International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (4): 174-189
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved

# Solubility and Dissolution Enhancement of Poorly Aqueous Soluble Drug Ibrutinib by Self Emulsifying Drug Delivery System

**M. Sunitha Reddy* and Gavvalapally Swapna**
**Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana-500085, India.**

Received: 10 Jul 2019 / Accepted: 19 Aug 2019 / Published online: 1 Oct 2019
***Corresponding Author Email:** baddam_sunitha@jntuh.ac.in

## Abstract
The present work mainly emphasized on the enhancement of solubility of Ibrutinib by developing Self-emulsifying lipid formulations. Ibrutinib is a BCS class II drug with poor aqueous solubility (oral bioavailability 3.9%). The saturated solubility of Ibrutinib in various oils, surfactants and co-surfactants was determined using UV-spectroscopy. The excipients were screened and selected based on their maximum solubility and compatibility for Ibrutinib. SEDDS formulations of Ibrutinib were developed using different Oils, Surfactants and Co-Surfactant combinations (4:1 and 3:1). Pseudo ternary phase diagrams were constructed using Triplot V 4.1.2 software and based on Pseudo ternary phase diagrams, nano-emulsification area was evaluated. Formulations were designed based on Pseudo ternary phase diagrams using various proportions of oil (Capmul MCM C8 EP), surfactants (Kolliphor EL) and co-surfactants (Labrasol). The prepared four formulations were selected among them F3 was optimized and carried out for further evaluations like robustness to dilution (Passed), dispersibility test (Grade A), self-emulsification time (28 ±1.08 sec), percentage transmittance (Clear emulsions), drug loading efficiency (96.49 ± 0.48%), thermodynamic stability study (Passed), emulsion globule size (17.6 d.nm) and zeta potential (-10.6 mV), invitro drug release studies. Among the four formulations, F3 (C8KEL3LA1 1:9) was optimized formulation because it gave the best results in terms of required In-vitro drug release. The dissolution rate of F3 SEDDS (84.22 ± 0.20 %) was compared with Ibrutinib (API) (54.98 ± 0.32 %). The results indicated that the solubility and dissolution rate of Ibrutinib SEDDS has significant increase of 1.53 times when compared to pure drug (API). The results of the present studies demonstrate that Ibrutinib SEDDS can be used as a potential means for improving solubility and dissolution rate of Ibrutinib.

**Keywords**
Ibrutinib, Oils, Surfactants, Co-surfactants, SEDDS, Pseudo ternary phase diagrams, Zeta potential, Thermodynamic stability study.

*****

## INTRODUCTION:
Majority of the new chemical entities (NCE) developed today are sparingly soluble in water and show poor bioavailability. It is because their properties are shifting towards higher molecular weight and high lipophilicity.

The therapeutic efficacy and bioavailability of any drug depends upon the solubility of drug. One of the important parameters to achieve the desired concentration of drug in systemic circulation for the pharmacological response is drug solubility. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation [1, 2, and 3].

Various formulation strategies have been reported to enhance the solubility of drugs, these includes, particle size reduction, pH adjustment, co- solvency [4], complexation [5], solid dispersions [6] , SEDDS (self-emulsifying drug delivery systems) etc. However, each technique has its own advantages and limits. Among all these techniques SEDDS appear to be potential method for the solubility enhancement due to its ease of formulation and evaluation.

SEDDS 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. SEDDS require very less energy to emulsify, and so they undergo spontaneous emulsification in the lumen of gut up on dilution in aqueous phase under the gentle agitation provided by the GI motility. The emulsions so formed are easily absorbed from the gastrointestinal tract through the villi as chylomicrons.

As oral route is one of most commonly used method for administration of drugs and drug delivery. The poorly soluble drugs such as HIV protease inhibitors, glycoprotein inhibitors and anticancer drugs have problems to produce and retain a good solubility in GIT.

Hence, Self-emulsifying drug delivery system approach is presently used to tackle the formulation challenges of poorly soluble medication, by rising dissolution rate and maintaining the drug in solution throughout its period in GIT

Ibrutinib is a BCS II drug with poor solubility and mean bioavailability (3.9%). Ibrutinib is an anti-neoplastic agent. Ibrutinib (Imbruvica) is a small molecule drug that binds permanently to a protein, Bruton's tyrosine kinase (BTK), that is important in B cells. It is used to treat B cell cancers like mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom's macroglobulinemia [7, 8].

The objective of the present study was to optimize Ibrutinib SEDDS to maintain nanosized globules on dilution by GI fluids with an aim to increase solubility and dissolution rate of Ibrutinib SEDDS.

## MATERIALS AND METHODS:

### Materials:

Ibrutinib was generous gift from NATCO Phrma Ltd (Hyderabad, India), Peceol, Labrasol, Transcutol HP were kind gifts from Gattefosse, France. Kolliphor HS 15, Kolliphor RH40, Kolliphor EL were kind gifts from BASF. Crodamol PC-LQ, Capmul MCM C8 EP, Capmul PG 8NF, Captex 200 were kind gifts from Abitec Corporation, USA.PEG grades (200,300,400) were purchased from Merck specialities pvt. ltd.Tween 85 was kind gift from sigma life sciences, India. Span 80 was obtained from lobachemie and Simusol 1292 and olive oil were kind gifts from seppic and oleomonterreasl respectively. Other analytical reagents were purchased from Research lab fine chem industry.

### UV Spectrophotometric analysis of Ibrutinib in methanol:

10 mg of Ibrutinib was accurately weighed and transferred into 10 ml volumetric flask, dissolved in methanol and made up to the volume.

From the standard stock solution, concentrations 2, 4, 6, 8 and 10 ppm were prepared using methanol. The UV-Visible spectrophotometer absorbance of Ibrutinib was scanned from wavelength of 400-200nm.The spectrum shows maximum absorbance at 258 nm. The wavelength ($\lambda_{max}$) selected was 258 nm and utilized for further analysis, in the present investigation.

From the standard stock solution, concentrations 2, 4, 6, 8 and 10 ppm were prepared using methanol. The absorbance was measured at 258 nm. Standard plot was drawn using the data obtained.

### UV Spectrophotometric analysis of Ibrutinib in 0.1N HCl:

10 mg of Ibrutinib was accurately weighed and transferred into 10 ml volumetric flask, 2 ml of methanol was added to dissolve the drug and made up to the final volume using 0.1N HCl.

From the standard stock solution, concentrations 2, 4, 6, 8, 10, 12 and 14 ppm were prepared using 0.1N HCl. The spectrum shows maximum absorbance at 223 nm. The wavelength ($\lambda_{max}$) selected was 223 nm and utilized for further analysis, in the present investigation.

From the standard stock solution, concentrations 2, 4, 6, 8, 10, 12 and 14 ppm were prepared using 0.1N HCl. The absorbance was measured at 223 nm. Standard plot was drawn using the data obtained.

### Solubility studies:

The solubility of Ibrutinib was determined in various oils, surfactants and co-surfactants. Excess amount of drug was added to 1 gram of each excipient in different cap vials. The mixtures were cyclo-mixed

immediately using cyclo-mixer (REMI CM 101) for 2 minutes to increase drug solubilization. The mixtures are then placed for heating at 40-50°c for 5 minutes. The resultant mixture was then kept aside for equilibration at room temperature in an isothermal mechanical shaker rotary shaker (REMI RS 12 R) at a speed of 100 rpm for 72hours. The supersaturated solutions were then centrifuged at a speed of 3000 rpm for 15 minutes to remove the undissolved drug. The supernatant was separated, and aliquots of supernatant fluid was drawn utilizing a micropipette and adequately diluted with methanol. The concentration of Ibrutinib in each excipient was determined spectrophotometrically at $\lambda_{max}$ 258 nm.

**Construction of Pseudo ternary phase diagram:**

Pseudo ternary phase diagrams were constructed using water titration method at room temperature to identify self-nano emulsifying regions and to select suitable concentrations of oils, surfactant and co-surfactant for formulation of SEDDS. The ratio of surfactant to co-surfactant (S.mix) was also optimized using pseudo ternary phase diagram. Surfactant and co-surfactant (S.mix) in each group were mixed in weight ratios (4:1, 3:1). For each phase diagram, 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, 1:9 in different glass vials. Each mixture was titrated with water and are vortexed for 2mins and allowed to equilibrate. The change in physical state from transparent to turbid were visually observed and marked on three component ternary phase where each axis represented oil, s.mix and water respectively. The different phase diagrams were plotted using Triplot version 4.1.2. Components used for construction of pseudo ternary phase diagram are Capmul MCM C8 EP (oil), kolliphor EL (surfactant), labrasol (co-surfactant) and distilled water (aqueous phase).

The phase diagrams were mapped at surfactant to co-surfactant ratios (4:1, 3:1).

**Drug-excipient compatibility studies by FT-IR spectroscopy:**

Excipient compatibility studies are conducted mainly to predict the potential incompatibility of drug (API) in the final dosage form. These studies provide justification for selection of excipients and concentrations in formulation as required in regulatory filings. These studies are important in drug development process, as the knowledge gained from excipients compatability studies is used to select dosage form components, delineate stability profile of drug, identify degradation products. Ibrutinib and excipients were analyzed by FT-IR spectrophotometer with data acquisition system OPUS.

**Formulation of Ibrutinib liquid SEDDS:**

Once nano-emulsifying region was identified using pseudo ternary phase diagrams, SEDDS formulation with desired component ratios were selected for Ibrutinib incorporation and optimization. A series of SEDDS formulations were prepared with varying weight ratios of selected oil (200-400 %w/w), surfactant (1200-1440 %w/w) and co-surfactant (360-400 %w/w). In all the formulations, amount of Ibrutinib (100mg) was kept constant. Amount of Ibrutinib was dispersed into mixture of oil to solubilize the lipophilic drug with continuous mixing in glass vials using vortex mixer. Surfactant and co-surfactant were accurately weighed into the mixture of oil and drug and then vortexed to ensure complete mixing until Ibrutinib was completely dissolved. These systems were warmed to 40°C using a water bath for 30mins with mild shaking until a clear solution was obtained. The prepared formulations were stored at room temperature for further investigation.

**Evaluation of Ibrutinib liquid SEDDS:**

**Dispersibility test [9]:**

The self-emulsification efficiency of Ibrutinib liquid SEDDS was evaluated using a standard USP dissolution apparatus type II . 0.1 ml of each formulation were added to 200 ml of distilled water maintained at 37 ± 0.5°C and gently agitated using a magnetic stirrer. The prepared SEDDS formulations were assessed visually according to rate of emulsification and final appearance of nano-emulsion.

**Self-emulsification time [10]:**

0.1ml of each formulation were added to 200 ml of distilled water maintained at 37 ± 0.5°C and gently agitated using a magnetic stirrer rotating at constant speed. The emulsification time (time required for a pre-concentrate to form a homogenous mixture upon dilution) was assessed visually by observing disappearance of SEDDS and final appearance of nanoemulsion.

**Robustness to dilution [11]:**

Robustness of different Ibrutinib SEDDS formulations to dilution was done by diluting 0.1ml of each formulations to 10, 100 and 1000 times with distilled water, 0.1N HCl and phosphate buffer of pH 6.8. The diluted formulations were mixed using a magnetic stirrer at 37 ± 0.5°C to simulate body temperature and gastric motility in GIT till complete homogenity. These systems were stored at ambient temperature for 24 hrs then visually observed for any signs of phase separation.

**Percentage transmittance [12]:**
Each Ibrutinib SEDDS formulation (0.1ml) was added to 10 ml volumetric flask containing 0.1N HCl, distilled water and phosphate buffer of pH 6.8 at 37 ± 0.5°C. After 1 min vortexing, each mixture is observed for % transmittance at $\lambda_{max}$ screened with API (Ibrutinib).

**Thermodynamic stability studies [13]:**
Thermodynamic stability is performed to determine effect of temperature and centrifugation. The formulations were added to millipore water (1:10) and centrifuged at 3500 rpm for 30 mins and observed for changes like phase separation or precipitation. The preparations which are stable are subjected to freeze thaw cycle. In freeze thaw cycle, Ibrutinib SEDDS are diluted with millipore water (1:20) and two freeze thaw cycle between -20°C to +25°C with storage at each temperature for not less than 48 hrs and observed for phase separation or precipitation.

**Drug loading efficiency [14]:**
Drug content in formulation was determined by taking 0.1ml of each formulation and diluted to 100ml with methanol. Drug loading efficiency was calculated by equation:

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

**Determination of Globule size and zeta potential [15]:**
SEDDS are vortexed with magnet after adding 100 times of distilled water in test tube or beaker. The globule size distribution and zeta potential of resultant formulation are determined after 1 hour by Dynamic Light Scattering (DLS) spectroscopy using a Zetasizer Nano ZS 90 Version 7.10 (Malvern Instruments). Size analysis is performed at 25°C placing disposable sizing cuvette and zeta potential is performed using an electrophoretic cell with an angle of detection of 90° measurement.

**In-vitro drug release studies:**
The in-vitro dissolution study of Ibrutinib liquid SEDDS were studied using USP Type II dissolution test apparatus (DS 8000 Lab India). Liquid filled capsules containing 100 mg of Ibrutinib are placed in buffer medium that consists of 900 ml of 0.1N HCl at 37± 0.5°C with 50 rpm. Aliquots (5ml) were withdrawn at selective time intervals such as 5,10,15,30,45 and 60 min respectively and replaced by buffer to maintain sink conditions. The samples are then screened for amount of drug release from standard graph at absorbance 258nm.

## RESULTS AND DISCUSSION:

**Determination of $\lambda_{max}$ and calibration curve of Ibrutinib in methanol:**
The wavelength ($\lambda_{max}$) was measured at 258 nm, using UV spectrophotometer with methanol as blank. Standard graph of Ibrutinib in methanol was plotted by concentration range from 2-14 µg/ml. The standard graph was plotted using the values shown in Table no 1. A graph of absorbance Vs concentration was plotted which indicated in compliance to Beer-lambert's law in concentration range. Standard plot of Ibrutinib in methanol was plotted by taking absorbance on X-axis and concentration on Y-axis, the plot is shown in Figure no 2. The regression coefficient $R^2$ was found to be 0.99888.

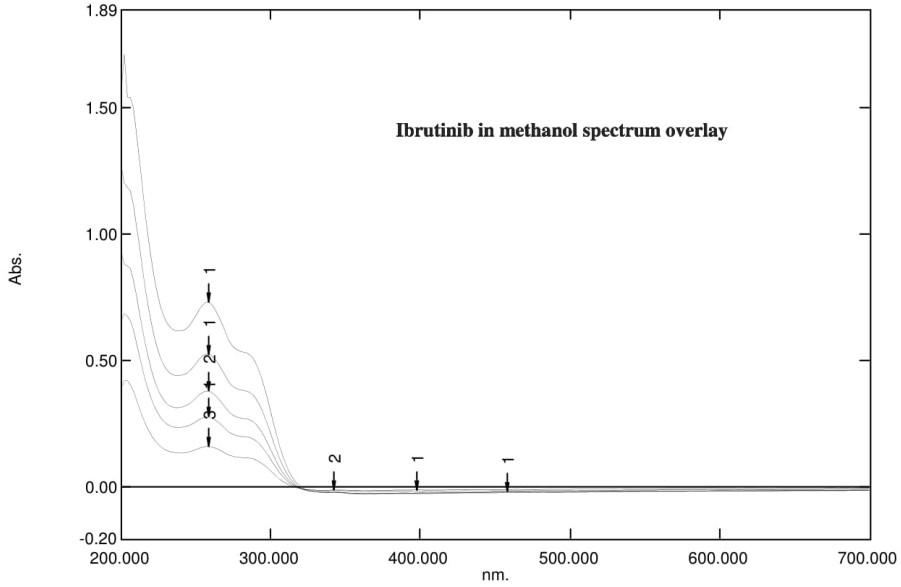



**Figure no: 1 Spectrum overlay of Ibrutinib in methanol**

**Calibration curve for Ibrutinib in methanol:**

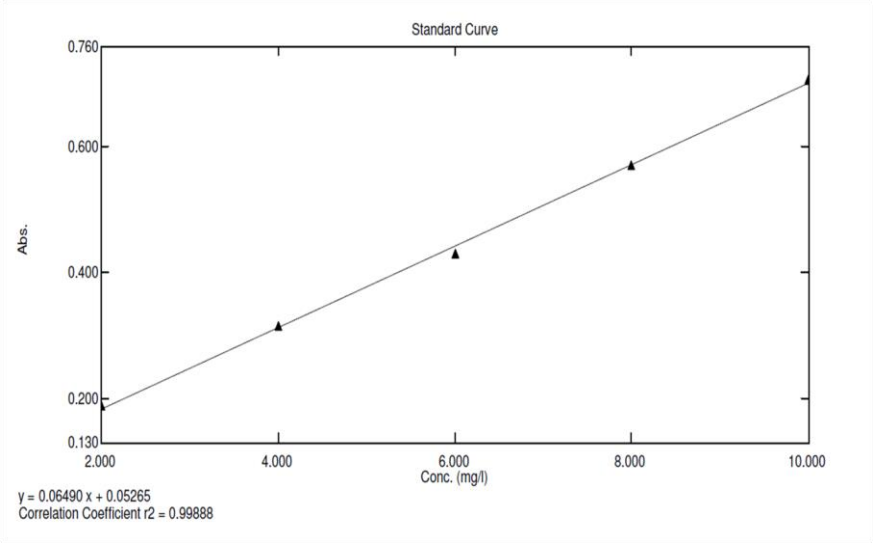



**Figure no: 2 Calibration curves of Ibrutinib in methanol**

**Table no: 1 Standard graph values of Ibrutinib in methanol.**

| Concentration (ppm) | Absorbance (nm) |
|---|---|
| 2 | 0.187 |
| 4 | 0.314 |
| 6 | 0.431 |
| 8 | 0.571 |
| 10 | 0.707 |

**Determination of λ max and calibration curve of Ibrutinib in 0.1N HCl:**

The wavelength (λ max) was measured at 250 nm, using UV spectrophotometer with as 0.1N HCl blank. Standard graph of Ibrutinib in 0.1N HCl was plotted by concentration range from 2-14 µg/ml. The standard graph was plotted using the values shown in Table no 2. A graph of absorbance Vs concentration was plotted which indicated in compliance to Beer-lambert's law in concentration range. Standard plot of Ibrutinib in 0.1N HCl was plotted by taking absorbance on X-axis and concentration on Y-axis, the plot is shown in Figure no 4. The regression coefficient $R^2$ was found to be 0.98423.

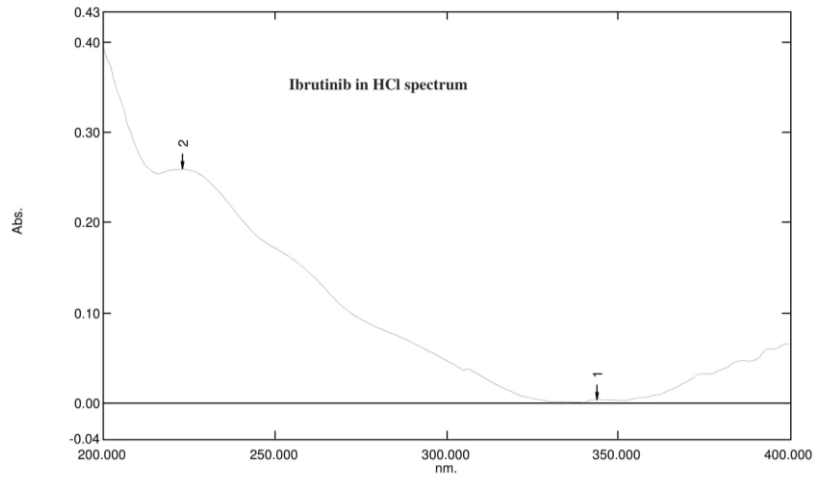



**Figure no: 3 Spectrum overlay of Ibrutinib in 0.1 N HCl**

**Calibration curve for Ibrutinib in 0.1 N HCl:**

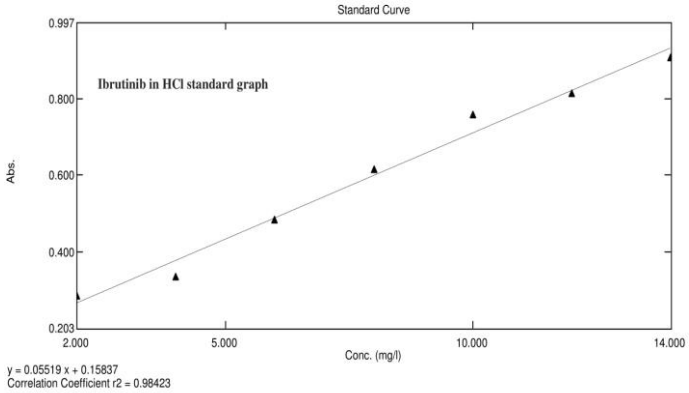



**Figure no: 4 Calibration curves of Ibrutinib in 0.1 N HCl.**

**Table no: 2 Standard graph values of Ibrutinib in 0.1N HCl.**

| Concentration (ppm) | Absorbance (nm) |
|---|---|
| 2 | 0.286 |
| 4 | 0.336 |
| 6 | 0.484 |
| 8 | 0.615 |
| 10 | 0.759 |
| 12 | 0.814 |
| 14 | 0.906 |

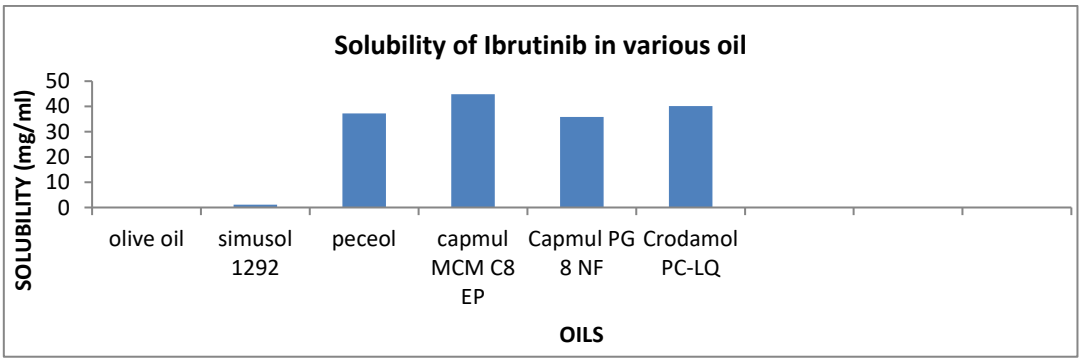
**Solubility of Ibrutinib in various excipients:**

Solubility of Ibrutinib in various oils, surfactants and co-surfactants were determined by UV-Visible spectrophotometer at 258 nm using methanol as blank. Oils include **Peceol,** Olive oil, **Capmul MCM C8 EP**, Capmul PG 8 NF, Simulsol 1292, Crodamol PC-LQ. Surfactants include **Kolliphpor EL**, Kolliphor RH 40, Kolliphor HS15, PEG 200, PEG 300, PEG 400, Tween 85, Span 80. Co-surfactants include **Labrasol**, Transcutol HP. The values are given in Table no: 4 and shown in Graph No: 1.

**Table no: 3 Solubility of Ibrutinib in various oils**

| OILS | SOLUBILITY (mg/ml) |
|---|---|
| Olive oil | 0.046±0.06 |
| Simulsol 1292 | 1.148±0.12 |
| Peceol | 37.258±0.22 |
| Capmul MCM C8 EP | 44.785±0.23 |
| Capmul PG 8 NF | 35.852±0.34 |
| Crodamol PC-LQ | 40.153±0.42 |

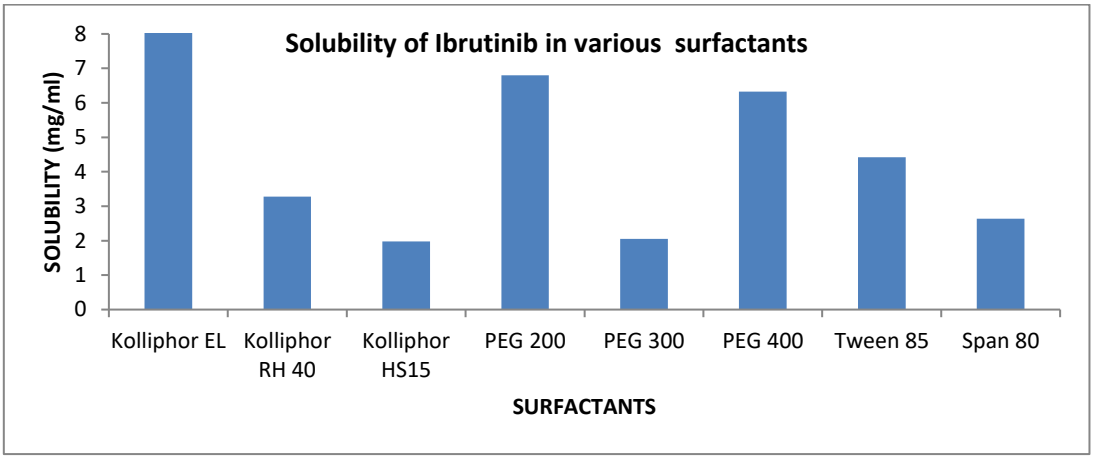
All values are expressed as Mean ±SD (n=3)




**Graph no: 1 Solubility of Ibrutinib in various excipients**

**Table no: 4 Solubility of Ibrutinib in various surfactants**

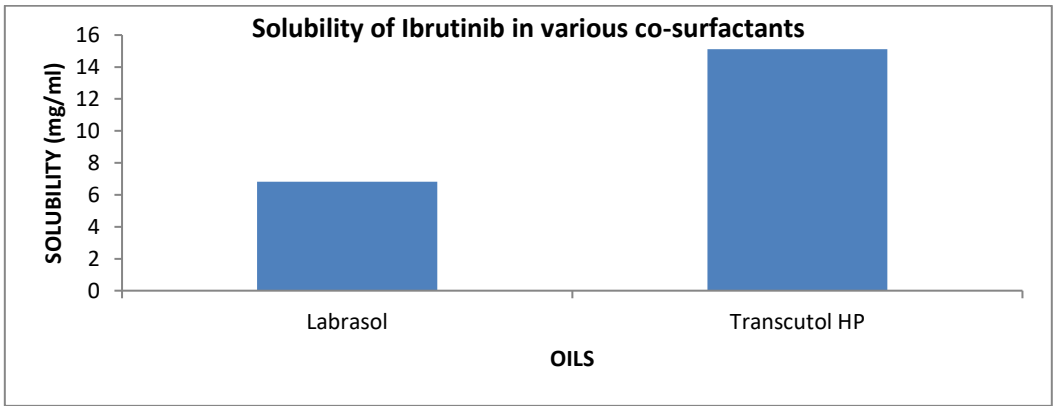
| SURFACTANTS | SOLUBILITY (mg/ml) |
|---|---|
| Kolliphpor EL | 8.034±0.08 |
| Kolliphor RH 40 | 3.277±0.36 |
| Kolliphor HS15 | 1.973±0.34 |
| PEG 200 | 6.797±0.28 |
| PEG 300 | 2.055±0.22 |
| PEG 400 | 6.326±0.15 |
| Tween 85 | 4.418±0.19 |
| Span 80 | 2.638±0.14 |




**Graph no: 2 Solubility of Ibrutinib in various excipients**

**Table no: 5 Solubility of Ibrutinib in various co-surfactants**

| Co-surfactant | SOLUBILITY) (mg/ml) |
|---|---|
| Labrasol | 6.813±0.36 |
| Transcutol HP | 15.108±0.38 |




**Graph no: 3 Solubility of Ibrutinib in various excipients**

**Drug-excipient compatibility studies by FT-IR spectroscopy:**

Fourier transform infrared spectra was taken by scanning 400 to 4000 $cm^{-1}$ range and resolution was 1 $cm^{-1}$. The major peaks recorded in spectra was compared with standard spectra of pure drug (Ibrutinib). It can be concluded that spectrum of pure drug (Ibrutinib) and combination of drug with additives, it was observed that all characteristic peaks of Ibrutinib were present in the combination spectrum. It indicates compatibility of pure drug (Ibrutinib) and additives.

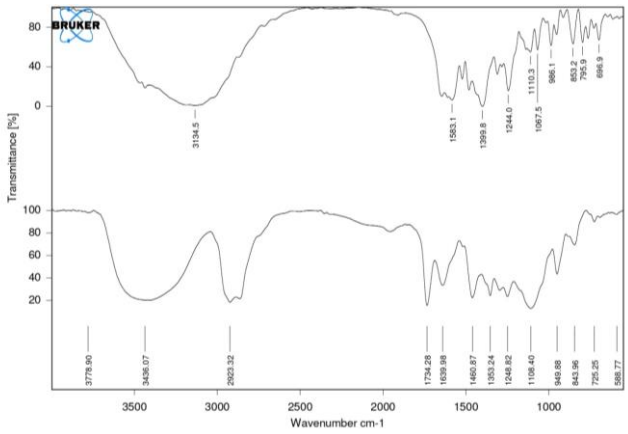



**Figure no: 7 Drug-excipients compatibility of Ibrutinib and materials C8KELLA used in formulation**

**Interpretation of IR spectra of Ibrutinib and formulation materials C8KELLA:**

**Table no:6 Interpretation data of Ibrutinib and formulation materials C8KELLA**

| ABSORPTION ($cm^{-1}$) | Group | Compound Class |
|---|---|---|
| 1650-1580 | N-H bending | Amine |
| 1550-1500 | N-O stretching | Nitro compound |
| 1390-1310 | O-H bending | Phenol |
| 1210-1163 | C-O stretching | Ester |
| 1124-1087 | C-O stretching | Secondary alcohol |
| 755± 20 | C-H bending | 1,2- disubstituted |
| 700 ± 20 | | Benzene derivative |

**Pseudo ternary phase diagram:**

From pseudo ternary phase diagram, it was found that the systems containing Capmul MCM C8 EP as oil phase, kolliphor EL as surfactant, labrasol as co-surfactant showed good nano emulsifying property.

For Smix 4:1 ratio formulations C8KELLA41 of 9:1 to 4:6, 1:9 showed bluish transparent emulsion (BTE), whereas 2:8,3:7 and 4:6showed bluish white emulsion (BWE).

For Smix 3:1 ratio formulations C8KELLA31 of 9:1 to 4:6, 1:9 showed bluish transparent emulsion (BTE), 3:7 showed milky white emulsion (MWE), whereas 2:8 & 4:6 showed bluish white emulsion (BWE).

**Table no: 7 GLOBULE SIZE AND ZETA POTENTIAL OF 4:1**

| Formulation | Globule size | PDI | Zeta potential |
|---|---|---|---|
| C8KELLA 1:9 | 201.9 | 0.216 | -38.8 |
| C8KELLA 8:2 | 100.4 | 0.217 | -47.6 |
| C8KELLA 7:3 | 91.29 | 0.419 | -38.9 |
| C8KELLA 6:4 | 137.4 | 0.385 | -29.7 |
| C8KELLA 5:5 | 126.3 | 0.542 | -27.2 |
| C8KELLA 4:6 | 138.3 | 0.347 | -25.5 |
| C8KELLA 3:7 | 214.5 | 0.404 | -20.6 |
| C8KELLA 2:8 | 185.2 | 0.377 | -19.8 |
| C8KELLA 1:9 | 171.6 | 0.225 | -17.1 |

**Figure no: 8 Physical appearance C8KELLA 4:1 with water titration method**

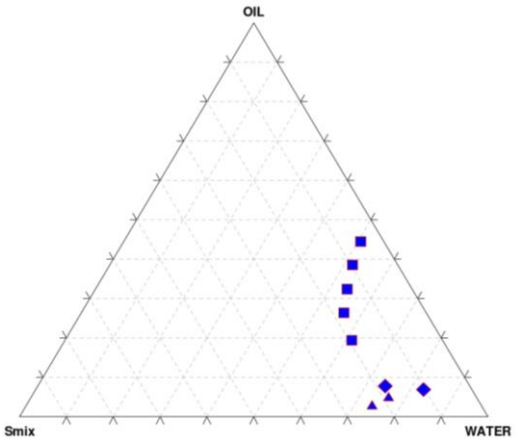



**Figure no: 9 Pseudo Ternary Phase Diagram of C8KELLA 4:1**

**Table no: 8 Globule Size and Zeta Potential Of 3:1**

| Formulation | Globule size | PDI | Zeta potential |
|---|---|---|---|
| C8KELLA 1:9 | 167.5 | 0.129 | -44.5 |
| C8KELLA 8:2 | 148.5 | 0.259 | -29.7 |
| C8KELLA 7:3 | 157.4 | 0.178 | -27.0 |
| C8KELLA 6:4 | 169.7 | 0.257 | -32.0 |
| C8KELLA 5:5 | 140.3 | 0.278 | -36.1 |
| C8KELLA 4:6 | 169.1 | 0.346 | -19.2 |
| C8KELLA 3:7 | 219.2 | 0.364 | -22.1 |
| C8KELLA 2:8 | 164.3 | 0.431 | -15.3 |
| C8KELLA 1:9 | 189.6 | 0.644 | -10.6 |

**Figure no: 10 Physical appearance of C8KELLA 3:1 with water titration method**

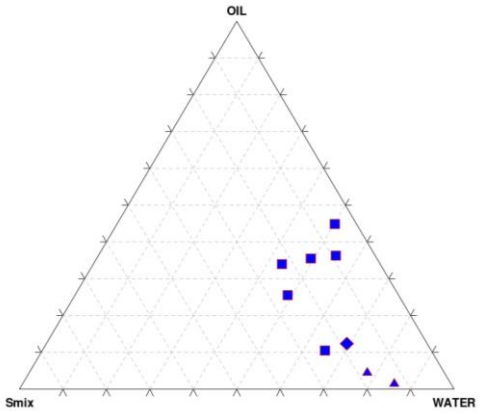



**Figure no: 11 Pseudo Ternary Phase Diagram of C8KELLA 3:1**

**Table no: 9 Composition of Prepared Ibrutinib SEDDS Formulations:**

| S.No | Formulation | API(Ibrutinib) w/w% | Capmul MCM C8 EP w/w% | Kolliphor EL w/w% | Labrasol w/w% | Total |
|---|---|---|---|---|---|---|
| 1 | C8KEL4LA1 1:9 | 100 mg | 200 | 1440 | 360 | 2 ml |
| 2 | C8KEL4LA1 2:8 | 100 mg | 400 | 1280 | 320 | 2 ml |
| 4 | C8KEL3LA1 1:9 | 100 mg | 200 | 1350 | 450 | 2 ml |
| 5 | C8KEL3LA 1 2:8 | 100 mg | 400 | 1200 | 400 | 2 ml |

**Evaluation of Ibrutinib self-emulsifying drug delivery formulations:**

**Self-emulsification time:**

The SEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. From the results obtained Table no 9 , it was clear that the formulations were self-emulsified within 29 ±1.05 to 36 ±1.50 seconds and indicates ability for easy and rapid emulsification.

**Table no: 10 Self emulsification time values for Ibrutinib liquid SEDDS.**

| FORMULATION | Self-emulsification time (sec) | Remarks |
|---|---|---|
| C8KEL4LA1 1:9 | 30 ±1.22 sec | Good |
| C8KEL4LA1 2:8 | 35 ±1.62 sec | Good |
| C8KEL4LA1 4:6 | 36 ±1.51 sec | Good |
| C8KEL3LA1 1:9 | 28 ±1.08 sec | Good |
| C8KEL3LA 1 2:8 | 29 ±1.05 sec | Good |
| C8KEL3LA1 4:6 | 32 ±1.50 sec | Good |

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

**Dispersibility test:**

The formulations were visually assessed using the grading system previously mentioned and the results were shown in Table no 10. Visual observations showed that all SEDDS formulations were found to be grade A. The rapid self-emulsification of the investigated systems can be attributed to their low oil content (200-400 %w/w).

**Table no: 10 Dispersibility test values for Ibrutinib liquid SEDDS.**

| FORMULATION | OBSERVATION | GRADE |
|---|---|---|
| C8KEL4LA1 1:9 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |
| C8KEL4LA1 2:8 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |
| C8KEL4LA1 4:6 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |
| C8KEL3LA1 1:9 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |
| C8KEL3LA 1 2:8 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |
| C8KEL3LA1 4:6 | Rapidly forming emulsion having a clear or bluish appearance within 1 minute | A |

**Robustness to dilution:**
SEDDS are subjected to dilutions for identifying the formulations without any phase separation and drug precipitation. After dilution of all SEDDS formulations, the emulsions were found to remain clear, bluish, transparent and showed no phase separation even after 24 hours as shown in Table no 11 indicates that emulsified oil globules are without phase separation.

**Table no: 11 Robustness to dilution values for Ibrutinib liquid SEDDS.**

| FORMULATION | Distilled water | 0.1N HCl | 6.8 Phosphate buffer |
|---|---|---|---|
| C8KEL4LA1 1:9 | Passed | Passed | Passed |
| C8KEL4LA1 2:8 | Passed | Passed | Passed |
| C8KEL4LA1 4:6 | Passed | Passed | Passed |
| C8KEL3LA1 1:9 | Passed | Passed | Passed |
| C8KEL3LA 1 2:8 | Passed | Passed | Passed |
| C8KEL3LA1 4:6 | Passed | Passed | Passed |

**Thermodynamic stability studies:**
No phase separation is observed for formulations CKEL4LA1 1:9, 2:8 and CKEL3LA1 1:9, 2:8 and indicates stable formulations under effect of temperature. Phase separation is observed for formulations CKEL4LA1 4:6 and CKEL3LA1 4:6 thus indicates unstable under effect of temperature. The values are represented in Table no 12.

**Table no: 12 Thermodynamic stability study values for Ibrutinib liquid SEDDS.**

| FORMULATION | Freeze thaw cycles (2 cycles NLT 48 hrs) | Centrifugation (3500 rpm for 30 min) |
|---|---|---|
| C8KEL4LA1 1:9 | Passed | Passed |
| C8KEL4LA1 2:8 | Passed | Passed |
| C8KEL4LA1 4:6 | Failed | Failed |
| C8KEL3LA1 1:9 | Passed | Passed |
| C8KEL3LA1 2:8 | Passed | Passed |
| C8KEL3LA 4:6 | Failed | Failed |

**Drug loading efficiency:**
The drug loading efficiency of all SEDDS formulations were found in the range of 98.27 ± 0.46% for F1 to 96.49 ± 0.48% for F4, indicating uniform drug dispersion in formulations shown in Table no 13. It was also observed that the formulations F1 and F3 have the highest drug content, due to higher concentration of surfactant and co-surfactant in these two formulations that possess high solubilization capacity to solubilize 100 mg dose of Ibrutinib.

**Table no: 13 Drug loading efficiency values for Ibrutinib liquid SEDDS.**

| FORMULATION | Drug loading efficiency |
|---|---|
| C8KEL4LA1 1:9 | 98.27±0.46 |
| C8KEL4LA1 2:8 | 96.84±0.27 |
| C8KEL3LA1 1:9 | 98.96±0.79 |
| C8KEL3LA1 2:8 | 96.49±0.48 |

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

**Percentage transmittance:**
All formulations showed percentage transmittance more than 95% indicating that the four formulations are clear emulsions.

**Table no: 14 Percentage transmittance values for Ibrutinib liquid SEDDS.**

| FORMULATION | Distilled water | 0.1N HCl | 6.8 phosphate buffer solution |
|---|---|---|---|
| C8KEL4LA1 1:9 | 98.53±0.48 | 97.64±0.34 | 98.07±0.51 |
| C8KEL4LA1 2:8 | 95.10±0.64 | 98.79±0.21 | 97.63±0.39 |
| C8KEL4LA1 4:6 | 96.36±0.74 | 97.18±0.54 | 94.57±0.45 |
| C8KEL3LA1 1:9 | 95.94±0.38 | 98.36±0.61 | 98.25±0.64 |
| C8KEL3LA 1 2:8 | 96.17±0.52 | 96.58±0.21 | 97.68±0.75 |
| C8KEL3LA1 4:6 | 94.12±0.69 | 95.57±0.36 | 94.81±0.21 |

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

**Determination of globule size and zeta potential:**

**Table no: 15 Globule size and Zeta potential values for Ibrutinib liquid SEDDS.**

| FORMULATION | Globulesize (d.nm) | PDI | Zeta potential (MV) |
|---|---|---|---|
| C8KEL4LA11:9 | 193.6 | 0.672 | -22.8 |
| C8KEL4LA1 2:8 | 185.2 | 0.377 | -12 |
| C8KEL3LA11:9 | 172.6 | 0.352 | -10.6 |
| C8KEL3LA12:8 | 173.9 | 0.359 | -6.77 |

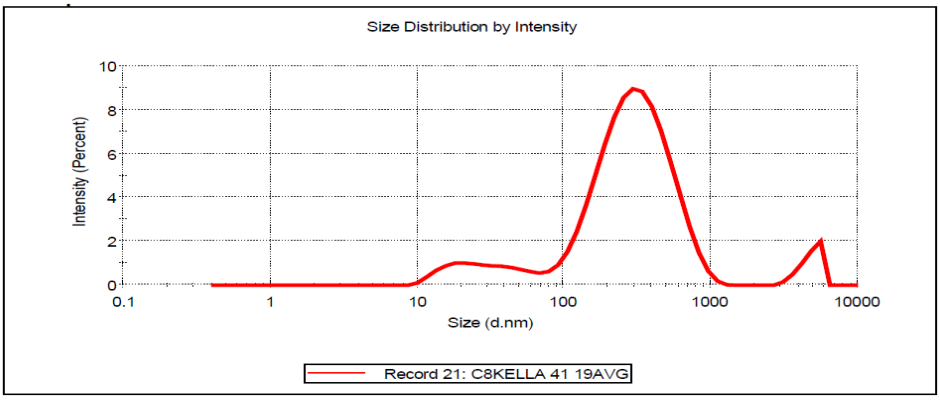
**All values are expressed as Mean ±SD (n=3)**

**GLOBULE SIZE OF CKEL4LA1 1:9:**

Results

| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 193.6 | Peak 1: | 337.1 | 84.5 | 178.2 |
| PdI: | 0.672 | Peak 2: | 31.20 | 10.3 | 15.85 |
| Intercept: | 0.928 | Peak 3: | 4806 | 5.2 | 725.1 |

Result quality : Good

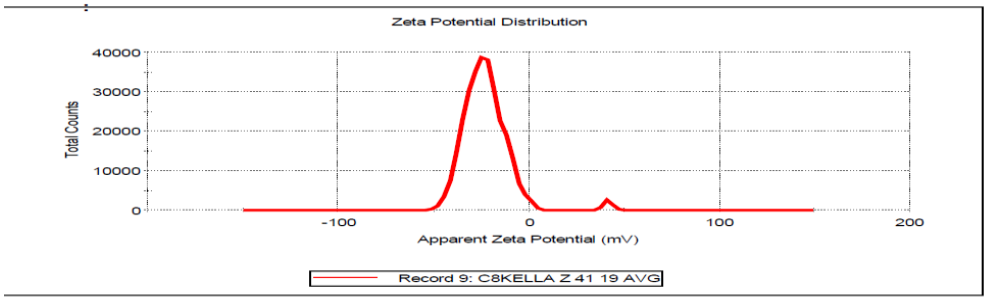



**ZETA POTENTIAL OF CKEL4LA1 1:9:**

Results

| | | | Mean (mV) | Area (%) | St Dev (mV) |
|---|---|---|---|---|---|
| Zeta Potential (mV): | -22.8 | Peak 1: | -23.8 | 98.4 | 9.75 |
| Zeta Deviation (mV): | 12.5 | Peak 2: | 41.5 | 1.6 | 2.46 |
| Conductivity (mS/cm): | 0.0312 | Peak 3: | 40.7 | 0.1 | 0.00 |

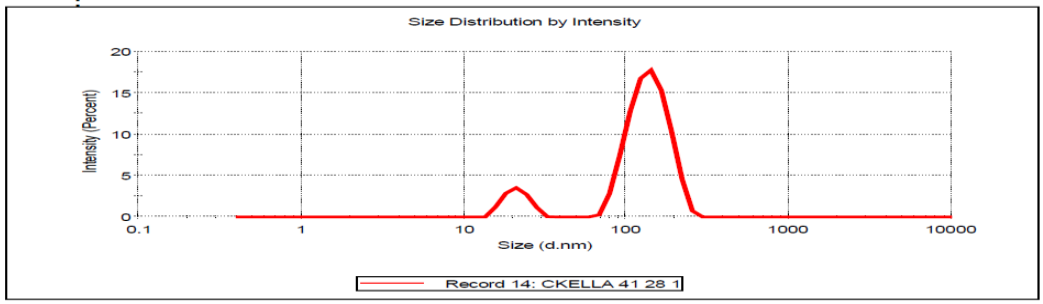
Result quality : Good



**GLOBULE SIZE OF CKEL4LA1 2:8:**

Results

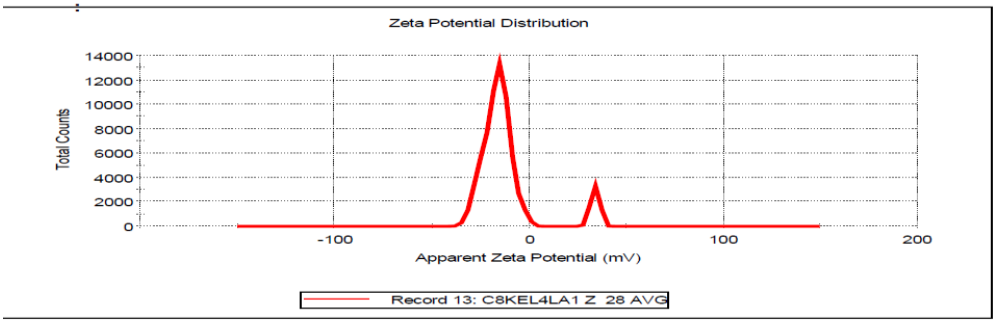
| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 185.2 | Peak 1: | 140.9 | 88.6 | 37.39 |
| PdI: | 0.377 | Peak 2: | 21.30 | 11.4 | 3.630 |
| Intercept: | 0.928 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality : | Refer to quality report | | | | |




**ZETA POTENTIAL OF CKEL4LA1 2:8:**

Results

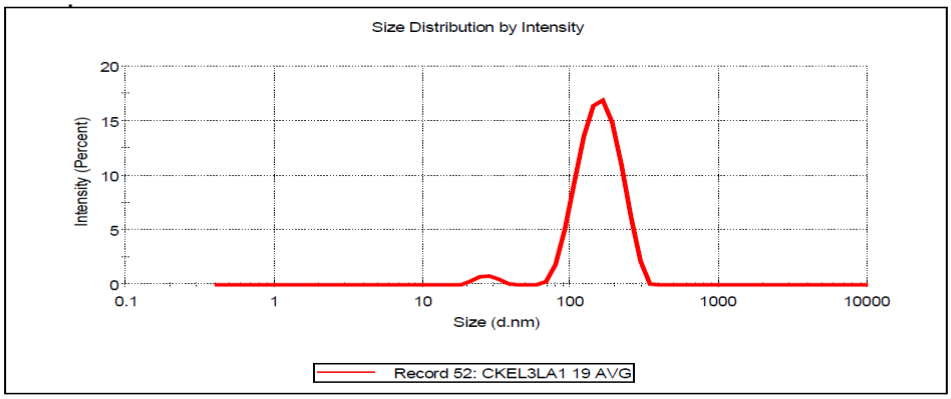
| | | | Mean (mV) | Area (%) | St Dev (mV) |
|---|---|---|---|---|---|
| Zeta Potential (mV): | -12.0 | Peak 1: | -16.7 | 91.0 | 6.76 |
| Zeta Deviation (mV): | 15.6 | Peak 2: | 33.9 | 9.0 | 2.40 |
| Conductivity (mS/cm): | 0.0106 | Peak 3: | 0.00 | 0.0 | 0.00 |
| Result quality : | Good | | | | |




**GLOBULE SIZE OF CKEL3LA1 1:9:**

Results

| | | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 172.6 | Peak 1: | 162.3 | 97.5 | 49.75 |
| PdI: | 0.352 | Peak 2: | 27.44 | 2.5 | 4.402 |
| Intercept: | 0.930 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality : | Good | | | | |

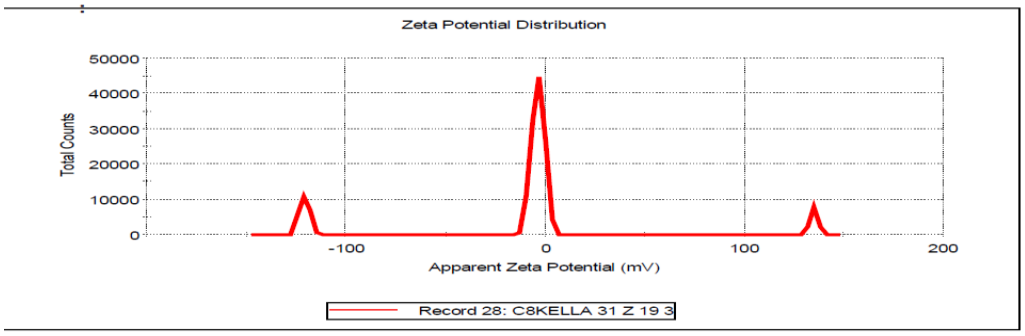


**ZETA POTENTIAL OF CKEL3LA1 1:9:**

Results

| | | Mean (mV) | Area (%) | St Dev (mV) |
|---|---|---|---|---|
| Zeta Potential (mV): -10.6 | Peak 1: | -3.68 | 76.8 | 3.31 |
| Zeta Deviation (mV): 59.8 | Peak 2: | -121 | 15.3 | 2.58 |
| Conductivity (mS/cm): 0.0115 | Peak 3: | 135 | 7.9 | 1.98 |

Result quality Good

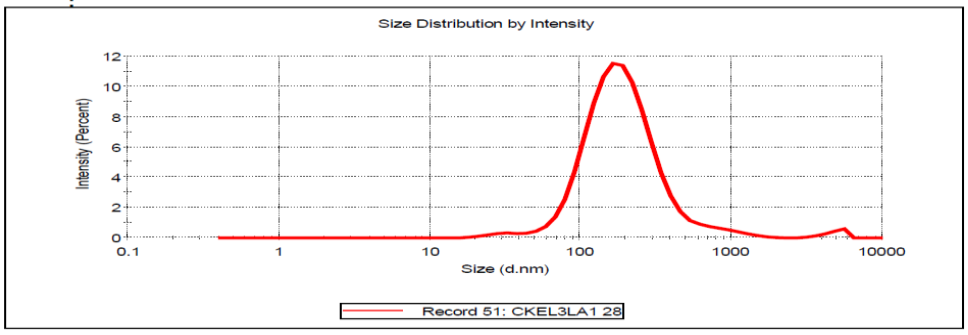



**GLOBULE SIZE OF CKEL3LA1 2:8:**

Results

| | | Size (d.n... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|
| Z-Average (d.nm): 173.9 | Peak 1: | 221.0 | 97.3 | 167.2 |
| PdI: 0.359 | Peak 2: | 4833 | 1.5 | 715.4 |
| Intercept: 0.907 | Peak 3: | 30.02 | 1.2 | 5.797 |

Result quality Good

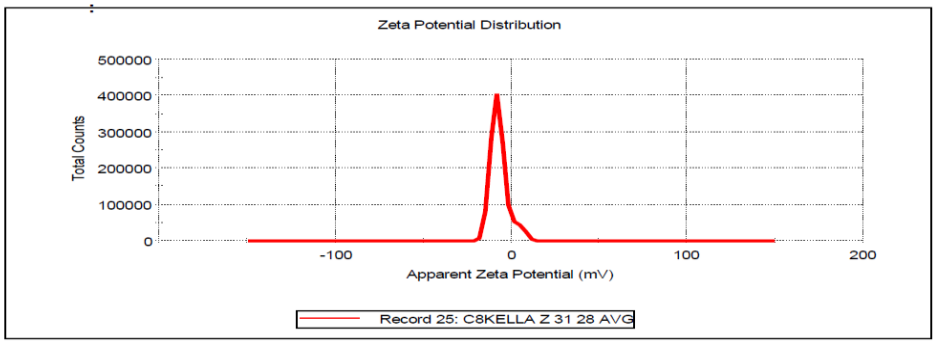



**ZETA POTENTIAL OF CKEL3LA1 2:8:**

Results

| | | Mean (mV) | Area (%) | St Dev (mV) |
|---|---|---|---|---|
| Zeta Potential (mV): -6.77 | Peak 1: | -6.77 | 100.0 | 5.18 |
| Zeta Deviation (mV): 4.95 | Peak 2: | 0.00 | 0.0 | 0.00 |
| Conductivity (mS/cm): 0.00586 | Peak 3: | 0.00 | 0.0 | 0.00 |

Result quality Good




***In vitro* drug release studies:**

The pure drug Ibrutinib percentage drug release was 54.98% at the end of 60 mins. When compared to pure drug release, the F3 formulation showed 84.22 % drug release at the end of release time. So finally, F3 formulation was optimized, it shows good drug release and optimized SEDDS formulation F3 has

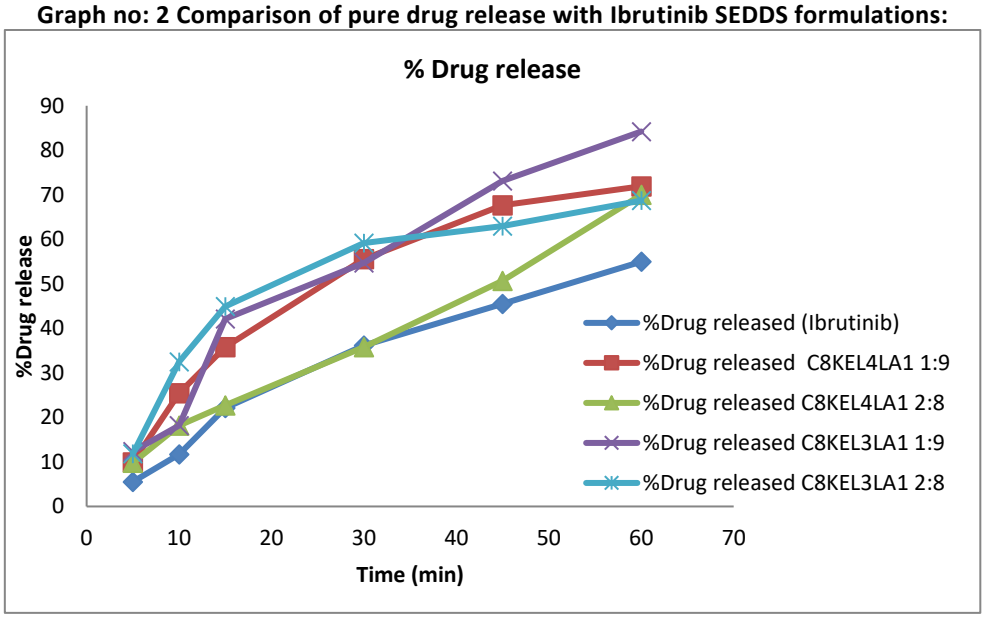
enhanced solubility of poorly soluble drug (Ibrutinib) by 1.53 times.

**Table no: 16 Dissolution data for pure drug and SEDDS formulations of Ibrutinib:**

| Time (min) | % DR(API) | %DR C8KEL4LA1 1:9 | %DR C8KEL4LA1 2:8 | %DR C8KEL3LA1 1:9 | %DR C8KEL3LA1 2:8 |
|---|---|---|---|---|---|
| 5 | 5.54 ±0.74 | 9.92 ±0.12 | 9.81 ±0.08 | **12.35** ±0.08 | 11.83± 0.08 |
| 10 | 11.72± 0.25 | 25.47 ±0.15 | 18.20 ±0.18 | **18.20** ±0.16 | 32.46 ±0.16 |
| 15 | 22.16±0.28 | 35.80 ±0.21 | 22.69±0.16 | **42.12** ±0.24 | 44.90 ±0.12 |
| 30 | 36.14 ±0.17 | 55.6 ±0.26 | 35.80 ±0.14 | **54.72** ±0.27 | 59.13 ±032 |
| 45 | 45.52±0.32 | 67.68 ±0.32 | 50.69 ±0.25 | **73.09** ±0.18 | 62.98 ±0.26 |
| 60 | 54.98 ±0.22 | 71.92 ±0.13 | 69.99 ±0.14 | **84.22± 0.36** | 68.71 ±0.38 |

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

**Graph no: 2 Comparison of pure drug release with Ibrutinib SEDDS formulations:**




**CONCLUSION:**

Ibrutinib was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a self-emulsifying drug delivery system.

- BCS class II
- Log P 3.97

The optimized formulation F3 showed no phase separation or precipitation of drug during thermodynamic stability studies. Self-emulsification time was under 1 minute. The percentage transmittance of F1 was over 95% showing clear emulsions. Drug loading efficiency was found to be 98.96 ± 0.79%. Globule size of F was observed to be 172.6 d.nm and zeta potential -10.6 mV.

Optimized formulation F3 has successfully showed drug release for 60 mins and the drug release pattern was good. The pure drug Ibrutinib percentage drug release was 54.98 ±0.22% at the end of 60 mins. When compared to pure drug release, the F3 formulation showed 84.22± 0.36 % drug release at the end of release time. So finally, F3 formulation was optimized, it shows good drug release and optimized SEDDS formulation F3 has enhanced solubility of poorly soluble drug (Ibrutinib) by 1.53 times. The enhanced in-vitro dissolution profile from liquid SEDDS is an indication of improved solubility and dissolution rate of the drug (Ibrutinib). Hence prepared SEDDS have capability for delivering poorly aqueous soluble drug Ibrutinib in soluble state in Gastrointestinal Tract.

**REFERENCES:**

[1] M. Sunitha Reddy; P.srinivas goud; S.S.Apte. Solubility enhancement of Candensartan Cilexitil by Self emulsifying drug delivery systems, IJPSR, 2012; 3(7); 2098-2104.

[2] Chaumeil J.C. Micronisation, a method of improving the bioavailability of poorly soluble drugs, Methods and Findings in Experimental and Clinical Pharmacology,

European Journal of Pharmaceutical Sciences, 2000; 10, 17–*2*

[3].Graham H, McMorland M, Joanne D, Wayne K, Peggy L.E, James E.A, James H.K.K, David R.G, Kerri R. E"ect of pH-adjustment of bupivacaine on onset and duration of epidural analgesia in parturients, 1986; 33(5), 537-541.

[4] Millard JW, Alvarez-Nunez FA, Yalkowsky SH., Solubilization by cosolvents. Establishing useful constants for the log-linear model. International Journal of pharmacy and Pharmaceutical sciences, 2002; 245,153–166.

[5] Scalia, S., Villani, S. Scatturin, A, Vandelli, M.A, Forni, F. Complexation of sunscreen agent, butylmethoxy dibenzoyl methane, with hydroxyl propyl - β – cyclodextrin, International Journal of Pharmaceutics, 1998; 175, 205-213.

[6] Khoo S.M., Porter C.J.H., Charman W.N. The formulation of halofantrine as either nonsolubilising PEG 6000 or solubilising lipid based solid dispersions: physical stability and absolute bioavailability assessment. International Journal of Pharmaceutics, 2000; 205, 65-78.

[7] www.pubmed.com

[8] www.drugbank.com

[9] Baddam Sunitha Reddy , Harish G, Md.Fazal Ul Haq. Formulation and invitro characterization of solid SNEDDS of Rilpivirine. Int J Pharm Sci Res 2016;7: 3117-29.

[10] Reddy MS, Sowjanya N. Formulation and invitro characterization of solid SNEDDS of Simvastatin J Pharm Sci 2015; 7: 40-8.

[11] Reddy MS,Rudra R,Haq F. Formulation and evaluation of s-SNEDDS of Ritonavir drug. IndoAmerican J Pharm Res 2015; 5:1-10.

[12] M.Sunitha reddy,Yama narendra,S.Md Fazal Ul Haq. Solubility enhancement of poorlysoluble drug Ketoconazole by self-emulsifying drug delivery system. International journal ofpharmacy and biological sciences. 2018; 8(1): 111-127.

[13] M.Sunitha reddy; D.Mounica; Mohammad Fazal Ul Haq ; K.Anie Vijetha. Solubility enhancement of poorly water soluble drug Irbesartan by self-emulsifying drug delivery system.WJPPS, 2018; 8(1):770-785.

[14] M. Sunitha Reddy, B. Sravanthi. Formulation and InVitro Characterization of Solid-self Nanoemulsifying Drug Delivery System of Atorvastatin Calcium, 2017; Asian Journal of Pharmaceutics, 11 (4); S991-S999.

[15] Singh AK, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, Khar RK. Exemestane Loaded Self-Micro Emulsifying Drug Delivery System (SMEDDS): Development and Optimization. AAPS Pharm Sci Tech., 2008; 9: 628–34.