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# FORMULATION AND *IN-VITRO* CHARACTERIZATION OF SELF MICROEMULSIFYING DRUG DELIVERY SYSTEMS OF RIVAROXABAN

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**Keywords:**

Rivaroxaban, Oils, Surfactants, Co-surfactants, Pseudo-ternary phase diagram, Solubility study

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**ABSTRACT:** The drug Rivaroxaban which was poorly soluble was selected for formulation of SMEDDS due to its poor aqueous solubility and its oral bioavailability which is 66%. Self micro emulsifying drug delivery system was developed to improve its solubility and bioavailability. Solubility of Rivaroxaban is determined in various oils, Surfactants, and co-surfactants by UV-Spectrophotometric method. Rivaroxaban has been shown maximum solubility in oil Peceol oil, surfactant Tween 80 and co surfactant Transcutol HP. A series of Pseudo ternary phase diagrams are constructed to identify micro emulsion region. Various compositions of Oil and $S_{mix}$ are titrated with water to identify micro emulsion region. From pseudo-ternary phase diagrams systems consisting of Peceol oil as oily phase, Tween 80 surfactant, Transcutol HP as co surfactant are selected for formulation. SMEDDS are prepared by selecting oil: $S_{mix}$ ratio 1:9 ….9:1 and $S_{mix}$ ratio 1:3, 1:4. Two mixtures (PTWT-2(1:9), PTWT-2(2:8) are selected for formulation of SMEDDS by keeping amount of drug constant (20mg) in all formulations. Prepared formulations are evaluated for Self emulsification and visual assessment, Phase separation and precipitation of the drug, Robustness to dilution, Percentage Transmittance, drug loading efficiency, FT-IR Studies, Thermodynamic stability studies, Droplet size, PDI and Zeta potential. All five formulations are emulsified in 25-30 seconds *i.e.* in less than 1 min. No formulation had showed precipitation and phase separation of drug. All formulations are robust to dilution. All formulations have shown percentage transmittance more than 95% indicating clear emulsions. All formulations have drug loading efficiency more than 90%. Thermodynamic stability studies had indicated that all formulations are stable after centrifugation and freeze thaw cycle. Droplet size was found to be 215.3nm and Zeta potential - 8.34 nm and FT - IR spectrums shown no interaction between drug and excipients. Cumulative percentage drug release of Rivaroxaban is 81.32%. The SMEDDS formulation clearly showed improved and increased drug dissolution for poorly soluble drug. This helps to keep the drug in soluble state in GIT. So the prepared SMEDDS have capability for delivering poorly water soluble drug Rivaroxaban in soluble state in GIT.

**INTRODUCTION:** The drugs are most often administered by oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is difficult because of their low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality[1]. There are a number of formulation strategies that could be used to improve the bioavailability of class II drugs, either by increasing the dissolution rate or by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen. For successful oral delivery of such poorly water soluble drugs it is

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necessary to improve their solubility. Different technological strategies are developed to increase solubility of poorly soluble drugs like Particle size reduction, Salt formation, Hydrotrophy, Solid dispersions, pH adjustment, Use of surfactants, Complexation, Super critical fluid process, Co solvency etc. Each strategy has its own limitations owing to development of other formulation strategies like lipid based formulations [2 - 5].

## MATERIALS AND METHODS:

**Materials:** Rivaroxaban was a generous gift from from MSN Ltd (Hyderabad, India). Peceol, Oleic acid, Peanut oil, Labrafil M 1944, Acetonitrile, Labrasol, Transcutol HP, Castor oil and sunflower oil, Cremophore Rh 40, Gelucire, Miglyol, Polyethylene glycol, Methanol, Ethanol Tween-80, Hydrochloric acid, potassium bromide, Membrane filters, Capsules.

**Solubility Analysis:** Apparent solubilities of rivaroxaban were determined in different oils, surfactants and co-surfactants at ambient temperature for the selection of appropriate oil and surfactant. About 1gm of each of vehicles was taken to different cap tube, where excess of Rivaroxaban was added was added in each vehicle. After sealing, the mixtures were heated at 50 °C in a water bath shaker to facilitate the solubilization. Then, the mixtures were agitated with shaker at room temperature for 48 hours [6]. After reaching equilibrium, samples were collected and centrifuged at 10,000 rpm for 15 min. 100µL of supernatant was collected and suitably diluted with acetonitrile and rivaroxaban was quantified by using UV spectrophotometry at 250 nm [7].

**Construction of Pseudo-Ternary Phase Diagrams:** Pseudo-ternary phase diagrams were constructed for selected oil, surfactant, and co-surfactant with water at room temperature by water titration method [8]. The surfactant was mixed with co-surfactant in ratio 4:1, 3:1, 1:4, 1:3 respectively. Aliquots of surfactant/co-surfactant mixture were then mixed with oil at ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 in different vials and then titrated with water at room T °C. The samples were then equilibrated for 30 seconds and visually observed after each addition. Based on visual observation the systems were classified as nano emulsion, micro emulsion, coarse dispersion and gel phases. Pseudo ternary phase diagrams were then constructed using Triplot software version 4.1.2. The samples which were bluish white in appearance were considered as micro-emulsions.

**Characterization of SMEDDS:**

**Self Emulsification and Visual Assessment:** The prepared emulsions were added drop wise to 250ml of water. Self emulsifying mixtures should quickly disperse in water with mild shaking [9].

**Dispersibility Test:** Self emulsification property of SMEDDS formulations was evaluated by visual assessment. Time taken for the formation of micro emulsion was determined by drop wise addition of formulation to 250 mL of distilled water, simulated gastric fluid and phosphate buffer of pH 6.8 in separate glass beakers at 37 °C. The contents were gently stirred using magnetic stirrer at 100 rpm. The tendency to form an emulsion was assessed as "good" when emulsification occurs rapidly in less than 1 minute with clear (or) transparent appearance. The tendency to form an emulsion was assessed as "bad when there is less clear emulsion formation. Depending on visual appearance and time taken for self emulsification, formulations are graded as,

**Grade I:** Rapidly forming (within 1min) micro emulsion having a clear (or) bluish appearance.

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

**Grade III:** Fine milky emulsion that formed within 2 minutes.

**Grade IV:** Dull, greyish white emulsion with a slight oily appearance that is slow to emulsify (more than 2 minutes).

**Phase Separation and Stability Study of Emulsions:** Each SMEDDS formulation (50µL) was added to a vials containing 5mL of double distilled water, simulated gastric fluid at room T °C and cyclomixed for 1 minute then each mixture was stored and observed for phase separation and precipitation of drug at intervals 2, 4, 6, 8, 12, 24 hours period of time [10].

**Robustness to Dilution:** Prepared SMEDDS formulations were subjected to dilution in ratios

1:100 and 1:1000 folds with distilled water, 0.1 N HCl and phosphate buffer of pH 6.8. The diluted micro emulsions were stored for 24 hrs and visually observed for any signs of phase separation (or) precipitation of drug [11 - 13].

**Percentage Transmittance:** Each SMEDDS formulation (100µL) was added to a vial containing 10mL of double distilled water, 0.1 N HCl and phosphate buffer of pH 6.8 at room T °C and cyclomixed for 1 minute. Each sample was observed for %Transmittance at 250nm.

**Drug Loading Efficiency:** Drug content in formulation was determined UV-Spectrophoto-metrically. 50mg of each formulation was accurately weighed and dilute to 100mL with acetonitrile. Resultant solutions were analyzed spectroscopically following suitable dilution [14].

Drug loading efficiency was calculated by equation:

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

**FT-IR Studies:** FT-IR Spectrum of pure drug and drug-excipients were obtained by FT-IR Spectro-photometer (Bruker-Alpha). The spectrums of drug, excipients and drug-excipients were taken with the accumulation 24 scans and a resolution of 4$cm^{-1}$ over the range of 400-4000$cm^{-1}$. The spectrums of drug-excipient mixtures so obtained were compared with spectrum of pure drug for any interactions [15].

**Thermodynamic Stability Studies:** The prepared SMEDDS formulations were subjected to thermodynamic stability studies to study the effect of centrifugation and temperature on stability of micro emulsions [16 - 17].

**Centrifugation Study:** The formulations were added to deionized water in ratio 1:20 and centrifuged at 3500 rpm for 30 min and observed for phase separation (or) precipitation.

**Freeze Thaw Cycle:** The formulations which are stable under centrifugation were subjected to freeze thaw cycle. In this study, SMEDDS formulations were diluted with deionized water in 1:20 ratio and subjected to two freeze thaw cycles between -20 °C and +25 °C by storing at each temperature for 48 hrs and after 48 hrs samples were observed for phase separation (or) precipitation.

***In vitro* Drug Release Study:** *In-vitro* drug release study was done for pure drug, and SMEDDS of Rivaroxaban. Percentage drug release and cumulative percentage drug release were calculated from absorbance and concentration that were obtained with the help of standard graph of rivaroxaban. *In-vitro* drug release study was performed for 60 min in 0.1N HCl.

**Droplet Size and Zeta Potential Determination:** Prepared SMEDDS formulations were added to distilled water in ratio 1:1000 in test tube and mixed for 1 minute using a cyclo mixer. The droplet size, PDI and zeta potential of the emulsions were determined at 25 °C by dynamic light scattering (DLS) technique at 90° angle Using a Zeta sizer nano ZS90.

**Preparation of Liquid SMEDDS:** Varying ratio of oil, surfactant, and co-surfactant were selected for formulation systems. Rivaroxaban was kept constant (20mg) for all formulations. Surfactant/co-surfactant mixture ($S_{mix}$) was prepared by mixing suitable proportions of surfactant, co-surfactants and they were cyclomixed. Rivaroxaban was accurately weighed and dissolved in suitable proportions of oil/ $S_{mix}$ mixture. The formulations were cyclomixed for 1minute to facilitate uniform mixing and then heated in thermostatic water bath at 40 °C to facilitate drug Solubilization. Then all formulations were cyclomixed until transparent preparations were obtained. Finally prepared liquid SMEDDS of Rivaroxaban were kept aside at room Temperature for 48 hrs and examined for signs of turbidity (or) phase separation and the formulation is characterised for various parameters.

## RESULTS AND DISCUSSION:

**Solubility of Rivaroxaban in Various Oils:** Solubility of Rivaroxaban in various oils was determined by UV spectrophotometer. The saturation solubility of Rivaroxaban in various oils is shown in **Table 1**. Peceol was selected for the formulation which forms good emulsion.

**Solubility of Rivaroxaban in Various Surfactants:** Solubility of Rivaroxaban was determined in various surfactants. From these surfactants Tween 80 is selected for formulation

which has highest solubility and good emulsifying ability. Results are shown in **Table 2.**

**TABLE 1: SOLUBILITY OF RIVAROXABAN IN VARIOUS OILS**

| Oils | Solubility(mg/mL) |
|---|---|
| Peceol | 19.2 ± 0.15 |
| Sunflower oil | 11.7 ± 0.2 |
| Oleic acid | 16.7 ± 0.25 |
| Castor oil | 1.8 ± 0.30 |
| Peanut oil | 2.8 ± 0.15 |
| Labrafil M 1944 | 11.2 ± 0.1 |
| Capmul | 0.8 ± 0.15 |
| Captex | 0.96 ± 0.01 |

All values are expressed as Mean, n = 3

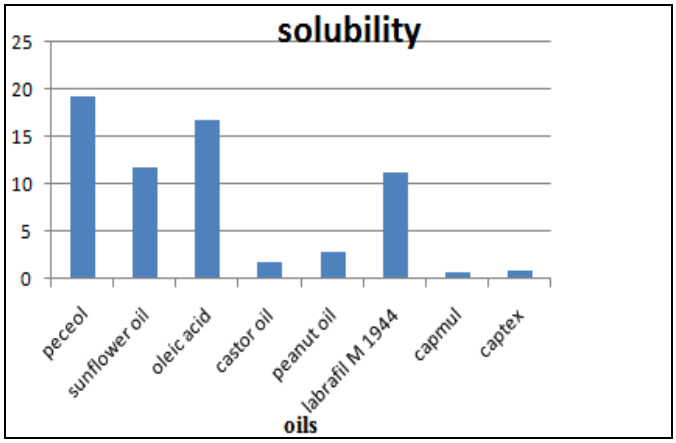


**FIG. 1: SOLUBILITY OF RIVAROXABAN IN VARIOUS OILS**

**TABLE 2: SOLUBILITY OF RIVAROXABAN IN VARIOUS SURFACTANTS**

| Surfactants | Solubility(mg/mL) |
|---|---|
| Cremophore RH 40 | 6.2 ± 0.1 |
| Gelucire | 5.0 ± 0.1 |
| Tween 80 | 14.5 ± 0.15 |
| Labrasol | 4.3 ± 0.1 |
| Miglyol | 6.2 ± 0.15 |

All values are expressed as Mean, n = 3

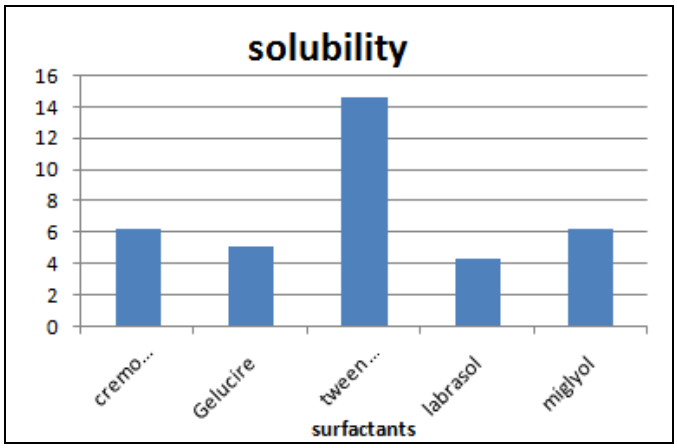


**FIG. 2: SOLUBILITY OF RIVAROXABAN IN VARIOUS SURFACTANTS**

**Solubility of Rivaroxaban in Various Co-surfactants:** Solubility of Rivaroxaban in various co-surfactants was determined. From this transcutol HP is selected for the formulation. Solubilities of various co surfactants are shown in **Table 3**.

**TABLE 3: SOLUBILITY OF RIVAROXABAN IN VARIOUS CO-SURFACTANTS**

| Co surfactants | Concentration(mg/mL) |
|---|---|
| PG | 7.7 ± 0.30 |
| Ethanol | 7.8 ± 0.25 |
| Transcutol | 16.3 ± 0.15 |

All values are expressed as Mean n = 3

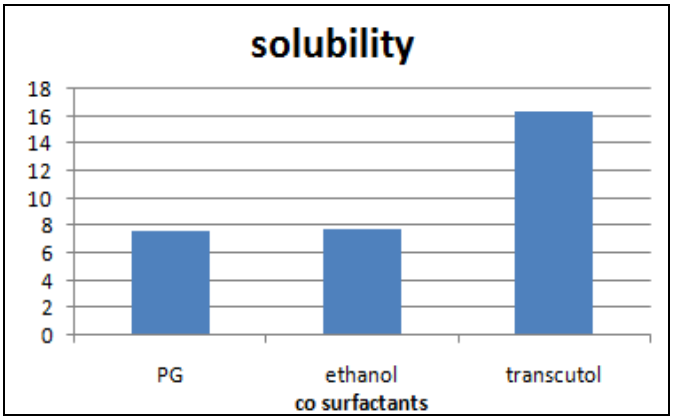


**FIG. 3: SOLUBILITY OF RIVAROXABAN IN VARIOUS CO-SURFACTANTS**

**Selection of Excipients:** Based on the solubility studies done on various oils, surfactants and co surfactants, excipients which have shown more solubility was selected for the formulation.

- Oil: Peceol
- Surfactant: Tween 80
- Co-surfactant: Transcutol HP

**Pseudo-ternary Phase Diagrams:** Pseudo-ternary Phase Diagrams are constructed to identify the micro emulsion regions and to identify suitable composition of oil, surfactant and co-surfactant for formulation of SMEDDS. From Pseudo-ternary phase diagrams it has been found that the systems consisting of Peceol as oily phase, Tween 80 as surfactant and Transcutol HP as co-surfactant showed good micro emulsifying property though drug has been shown more solubility in systems containing peceol as oil phase, Tween 80 as surfactant and transcutol HP as co surfactant based on solubility studies. It was also found that systems containing Tween 80 as surfactant showed appearance of micro emulsion.

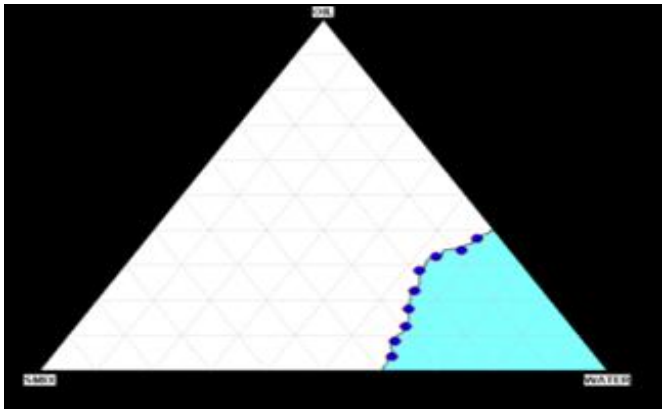

**FIG. 4: PSEUDO TERNARY PHASE DIAGRAM OF PTWT1**

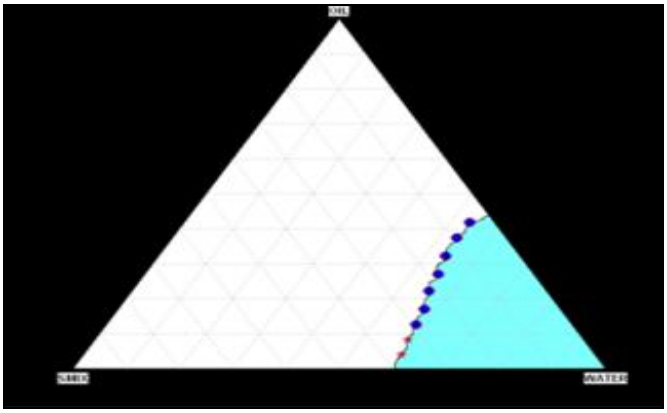

**FIG. 5: PSEUDO TERNARY PHASE DIAGRAM OF PTWT2**

**Size and Zeta Potential Determination:** Prepared formulations are analysed in zeta sizer for the determination of size and zeta potential values they are shown in various tables below.

**TABLE 4: PTWT1 FORMULATION**

| Oil: $S_{mix}$ | Size of emulsion droplets (dnm) | Region | Zeta Potential (mV) | PDI |
|---|---|---|---|---|
| PTWT1 1:9 | 357.2 | Micro | -16.9 | 0.621 |
| PTWT1 2:8 | 349.3 | Micro | -10.3 | 0.435 |
| PTWT1 3:7 | 220.2 | Micro | -6.7 | 0.645 |
| PTWT1 4:6 | 219.1 | Micro | -7.8 | 0.723 |
| PTWT1 5:5 | 212.1 | Micro | -4.7 | 0.834 |
| PTWT1 6:4 | 219.5 | Micro | -0.4 | 0.765 |
| PTWT1 7:3 | 218.3 | Micro | -2.2 | 0.923 |
| PTWT1 8:2 | 220.4 | Micro | -3.6 | 0.687 |
| PTWT1 9:1 | 219.1 | Micro | -1.3 | 0.832 |

**TABLE 5: PTWT2 FORMULATION**

| Oil: $S_{mix}$ | Size of emulsion droplets (dnm) | Region | Zeta Potential (mV) | PDI |
|---|---|---|---|---|
| PTWT2 1:9 | 215.3 | Micro | -8.34 | 0.337 |
| PTWT2 2:8 | 219.3 | Micro | -7.88 | 0.425 |
| PTWT2 3:7 | 223.7 | Micro | -5.8 | 0.982 |
| PTWT2 4:6 | 216.8 | Micro | -6.4 | 0.786 |
| PTWT2 5:5 | 252.2 | Micro | -7.8 | 0.845 |
| PTWT2 6:4 | 247.2 | Micro | -6.4 | 0.654 |
| PTWT2 7:3 | 229.4 | Micro | -2.6 | 0.623 |
| PTWT2 8:2 | 219.6 | Micro | -3.5 | 0.785 |
| PTWT2 9:1 | 217.5 | Micro | -5.7 | 0.823 |

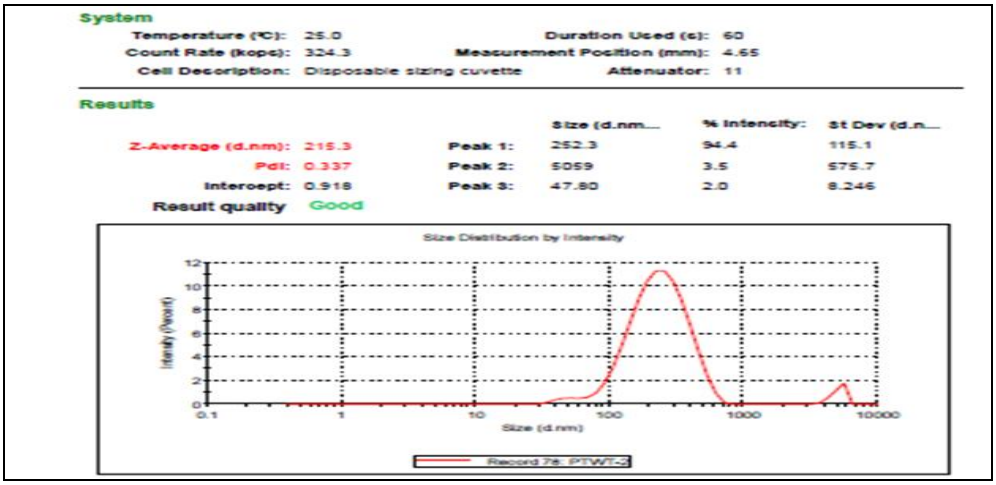


**FIG. 6: DROPLET SIZE DISTRIBUTION OF PTWT2 1:9**

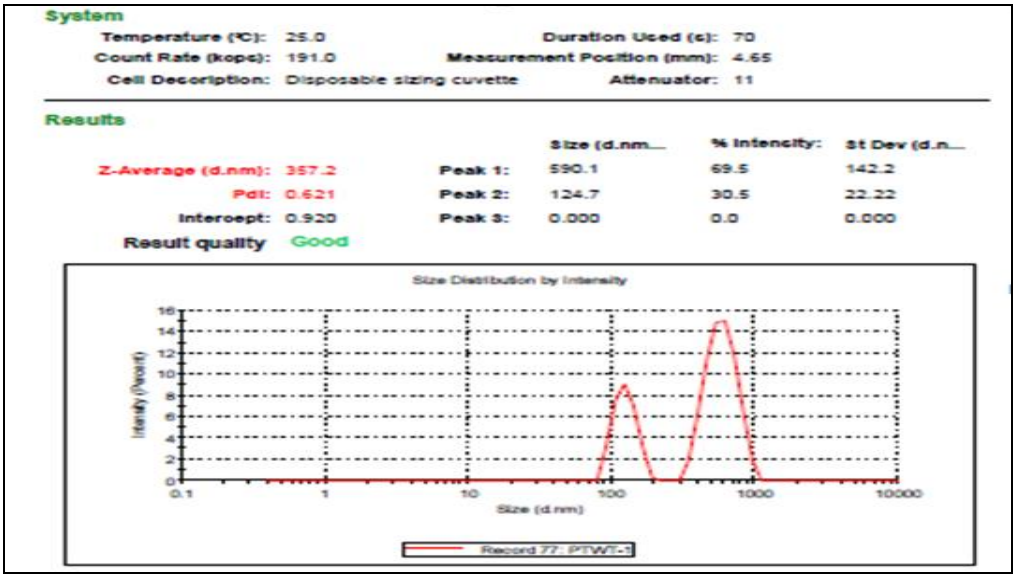


**FIG. 7: DROPLET SIZE DISTRIBUTION OF PTWT1 1:9**

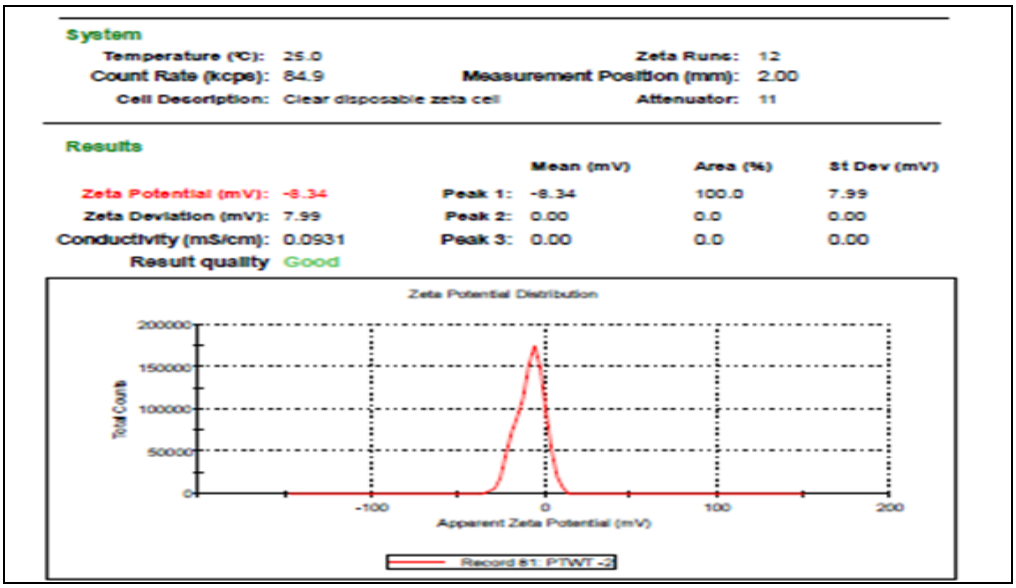


**FIG. 8: ZETA POTENTIAL OF PTWT2 1:9**


**FIG. 9: ZETA POTENTIAL OF PTWT1 1:9**

**Self Emulsification and Visual Assessment:** 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 6**. The prepared SMEDDS of Rivaroxaban were emulsified less than 1min (20-30 sec). Efficiency of all prepared emulsions was good.

**TABLE 6: SELF EMULSIFICATION TIME (SEC)**

| S. no | Formulation | Emulsification time | Remark |
|---|---|---|---|
| 1 | PTWT2 1:9 | 25 ± 1.2 sec | Good |
| 2 | PTWT2 2:8 | 27 ± 1.5 sec | Good |

**Dispersibility Test:** The two formulations showed grade 1 emulsions when the test is performed in distilled water, 0.1N HCl and phosphate buffer 6.8.

**TABLE 7: DISPERSIBILITY TEST RESULTS**

| Formulation name | Distilled water | 0.1N HCL | Phosphate buffer of pH 6.8 |
|---|---|---|---|
| PTWT2 1:9 | Grade 1 | Grade 1 | Grade1 |
| PTWT2 2:8 | Grade 1 | Grade 1 | Grade1 |

**Phase Separation and Stability Study of Emulsions:** Prepared SMEDDS formulations are observed for precipitation and phase separation of drug at intervals 2, 4, 6, 8, 12, 24 hrs periods of time and it was found that all formulations showed neither precipitation nor phase separation of the drug. Results are given in **Table 8**.

**TABLE 8: PHASE SEPARATION AND PRECIPITATION OF THE DRUG (n = 3)**

| S. no | Formulation | Precipitation | Phase separation |
|---|---|---|---|
| 1 | PTWT2 1:9 | No | No |
| 2 | PTWT2 2:8 | 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 24 hrs 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 (**Table 9**).

**TABLE 9: ROBUSTNESS TO DILUTION (n = 3)**

| S. no | Formulation name | Distilled water | 0.1N HCL | Phosphate buffer of pH 6.8 |
|---|---|---|---|---|
| 1 | PTWT2 1:9 | No | No | No |
| 2 | PTWT2 2:8 | No | No | No |

No-indicates no phase separation and precipitation

**Percentage Transmittance:** Each diluted sample was observed for % Transmittance at 250nm. Results are given in **Table 10**. All formulations showed % transmittance more than 95% indicating clear emulsions.

**TABLE 10: PERCENTAGE TRANSMITTANCE**

| S. no | Formulation name | Distilled water | 0.1N HCL | Phosphate buffer pH 6.8 |
|---|---|---|---|---|
| 1 | PTWT2 1:9 | 95.3±0.25 | 97.56±0.78 | 96.67±0.324 |
| 2 | PTWT2 2:8 | 96.56±0.98 | 94.68±0.43 | 95.3±0.567 |

All values are expressed as Mean ± SD (n = 3)

**Drug Loading Efficiency:** 50 mg of each SMEDDS formulation was diluted with 100 mL Acetonitrile. Resultant solutions are analyzed UV-Spectrophotometrically following suitable dilution. Absorbance of each solution is measured at 250 nm. Results are given in **Table 11**. It was found both formulations have drug loading efficiency more than 90%.

**TABLE 11: DRUG LOADING EFFICIENCY OF FORMULATIONS**

| S. no | Formulation name | Drug loading efficiency |
|---|---|---|
| 1 | PTWT2 1:9 | 96.34±0.678 |
| 2 | PTWT2 2:8 | 97.56±0.56 |

All values are expressed as Mean ± SD (n = 3)

**FT-IR Studies:** The spectrums of drug-excipient mixtures and the formulations so obtained were compared with spectrum of pure drug for any interactions. Characteristic peaks were observed at 2979 $cm^{-1}$, 2938 $cm^{-1}$, 2138 $cm^{-1}$, 1738 $cm^{-1}$, 1666 $cm^{-1}$, 1546 $cm^{-1}$, 1281 $cm^{-1}$ for CH stretching, OH stretching, CN stretching and C=C stretching, C-N stretching, C=O stretching, C-Cl stretching respectively. FT-IR spectrum of pure drug and the formulation were almost similar because of same functional groups. It indicates there was no interaction between Rivaroxaban and excipients used in formulation.

**Thermodynamic Stability Studies:** Thermodynamic stability study is designed to identify Meta-stable formulation. The SMEDDS are subjected to Centrifugation study and Freeze thaw cycle. The emulsions are stable during centrifugation at 3,500 rpm and alternative temperature cycles of -20 °C and +25 °C. There is no precipitation and phase separation of formulations. The results are given in **Table 12.**

**TABLE 12: THERMODYNAMIC STABILITY STUDIES**

| S. No | Formulation name | Centrifugation (3,500 rpm for 30min) | Freeze thaw cycle (-20 °C and +25 °C) |
|---|---|---|---|
| 1 | PTWT2 1:9 | *P | *P |
| 2 | PTWT2 2:8 | *P | *P |

*P-Passed

***In- vitro* Drug Release Study:** After performing the drug release study for 60 min in 0.1 N HCl pure drug showed the 71.45 % drug release and the PTWT2 1:9 showed 81.32 % drug release and PTWT2 2:8 showed 72.12 % drug release.

**TABLE 13: CUMULATIVE % RELEASE OF PURE DRUG AND FORMULATIONS**

| Time | Pure drug | PTWT2 1:9 | PTWT2 2:8 |
|---|---|---|---|
| 5 | 25.89 | 55.60 | 47.35 |
| 10 | 37.23 | 58.21 | 50.54 |
| 15 | 45.10 | 62.78 | 54.83 |
| 30 | 50.16 | 67.90 | 59.31 |
| 45 | 62.15 | 72.50 | 64.5 |
| 60 | 71.45 | 81.32 | 72.12 |

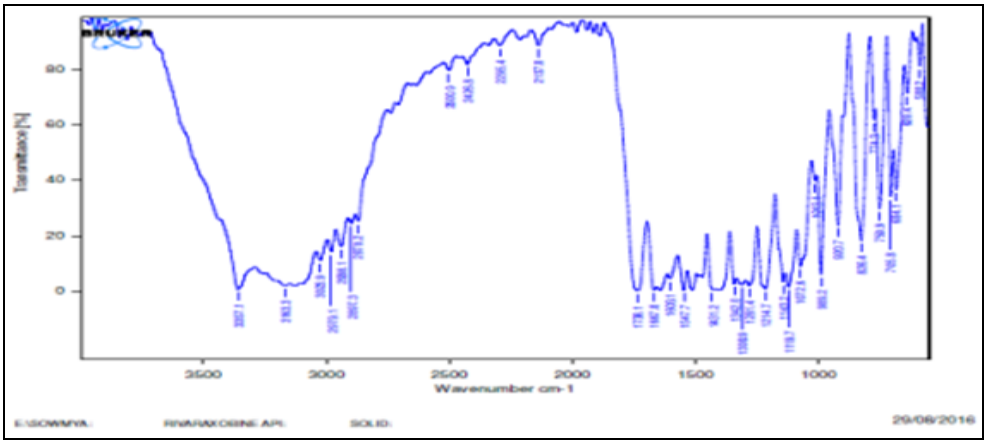


**FIG. 10: FT-IR SPECTRUM OF PURE DRUG (RIVAROXABAN)**

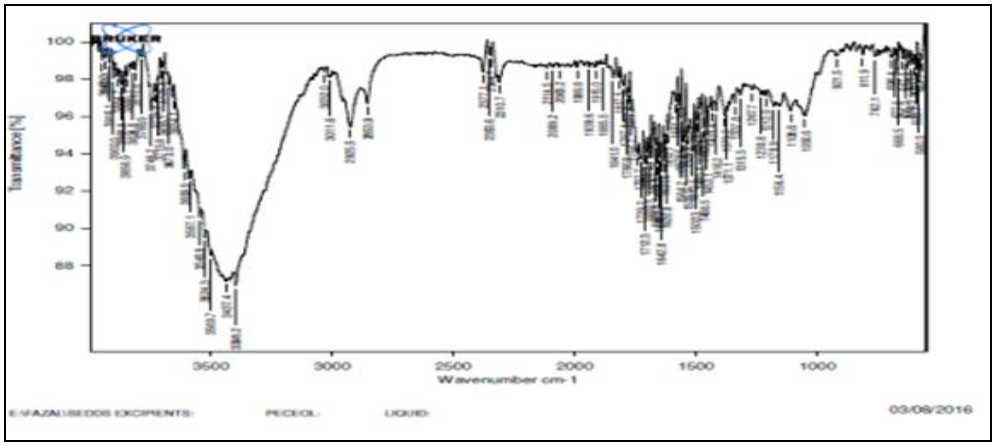


**FIG. 11: FT-IR SPECTRUM OF PECEOL**

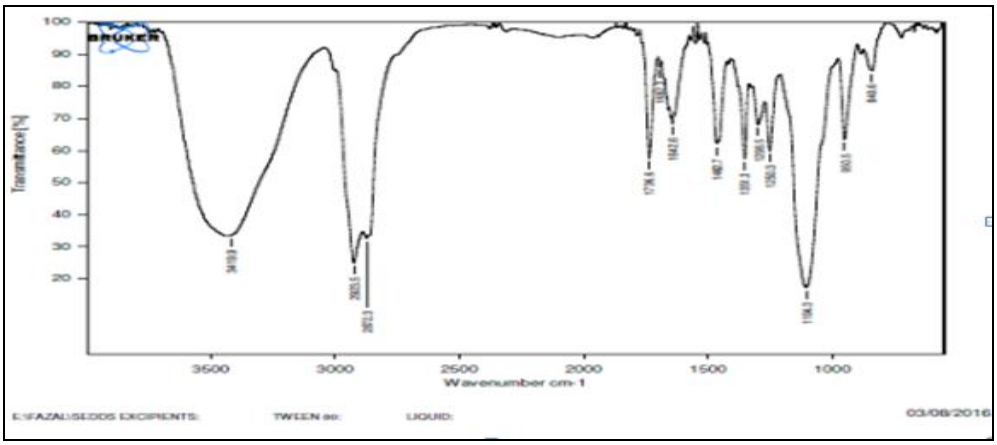


**FIG. 12: FT-IR SPECTRUM OF TWEEN 80**

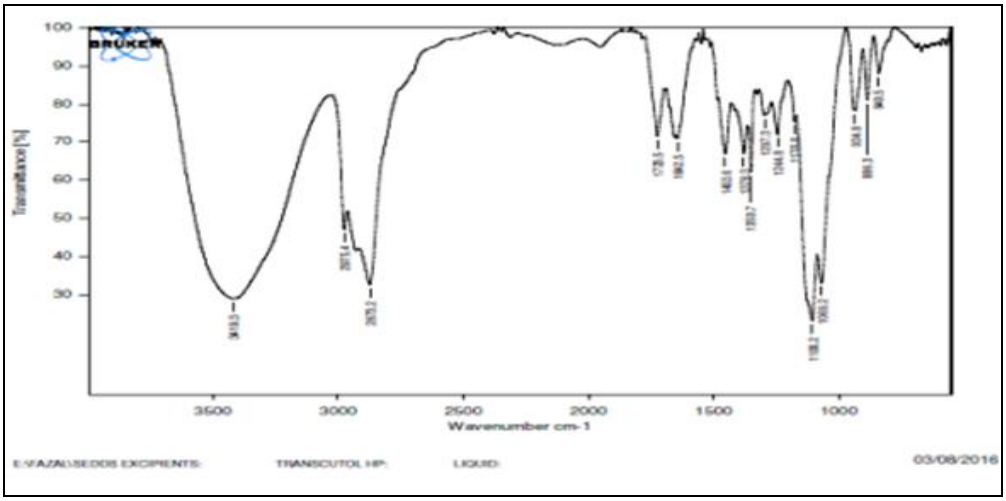


**FIG. 13: FT-IR SPECTRUM OF TRANSCUTOL HP**

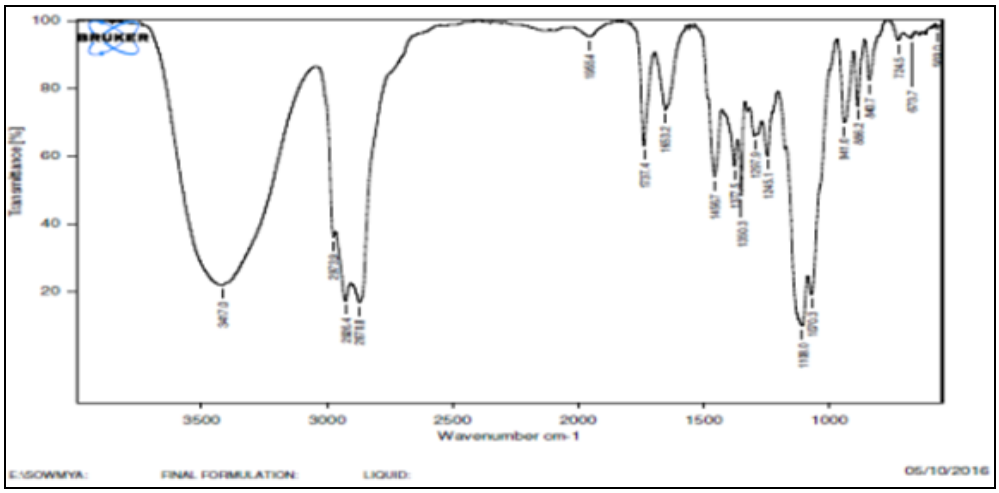


**FIG. 14: FT-IR SPECTRUM OF LIQUID SMEDDS**

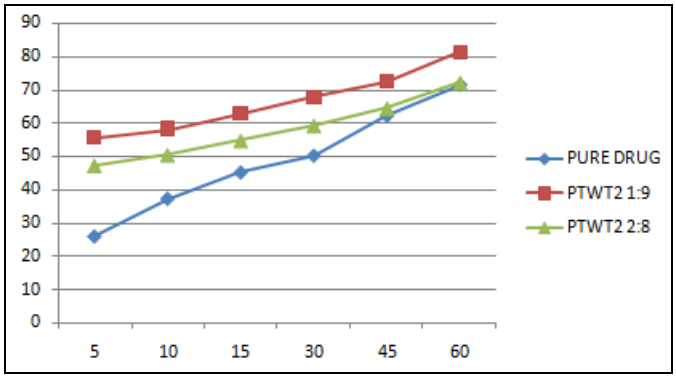


**FIG. 15: COMPARISION OF % DRUG RELEASE**

**SUMMARY AND CONCLUSION:** The drug Rivaroxaban which was poorly soluble was selected for formulation of SMEDDS due to its poor aqueous solubility and its oral bioavailability which is 66%. Self micro emulsifying drug delivery system was developed to improve its solubility and bioavailability. Solubility of Rivaroxaban is determined in various oils, surfactants, co-surfactants by UV-Spectrophotometric method. Rivaroxaban has been shown maximum solubility in oils peceol, co-surfactant, transcutol HP and surfactant Tween 80.

A series of Pseudo ternary phase diagrams are constructed to identify micro-emulsion region. Various compositions of Oil and $S_{mix}$ are titrated with water to identify micro-emulsion region. From pseudo-ternary phase diagrams systems consisting of peceol as oily phase, Tween 80 as surfactant, Transcutol HP as co surfactant is selected for formulation. SMEDDS are prepared by selecting oil: $S_{mix}$ ratio 1:9 ….9:1 and $S_{mix}$ ratio 1:4, 1:3.

Two mixtures (PTWT2 (1:9), PTWT2 (2:8)) are selected for formulation of SMEDDS by keeping amount of drug constant (20mg) in all formulations. Prepared formulations are evaluated for Self emulsification and visual assessment, Phase separation and precipitation of the drug, Robustness to dilution, Percentage Transmittance,

drug loading efficiency, FT-IR Studies, Thermodynamic stability studies, Droplet size, PDI and Zeta potential. All formulations are emulsified in 25-30 seconds *i.e.* in less than 1 min. No formulation had showed precipitation and phase separation of drug. All formulations are robust to dilution.

All formulations shown percentage transmittance more than 95% (95.3 ± 0.25 to 96.56 ± 0.98) indicating clear emulsions. All formulations have drug loading efficiency more than 90%. Thermodynamic stability studies had indicated that all formulations are stable after centrifugation and freeze thaw cycle. Droplet size was found to be 215.3nm and 219.3nm and PDI of two formulations was found to be 0.33-0.42 *i.e.* there are uniform size particles. Zeta potential was found to be - 8.34 and - 7.88 mV. FT-IR spectrum shown no interaction between drug and excipients.

Based on evaluation tests done for two liquid SMEDDS formulations and dissolution study the formulation PTWT2 (1:9) showed more drug release when compared to other formulation PTWT2(2:8) and also showed good self emulsification property with droplet size (215.3 nm) and more uniform particles (PDI = 0.33). The present studies indicates that SMEDDS can be potentially used a drug delivery system for delivering poorly water soluble drugs.

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**CONFLICTS OF INTEREST:** Nil

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