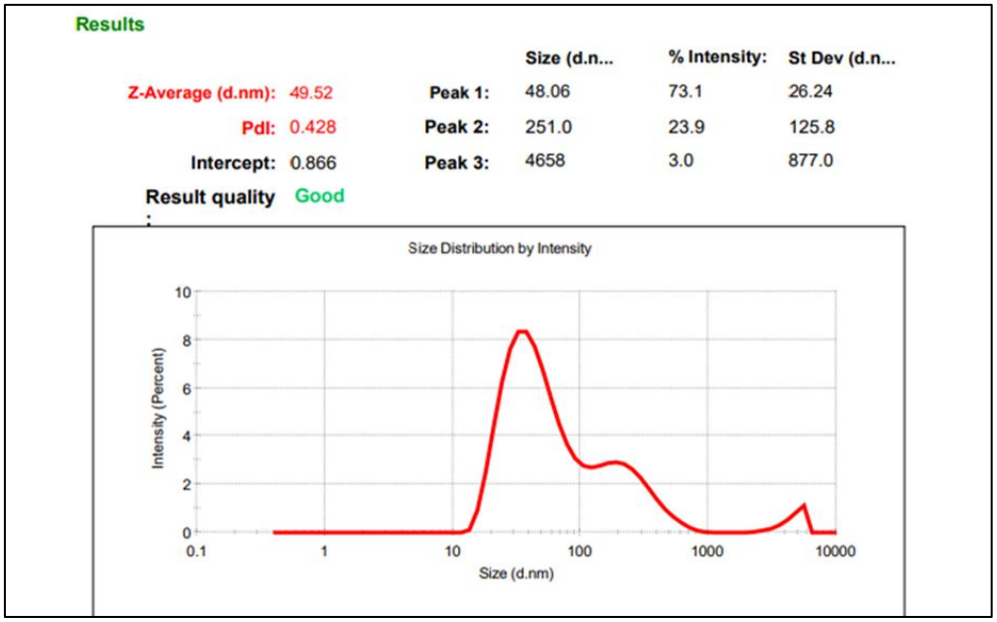

Figure 9: Globule Size of CL3P1

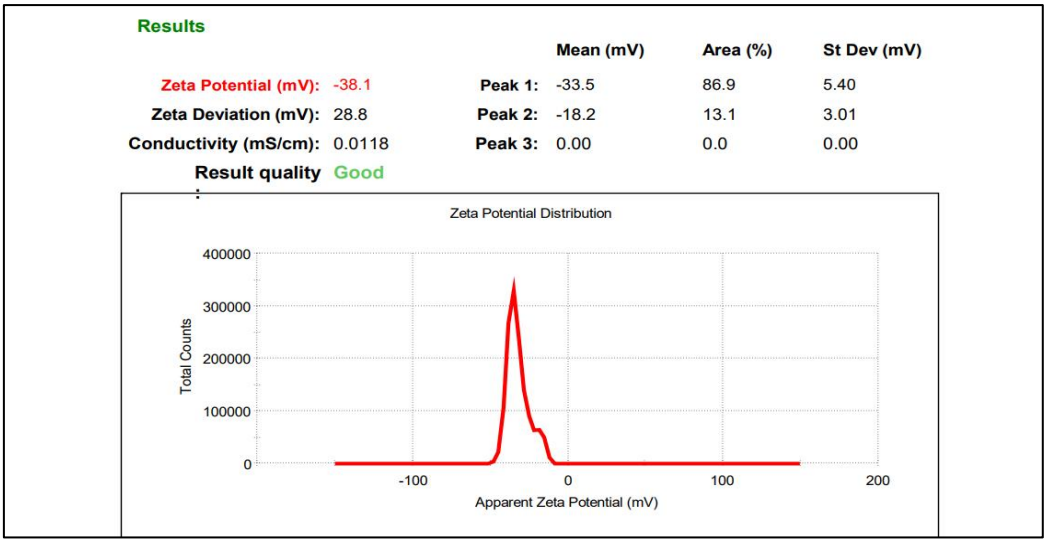

Figure 10: Zeta Potential of CL3P1

Figure 11: Globule Size of TCL3P1

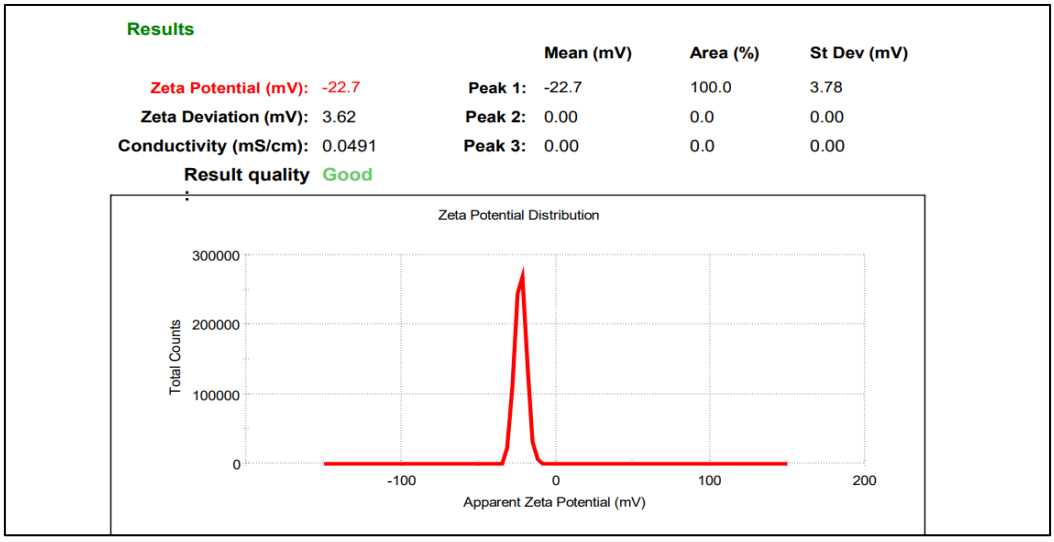

Figure 12: Zeta Potential of TCL3P1

Self emulsification time:

According to visual assessment formulations are graded for self-emulsification time. Self emulsifying mixtures should disperse rapidly in aqueous medium with mild shaking. Self emulsification time that was determined for prepared SMEDDS are given in Table 5. It was found that all formulations are emulsified in 22 to 43seconds i.e. performance of all formulations was said to be good.

Table 3: Self emulsification time (Seconds) (n=3)

SNO	FORMUALTION	SELF EMULSIFICATION TIME (min)	result
1.	TCL3P1	22sec	Good
2.	TCL4P1	43sec	Good

Dispersibility test: All the formulations of Ticagrelor SEDDS were slightly clear after conducting dispersibility test as mentioned in Table 6.

Table 4: Dispersibility test (n=3)

S. No	Formulation	Observation	Grade
	TCL3P1	Rapidly forming slightly less clear emulsion with bluish appearance	B
	TCL4P1	Bright milky emulsion	C

Phase separationand stability study of emulsions

Prepared SEDDS formulations are observed for precipitation and phase separation of drug at intervals 2, 4, 6, 8, 12, 24 hrs period of time and it was found that all formulations showed neither precipitation nor phase separation of the drug. Results are given in Table 7.

Table 5: Phase separation and precipitation of the drug (n = 3)

Formulation	Precipitation	Phase separation
TCL3P1	NO	NO
TCL4P1	NO	NO

Robustness to Dilution

Formulations are diluted with excess of Water, 0.1N HCl and Phosphate buffer of pH 6.8 and the diluted samples are stored for 24hrs and visually observed for precipitation (or) phase separation of drug. No precipitation (or) phase separation is found which indicates all formulations are robust to dilution. Results are given in Table 8.

Table 6: Robustness to dilution (n = 3)

Formulation	Distilled water	0.1 N HCL	Phosphate buffer pH 6.8
TCL3P1	Pass	Pass	Pass
TCL4P1	Pass	Pass	Pass

Thermodynamic stability studies

Thermodynamic stability study is designed to identify Metastable formulation. The SEDDS are subjected to Centrifugation study, Freeze thaw cycle and heating cooling cycle. The emulsions are stable during centrifugation at 3,500rpm and alternative temperature cycles of -20 °C and +25 °C, 4°C and 45°C. There is no precipitation and phase separation of formulations. The results are given in Table 9.

Table 7: Thermodynamic stability studies

Formulation	Centrifugation (3,500rpm for 30mi	Freeze thaw cycle (-20 oC and +25 o C)	Heating cooling cycle(4°C and 45°C
TCL3P1	Pass	Pass	Pass
TCL4P1	Pass	Pass	Pass

Drug loading efficiency

It was found that the formulation TCL3P1 have drug loading efficiency more than 98.2% and the formulation TCL4P1 which contain 87.4% loading. Results are given in Table 10.

Table 8: Drug loading efficiency of formulations (n=3)

Formulation	Drug loading efficiency
TCL3P1	98.2 ± 0.65
TCL4P1	87.4 ± 0.412

Evaluation of Solid SMEDDS of Ticagrelor

Flow properties of s-SMEDDS Flow properties such as Angle of Repose, Bulk density, Tapped density, Compressibility Index and Hausner's Ratio are determined and it was found that Prepared s-SNEDDS showed "Good" flow properties. Results are given in Table 11.

Table 9: Flow properties of s-SNEDDS of Ticagrelor (n=3)

FLOW PROPERTIES	RESULTS
Angle of repose	27.998 ± 1.302
Bulk density(g/mL)	0.367 ± 0.015
Tapped density (g/mL)	0.41 ± 0.015
Compressibility index (%)	9.85 ± 0.38
Hausner's ratio	1.11 ± 0.006

FT-IR studies: FT-IR Spectrum of pure drug, solid SMEDDS and Liquid SMEDDS formulation were obtained by FT-IR Spectrophotometer.

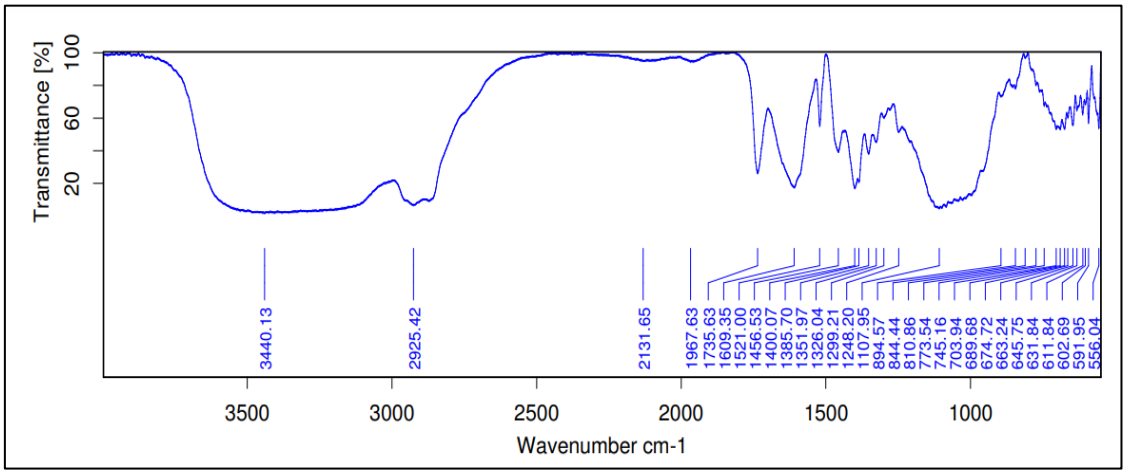

Figure 13: FT-IR Spectrum of pure drug (Ticagrelor)

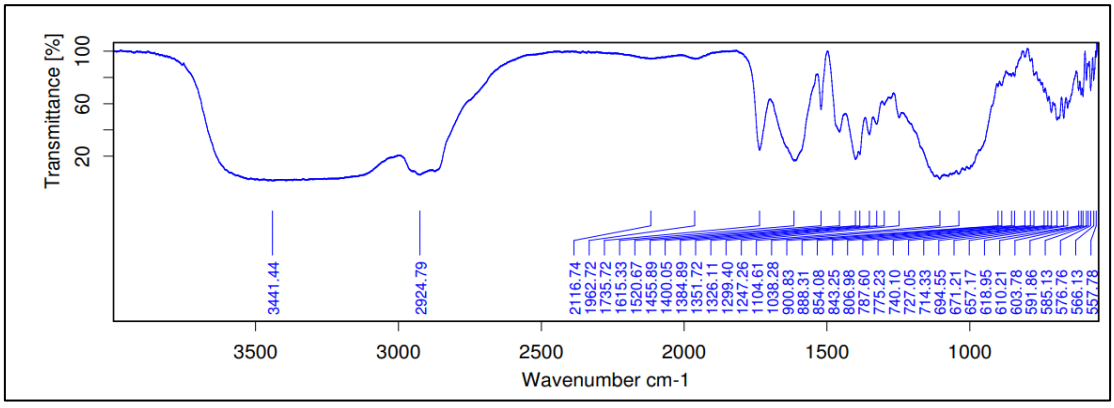

Figure 14: FT-IR Spectrum of Solid SMEDDS of Ticagrelor

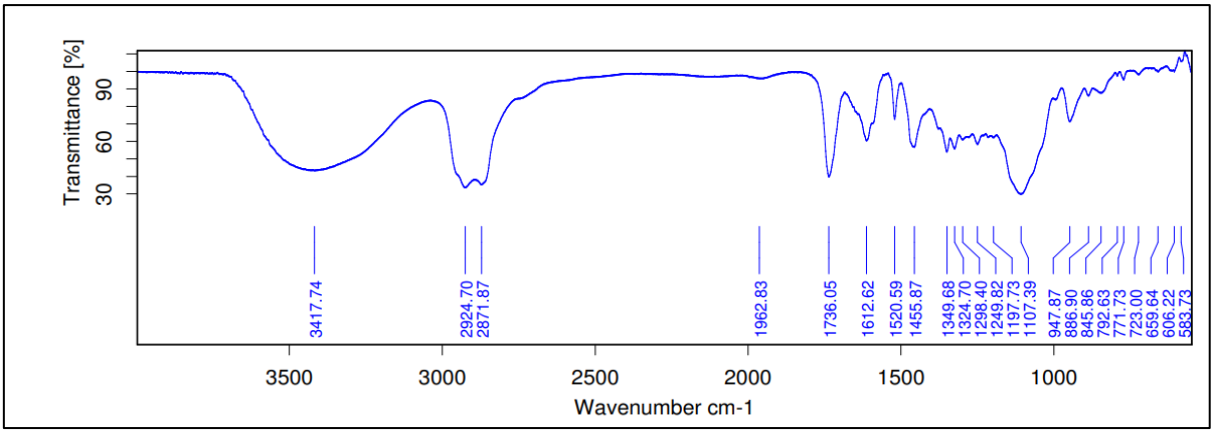

Figure 15: FT-IR Spectrum of Liquid SMEDDS of Ticagrelor

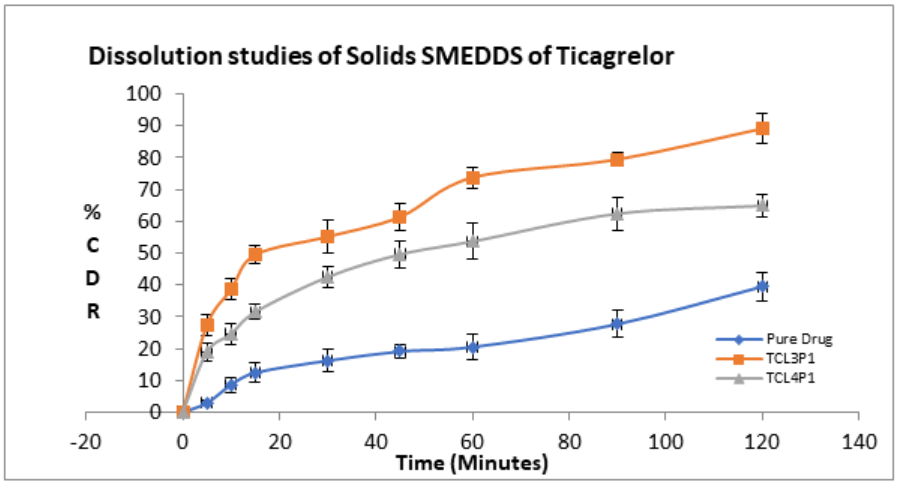

Fig 16: In vitro dissolution of Solid SMEDDS Ticagrelor in 0.1N HCL

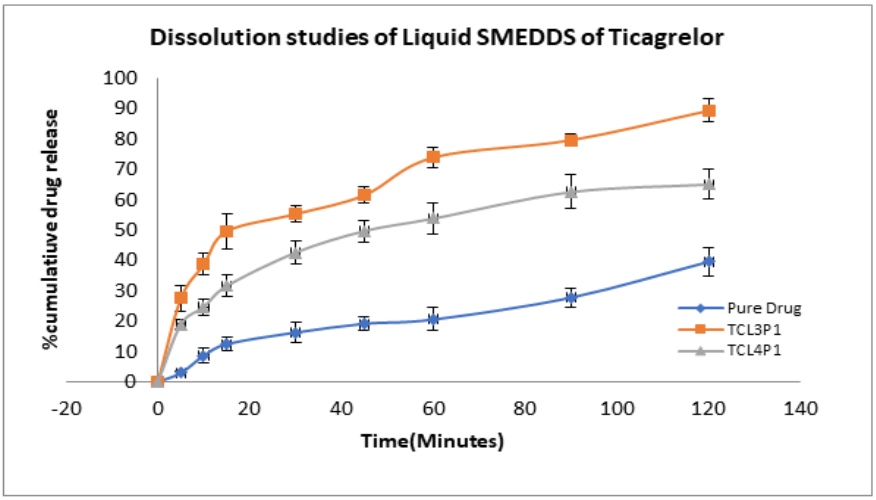

Fig 17: In vitro dissolution of Liquid SMEDDS Ticagrelor in 0.1N HCL

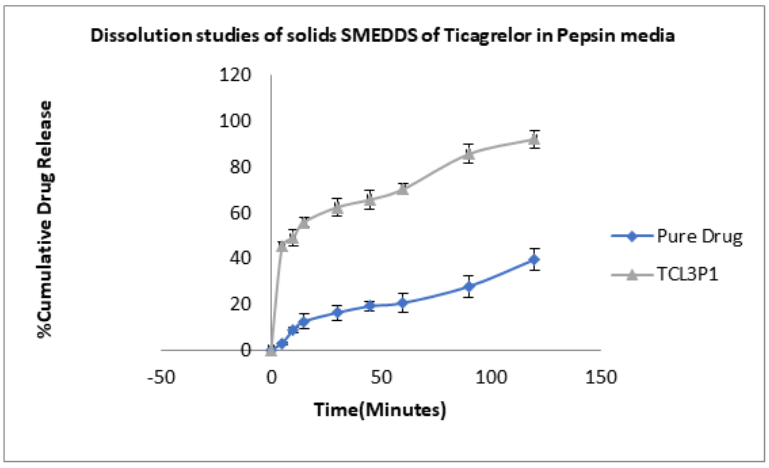

Fig 18: In vitro dissolution of Ticagrelor in pepsin

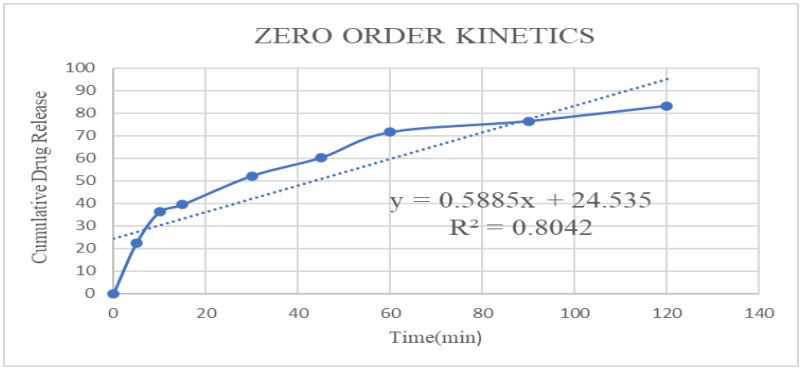

Fig 19: Zero order kinetics of L-SMEDDS

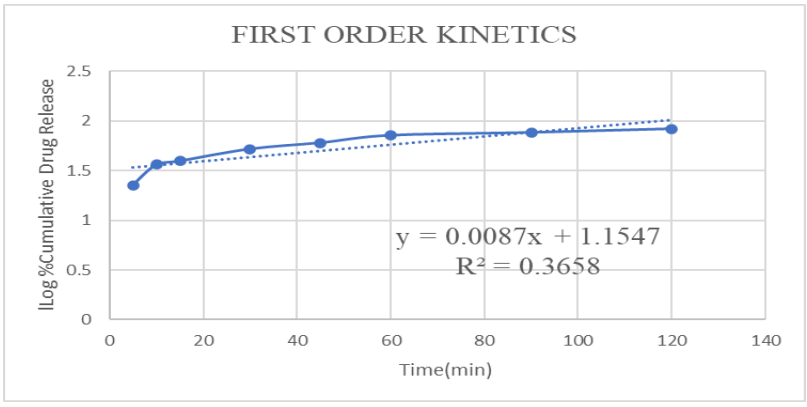

Fig 20: First order kinetics of L-SMEDDS

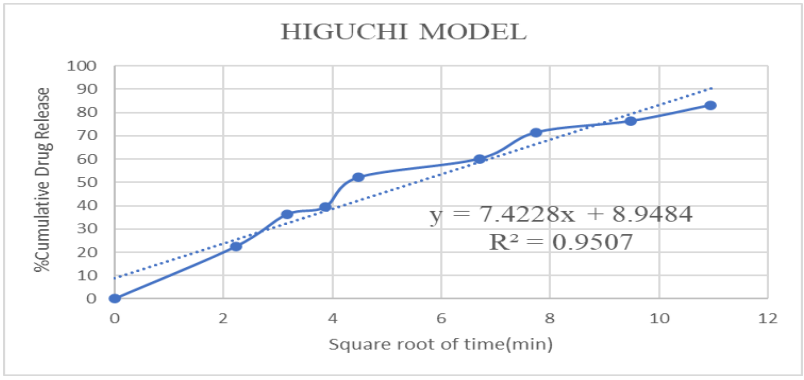

Fig 21: Higuchi model of L-SMEDDS

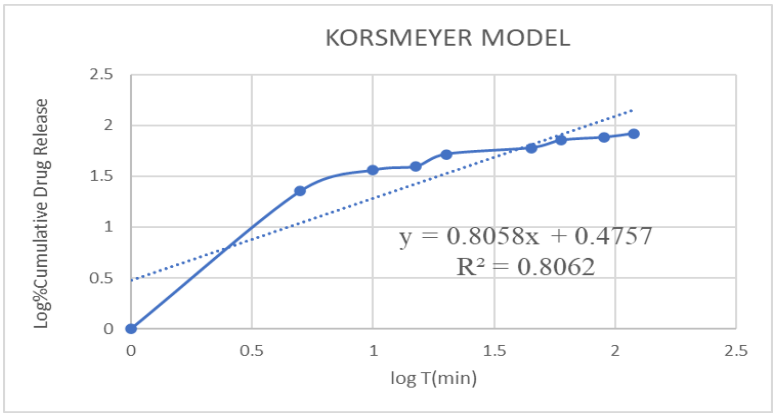

Fig 22: Korsmeyer model of L-SMEDDS

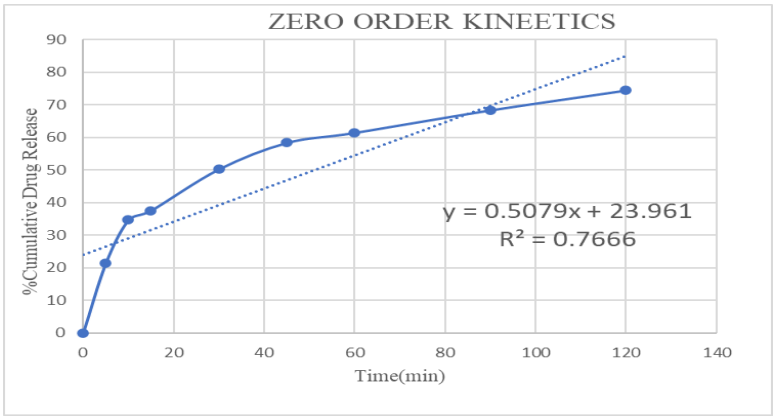

Fig 23: Zero order kinetics of S-SMEDDS

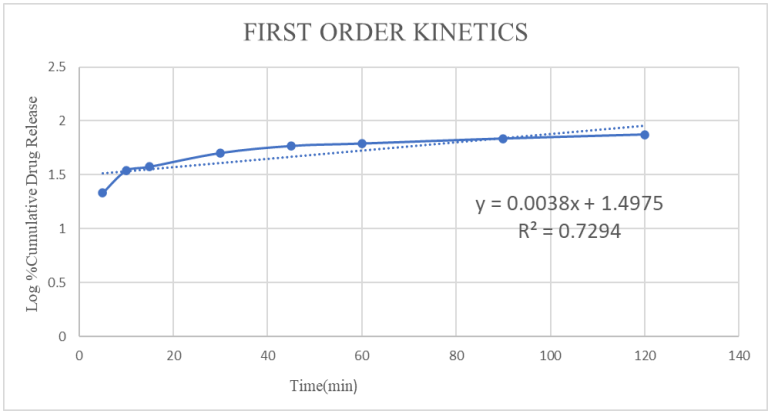

Fig 24: First order kinetics of S-SMEDDS

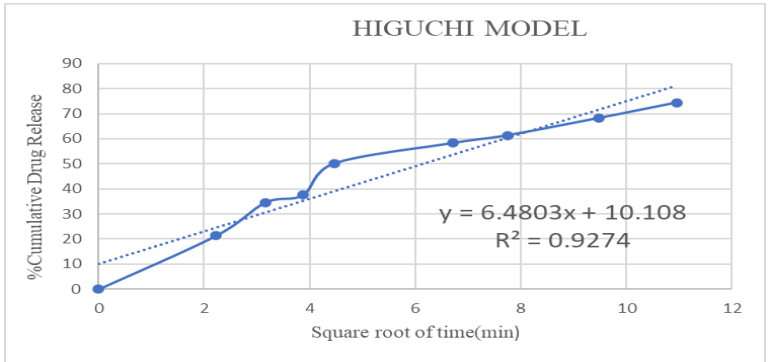

Fig 25: Higuchi model of S-SMEDDS

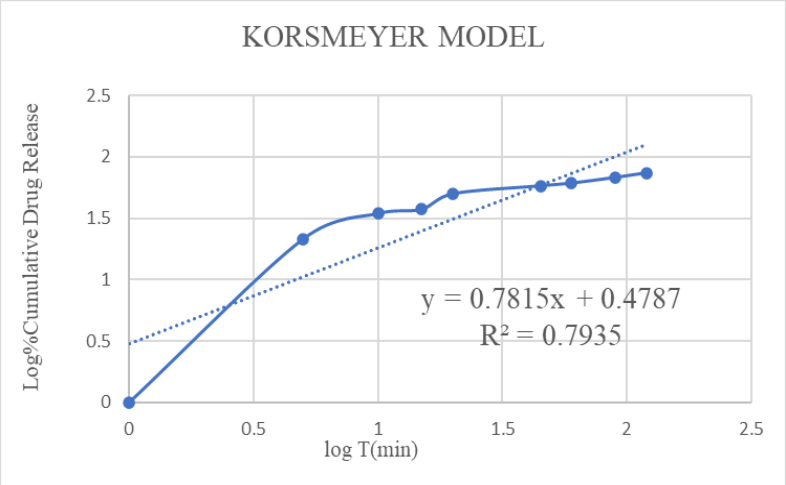

Fig 26: Korsmeyer model of S-SMEDDS

OBSERVATION

The drug release data obtained were extrapolated to Zero, First, Higuchi and Korsmeyer order kinetics to known the mechanism of action of TCL3P1 optimized formulation, if regression coefficient > 0.97 indicates that the formulation follows order kinetics.

SEDDS formulations are used to improve potential means of solubility and dissolution rate and Ticagrelor L-SMEDDS is independent of order kinetics.

Accelerated stability studies:

Formulated Tiacgrelor S-SMEDDS were stored at 40-45^{0}c temperature and 70-75 % RH for about 3 months and drug release was compared with day 1 results, results were shown in table no 10 and Figure 27.

Table 10: 3 months (Comparison table of Ticagrelor –SMEDDS day 1 with 3 months)

Time (min)	% Drug release of TCL3P1 S-SMEDDS formulation month 3	% Drug release of TCL3P1 S-SMEDDS formulation day 1
5	25.4± 0.36	28.4± 0.13
10	37.9± 0.43	39.6 ± 0.64
15	48.5± 0.26	50.5 ± 0.63
20	58.7± 0.64	60.2 ± 0.55
45	59.9± 0.39	65.4 ± 0.59
60	72.6± 0.46	75.8 ± 0.67
90	78.3± 0.29	80.5 ± 0.55
120	88.1± 0.56	90.2 ± 0.69

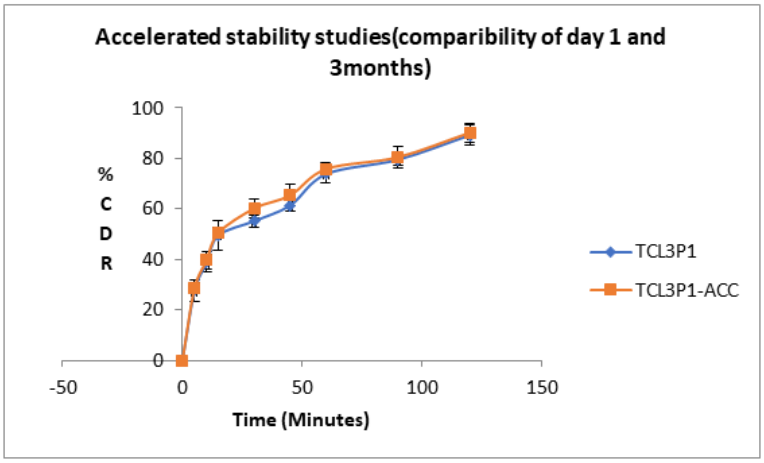

Fig 27: Comparison of Tiacgrelor S-SMEDDS day 1 with 3 months

CONCLUSION

An optimized SMEDDS formulation consisting of Ticagrelor, Capmul MCM E8 CP, Labrasol, Poly ethylene glycol (PEG) 400, were successfully developed. The developed formulations showed an increased solubility, dissolution rate and bio availability of Ticagrelor.Further the formulations were found to be thermodynamically stable, for dilution, Freeze thawing and centrifugation. None of the formulations showed drug precipitation or phase separation. The dissolution profiles of all the formulations selected showed a drug release of greater than 70% in 120mins. Among the formulations TCL3P1 showed a maximum drug release of 90.2% in 120mins.Thus our study confirmed that the SMEDDS formulations can be potentially used as an alternative to the traditional oral formulations for the poorly soluble drugs like Ticagrelor to improve its solubility and dissolution.

REFERENCES

1 Sarpal, K., Pawar, Y. B., & Bansal, A. K. (2010). Self-emulsifying drug delivery systems: a strategy to improve oral bioavailability. *Crips*, *11*(3), 42-49.

2 Reddy, M. S. (2017). Formulation and in vitro characterization of solid-self nanoemulsifying drug delivery system of atorvastatin calcium. *Asian Journal of Pharmaceutics (AJP)*, *11*(04), S991-S999.

3 Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V. K., Khosa, R. L., & Partapur, M. U. (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. *J Adv Pharm Educ Res*, *2*(1), 32-67.

4 Brahankar, D. M., & Jaiswal, S. B. (2009). *Biopharmaceutics and Pharmacokinetics: A treatise*. Vallabh Prakashan, 345-357.

5 Pouton, C. W. (2000). Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. *European journal of pharmaceutical sciences*, *11*, S93-S98.

6 Kang, B. K., Lee, J. S., Chon, S. K., Jeong, S. Y., Yuk, S. H., Khang, G., ... & Cho, S. H. (2004). Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *International journal of pharmaceutics*, *274*(1-2), 65-73.

7 Pub Chem "Drug profile of Ticagrelor". https://pubchem.ncbi.nlm.nih.gov/compound/Rivaroxaban#section=AbsorptionDistribution-and-Excretion.

8 Pandya, D., Patel, M., Ghediya, R., Shah, A., & Khunt, R. (2016). UV-Vis spectrophotometric assay determination of oral antiplatelet ticagrelor drug in pharmaceutical formulation: Application to content uniformity. *Journal of Chemical and Pharmaceutical Research*.

9 Goyal, U., Gupta, A., Rana, A. C., & Aggarwal, G. (2012). Self microemulsifying drug delivery system: A method for enhancement of bioavailability. *International journal of pharmaceutical sciences and research*, *3*(1), 66-69.

10 Reddy, M. S., Goud, P. S., & Apte, S. S. (2012). Solubility enhancement of candesartan cilexetil by self emulsifying drug delivery systems. *International journal of pharmaceutical sciences and research*, *3*(7), 2098-2104.

11 Madhu Babu, A., Prakash Rao, B., Sudhakar, P., & Sambasiva Rao, K. R. S. (2012). Formulation and evaluation of self nanoemulsifying drug delivery system of low solubility drug Simvastatin for improved solubility and bioavailability. *International journal of biological & pharmaceutical research*, 3(6), 767-774.

12 Reddy, M. S., & Sowjanya, N. (2015). Formulation and in-vitro characterization of solid self nanoemulsifying drug delivery system (S-SNEDDS) of Simvastatin. *Journal of pharmaceutical sciences and research*, *7*(1), 40-48.

13 Preeti, K. S., & Sudhanshu, S. (2011). Formulation and In-vitro characterization of self-nanoemulsifying drug delivery system of Cinnarzine. *Pharmacie Globale (IJCP)*, 9(8), 1-6.

14 Kshitija, K., & Swati, M. (2013). Self emulsifying drug delivery systems: A Review. International journal of pharmaceutical sciences and research, *IJPSR*, 4(12), 4494-4507.

15 Reddy, M. S., Goud, P. S., & Apte, S. S. (2012). Solubility enhancement of candesartan cilexetil by self emulsifying drug delivery systems. *International journal of pharmaceutical sciences and research*, *3*(7), 2098-2104.

16 Preeti, K. S., & Sudhanshu, S. (2011). Formulation and In-vitro characterization of self-nanoemulsifying drug delivery system of Cinnarzine. *Pharmacie Globale (IJCP)*, 9(8), 1-6.

17 More, H. N., Hazare, A. A. (2004). Practical Pharmaceutics (Physical Pharmacy) Manas Prakashan, Kolhapur, first edition, 86-105.

18 Patrick, J. S. Martin's Physical Pharmacy and Pharmaceutical sciences – Sixth edition, 48-52, 461-466.

19 Saifee, M., Zarekar, S., Rao, V. U., Zaheer, Z., Soni, R., & Burande, S. (2013). Formulation and in vitro evaluation of solid-self-emulsifying drug delivery system (SEDDS) of glibenclamide. *Am J Adv Drug Delivery*, *1*(3), 323-340.