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# SOLUBILITY AND DISSOLUTION ENHANCEMENT OF POORLY AQUEOUS SOLUBLE DRUG GEFITINIB BY SELF EMULSIFYING DRUG DELIVERY SYSTEM

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**Keywords:**

Gefitinib, SEDDS, Zeta potential, Bioavailability

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**ABSTRACT:** The present research work was aimed at the enhancement of solubility and dissolution rate of Gefitinib by Self Emulsifying Drug Delivery Systems (SEDDS). Gefitinib is a BCS class II drug with poor aqueous solubility (oral bioavailability 60%). The saturated solubility of Gefitinib in different oils, surfactants and co-surfactants were determined. The excipients were screened and selected showing maximum solubility and compatibility for Gefitinib. SEDDS formulations of Gefitinib were developed using selected Oils, Surfactants and Co-Surfactant combinations (4:1 and 3:1). Pseudo ternary phase diagrams were created using Triplot V 4.1.2 software and applying Pseudo ternary phase diagrams, the nano-emulsification region was identified. Formulations were optimized based on Pseudo ternary phase diagrams using various proportions of oil (Peceol), surfactants (Kolliphor HS 15) and co-surfactants (Labrasol). The prepared four formulations were selected among them F1 was optimized and carried out for further evaluations like robustness to dilution (Passed), dispersibility test (Grade A), self emulsification time (29 ± 1.05 sec), percentage transmittance (Clear emulsions), drug loading efficiency (98.735 ± 0.43%), thermodynamic stability study (Passed), emulsion globule size (104.2 d.nm) and zeta potential (-16.2 mV), *in-vitro* drug release studies. Among the four formulations, F1 (PK154LA1 1:9) was optimized formulation because it gave the optimum results in terms of required *in-vitro* drug release. The dissolution rate of F1 SEDDS (88.253 ± 0.20 %) was compared with Gefitinib (API) (41.139 ± 0.32 %). The results indicate the solubility and dissolution rate of Gefitinib SEDDS has a significant increase of 2.14 times when compared to a pure drug (API). Accelerated stability studies showed that the optimized formulation F1(PK154LA1 1:9) was found to be stable for 1 month with respect to Drug loading efficiency (97.975 ± 0.25%), globule size (105.0 d.nm), zeta potential (-18.1 mV) and dissolution study (88.171 ± 0.36%). There is no significant change in drug loading efficiency, globule size, PDI, zeta potential and dissolution study. The results of the present studies demonstrate that Gefitinib SEDDS can be used as a potential means for improving the solubility and dissolution rate of Gefitinib.

**INTRODUCTION:** A high number of newly released drugs exhibit poor aqueous solubility. These result in low absorption and less bioavailability.

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More than 30% of drugs (New chemical entities) have very low solubility in water. Lots of drugs are not reaching the market due to their poor properties like high molecular weight and lipophilicity, which reduces their solubility in an aqueous medium. Because of these reasons they have to administer in high doses to get the onset of action and show therapeutic response.

The oral route is one of the 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. The drug delivery industry scientist used a wide range of methods to improve solubility and dissolution rate of poorly aqueous soluble drugs, including formulations containing nano-particles, a solid solution formulation or SEDDS and stable amorphous form of the drug.

Several approaches besides the use of lipophilic prodrugs that increase drug permeation rate are lipid-based formulations. With an increase in a number of emerging hydrophobic drugs, several lipid-based formulations have improved their bioavailability by physicochemical (enhanced dissolution and solubility) mechanism. Self-emulsifying drug delivery system is presently used to tackle the formulation challenges of poorly aqueous soluble medication, by rising dissolution rate and maintaining the drug in solution throughout its period in GIT

Gefitinib is a BCS II drug with poor solubility and means bioavailability (60%). Gefitinib is an anti-neoplastic agent that inhibits the catalytic activity of numerous tyrosine kinases including Epidermal Growth Factor Receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Thus induces cell cycle arrest and inhibits angiogenesis.

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

## MATERIALS AND METHODS:

**Materials:** Gefitinib was an opulent gift from NATCO Pharma Ltd., (Hyderabad, India), Peceol, Labrasol, Lauroglycol FCC are variable gifts from Gattefosse, France. Kolliphor HS 15 as a gift sample from BASF. Captex 355, Capmul MCM C8 EP, Capmul MCM NF, Captex 200 were gift sample from Abitec Corporation, USA. Other analytical reagents were purchased from Research Lab Fine Chem Industry.

**UV Spectrophotometric Analysis of Gefitinib in Methanol:** 10 mg of Gefitinib was weighed precisely and transferred into a 10 ml volumetric flask, dissolved in methanol and made up to the volume.

From the standard stock solution, the required concentrations were prepared using methanol. The UV-Visible spectrophotometer absorbance of Gefitinib was scanned from a wavelength of 400-200 nm. The spectrum shows maximum absorbance at 326 nm. The wavelength ($\lambda_{max}$) identified was 326 nm and utilized for further analysis, in the present investigation.

The standard plot was drawn using the data obtained.

**UV Spectrophotometric Analysis of Gefitinib in 0.1N HCl:** 10 mg of Gefitinib was weighed precisely and transferred into a 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, the required concentrations were prepared using 0.1N HCl. The spectrum shows maximum absorbance at 250 nm. The wavelength ($\lambda_{max}$) identified was 250 nm and utilized for further analysis, in the present investigation.

Standard plot was drawn using the data obtained.

**Solubility Studies:** The solubility of Gefitinib 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 are cyclo-mixed immediately using cyclo-mixer (REMI CM 101) for 2 min to increase drug solubilization. The mixtures are then placed for heating at 40-50 °C for 5 min. The resultant mixture was then left for equilibration at room temperature 25 °C in an isothermal mechanical shaker rotary shaker (REMI RS 12 R) at a speed of 100 rpm for 72 h.

The supersaturated solutions were then centrifuged at a speed of 3000 rpm for 15 min to remove the undissolved drug. The supernatant was separated and aliquots of supernatant fluid were drawn utilizing a micropipette and adequately diluted with methanol. The concentration of Gefitinib in each excipient was determined spectrophotometrically at $\lambda_{max}$ 326 nm.

**Construction of Pseudo Ternary Phase Diagram:** Pseudo ternary phase diagrams were constructed using the water titration method at room temperature to identify self nano emulsifying regions and to select suitable concentrations of oils, surfactant and co-surfactant for the formulation of SEDDS. The ratio of surfactant to co-surfactant (Smix) was also optimized using a pseudo ternary phase diagram. Surfactant and co-surfactant (Smix) 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 was visually observed and marked on the 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 the construction of pseudo ternary phase diagram are peceol (oil), kolliphor HS 15 (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 Compatability Studies by FT-IR Spectroscopy:** Excipient compatibility studies are conducted mainly to predict the potential incompatibility of the drug in the optimized dosage form. These studies provide justification for the selection of excipients and concentrations in formulation as required in regulatory filings. These studies are important in the drug development process, as the knowledge gained from excipients compatibility studies is used to select dosage form components, delineate the stability profile of the drug, identify degradation products. Gefitinib and excipients were analyzed by the FT-IR spectro-photometer with the data acquisition system OPUS.

**Formulation of Gefitinib Liquid SEDDS:** Once the nano-emulsifying region was identified, SEDDS formulation with desired component ratios were selected for Gefitinib 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 (320-450% w/w). In all the formulations, the amount of Gefitinib (40 mg) was kept constant. The amount of Gefitinib was dispersed into a mixture of oil to solubilize the lipophilic drug with continuous mixing in glass vials using a vortex mixer. Surfactant and co-surfactant were accurately weighed into the mixture of oil and Gefitinib and then vortexed to ensure complete mixing until Gefitinib was completely dissolved. These systems were warmed to 40 °C using a water bath for 30 min with mild shaking until a clear solution was obtained. The prepared formulations were stored at room temperature for further investigation.

**Evaluation of Gefitinib Liquid SEDDS:**

**Dispersibility Test:** The self emulsification efficiency of Gefitinib 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 the rate of emulsification and the final appearance of nano-emulsion.

**Self Emulsification Time:** 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 rotating at a constant speed. The emulsification time (time required for a pre-concentrate to form a homogenous mixture upon dilution) was assessed visually by observing the disappearance of SEDDS and the final appearance of nano-emulsion.

**Robustness to Dilution:** Robustness of different Gefitinib SEDDS formulations to dilution was done by diluting 0.1ml of each formulation 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 homogeneity. These systems were stored at ambient temperature for 24 h then visually observed for any signs of phase separation.

**Percentage Transmittance:** Each Gefitinib SEDDS formulations (0.1 ml) was added to a 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 (Gefitinib).

**Thermodynamic Stability Studies:** Thermo-dynamic stability is performed to determine the effect of temperature and centrifugation. The formulations were added to millipore water (1:10) and centrifuged at 3500 rpm for 30 min and observed for changes like phase separation or precipitation. The preparations which are stable are subjected to a freeze-thaw cycle. In the freeze-thaw cycle, Gefitinib SEDDS are diluted with millipore water (1:20) and two freeze-thaw cycles between -20°C to +25°C with storage at each temperature for not less than 48 h and observed for phase separation or precipitation.

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

Drug loading efficiency = Amount of drug in formulation × 100 / Initial drug load

**Determination of Globule Size and Zeta Potential:** SEDDS are vortexed with a magnet after adding 100 times of distilled water in a test tube or beaker. The globule size distribution and zeta potential of the resultant formulation are determined after 1 h 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 Gefitinib liquid SEDDS was studied using USP Type II dissolution test apparatus (DS 8000 Lab India). Liquid filled HPMC capsules containing 40 mg of Gefitinib are placed in a buffer medium that consists of 900 ml of 0.1N HCl at 37 ± 0.5 °C with 50 rpm. Aliquots (5 ml) were withdrawn at selective time intervals such as 5, 10, 15, 30, 45, 60, 90 and 120 min respectively and replaced by the buffer to maintain sink conditions. The samples are then screened for the amount of drug release from the standard graph at absorbance 250 nm.

**Accelerated Stability Studies:** Stability studies for Gefitinib SEDDS were carried out according to ICH guidelines at different temperatures. The samples were maintained at 40 ± 2 °C / 75 ± 5% RH. The formulations were kept in a desiccator containing saturated calcium chloride at 75% RH and the desiccator was placed in an oven maintained at 40 °C. Samples were withdrawn at predetermined time intervals at 0,7,15 and 30 days. SEDDS equivalent to 40 mg of Gefitinib was evaluated for drug content at an estimated $\lambda_{max}$ 326 nm. Droplet size, zeta potential, *in-vitro* dissolution studies of Gefitinib SEDDS were evaluated.

**Kinetic Analysis of Dissolution Data:** To analyze *in-vitro* drug release data various kinetic models were used to describe the release kinetics. The zero-order indicates that the drug release rate is independent of its concentration.

$$C = K_O t$$

Where $K_O$ is zero-order rate constant expressed in units of concentration /time and t is time.

The first order describes the release from the system here the release rate concentration is dependent.

$$\text{Log } C = \text{Log}C - K_1 t/2.303$$

Where $C_0$ is the initial concentration of drug $K_1$ is the first order constant.

Higuchi describes the release of drugs from the insoluble matrix as a square root of time-dependent process based on fickian diffusion.

$$Q = KHt^{1/2}$$

Where $K_H$ is the constant that reflects the design variables of the system.

**Mechanism of Drug Release:** Korsmeyer *et al*., (1983) derived a simple relationship which indicates drug release from the polymeric system.

$$M_t/M\infty = K\ t^n$$

Where $M_t/M\infty$ is a fraction of drug released at the time t, K is the exponent. Then n value is used to characterize different release mechanisms. Release rate constant incorporating structural and geometric characteristics of the tablets, and n is the release.

The slope of the line was n. The n value is used to characterize different release mechanisms showed in **Table 1**.

**TABLE 1: DIFFUSION EXPONENT VALUE RANGES FOR DIFFERENT DRUG RELEASE MECHANISMS**

| S. no. | Diffusion exponent value (n) | Drug release mechanism |
|---|---|---|
| 1 | <0.45 | Fickian release |
| 2 | 0.45 to 0.89 | Non fickian release |
| 3 | 0.89 | Case transport |
| 4 | >0.89 | Super case II transport |

## RESULTS AND DISCUSSION:

**Determination of $\lambda_{max}$ and Calibration Curve of Gefitinib in Methanol:** The wavelength ($\lambda_{max}$) was measured at 326 nm, using a UV spectrophotometer with methanol as blank. The standard graph of Gefitinib in methanol was plotted by concentration range from 2-14 µg/ml. The standard graph was plotted using the values shown in **Table 2**.

A graph of absorbance *vs*. concentration was plotted which indicated in compliance with Beer-lambert's law in concentration range. A standard plot of Gefitinib in methanol was plotted by taking absorbance on X-axis and concentration on Y-axis, the plot is shown in **Fig. 3**. The regression coefficient $r^2$ was found to be 0.9988.

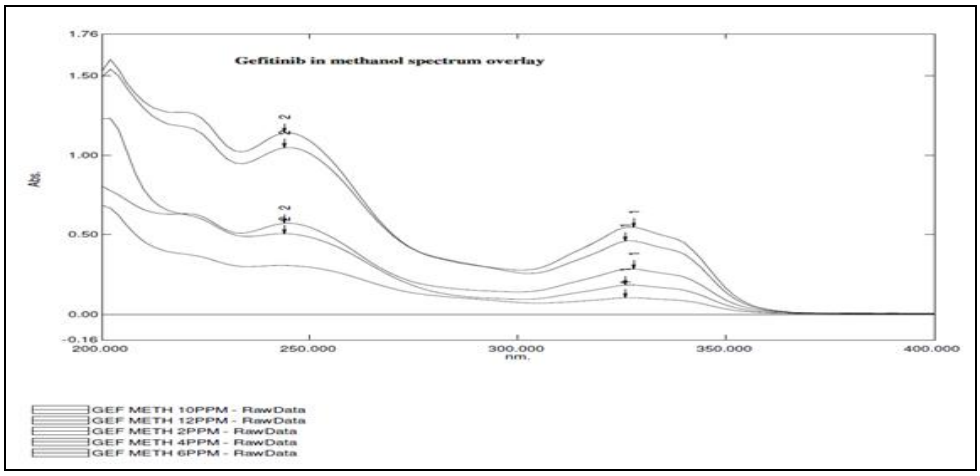



**FIG. 1: SPECTRUM OVERLAY OF GEFITINIB IN METHANOL**

| No. | P/V | Wavelength | Abs. | Description |
|---|---|---|---|---|
| 1 | ↑ | 326.000 | 0.39 | |
| 2 | ↑ | 242.000 | 1.03 | |
| 3 | ↓ | 304.000 | 0.24 | |
| 4 | ↓ | 234.000 | 1.01 | |

**FIG. 2: PEAK TABLE SHOWING DIFFERENT ABSORBANCE OF GEFITINIB IN METHANOL**

**Calibration Curve for Gefitinib in Methanol:**

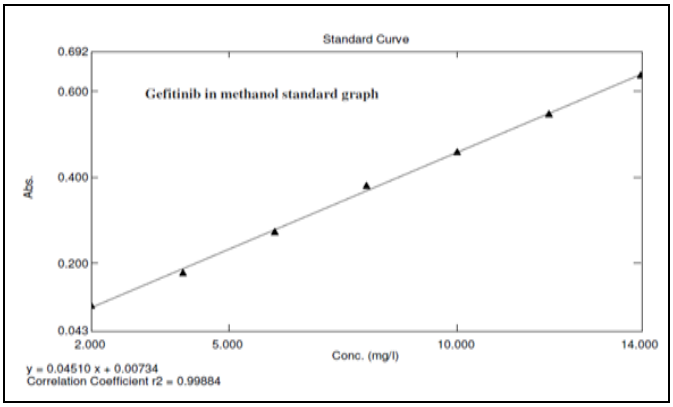



**FIG. 3: CALIBRATION CURVE OF GEFITINIB IN METHANOL**

**TABLE 2: STANDARD GRAPH VALUES OF GEFITINIB IN METHANOL**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 2 | 0.102 |
| 4 | 0.178 |
| 6 | 0.275 |
| 8 | 0.380 |
| 10 | 0.459 |
| 12 | 0.546 |
| 14 | 0.637 |

**Determination of $\lambda_{max}$ and Calibration Curve of Gefitinib in 0.1N HCl:** The wavelength ($\lambda_{max}$) was measured at 250 nm, using a UV spectrophotometer with 0.1N HCl blank. The standard graph of Gefitinib 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 3. A graph of absorbance *vs.* concentration was plotted which indicated in compliance to Beer-lambert's law in concentration range. The standard plot of Gefitinib in 0.1N HCl was plotted by taking absorbance on X-axis and concentration on Y-axis, the plot is shown in **Fig. 6**. The regression coefficient $r^2$ was found to be 0.999.

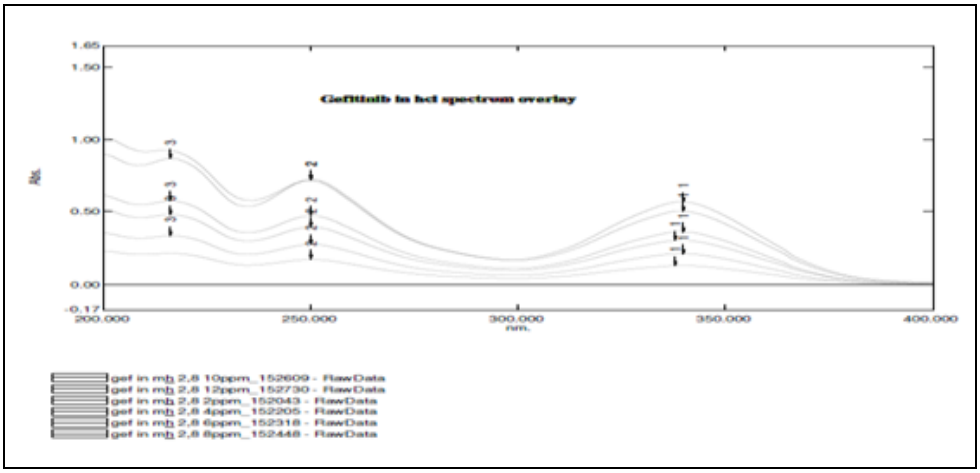



**FIG. 4: SPECTRUM OVERLAY OF GEFITINIB IN 0.1 N HCl**

| No. | P/V | Wavelength | Abs. | Description |
|---|---|---|---|---|
| 1 | ↑ | 340.000 | 0.51 | |
| 2 | ↑ | 250.000 | 0.72 | |
| 3 | ↓ | 300.000 | 0.17 | |
| 4 | ↓ | 236.000 | 0.58 | |

**FIG. 5: PEAK TABLE SHOWING DIFFERENT ABSORBANCE OF GEFITINIB IN 0.1N HCl**

## Calibration Curve for Gefitinib in 0.1 N HCl:

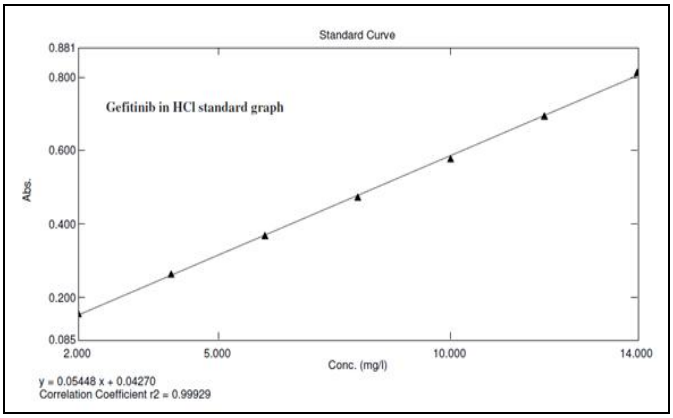



**FIG. 6: CALIBRATION CURVE OF GEFITINIB IN 0.1 N HCl**

**TABLE 3: STANDARD GRAPH VALUES OF GEFITINIB IN 0.1N HCl**

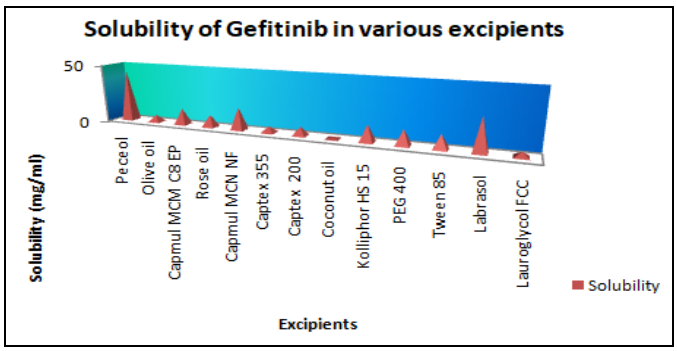
| Concentration (µg/ml) | Absorbance |
|---|---|
| 2 | 0.156 |
| 4 | 0.264 |
| 6 | 0.367 |
| 8 | 0.473 |
| 10 | 0.579 |
| 12 | 0.695 |
| 14 | 0.815 |

**Solubility of Gefitinib in Different Excipients:** Solubility of Gefitinib in different oils, surfactants and co-surfactants were determined by UV-Visible spectrophotometer at 326 nm using methanol as blank. Oils include Peceol, Olive oil, Capmul MCM C8 EP, Rose oil, Capmul MCN NF, Captex 355, Captex 200, Coconut oil. Surfactants include Kolliphor HS 15, PEG 400, Tween 85. Co-surfactants include Labrasol, Lauroglycol FCC. The values are given in **Table 4** and shown in **Graph 1**.

**TABLE 4: SOLUBILITY OF GEFITINIB IN VARIOUS EXCIPIENTS**

| S. no. | Excipients | Solubility (mg/ml) |
|---|---|---|
| 1 | Peceol | 44.155 ± 0.01 |
| 2 | Olive oil | 6.004 ± 1.02 |
| 3 | Capmul MCM C8 EP | 13.659 ± 0.368 |
| 4 | Rose oil | 10.359 ± 0.677 |
| 5 | Capmul MCN NF | 19.105 ± 0.378 |
| 6 | Captex 355 | 5.136 ± 0.167 |
| 7 | Captex 200 | 7.376 ± 0.399 |
| 8 | Coconut oil | 1.624 ± 0.381 |
| 9 | Kolliphor HS 15 | 14.071 ± 0.250 |
| 10 | PEG 400 | 13.097 ± 0.154 |
| 11 | Tween 85 | 11.957 ± 0.188 |
| 12 | Labrasol | 28.018 ± 0.672 |
| 13 | Lauroglycol FCC | 4.095 ± 0.356 |

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




**GRAPH 1: SOLUBILITY DATA OF GEFITINIB IN VARIOUS EXCIPIENTS**

**Drug-Excipient Compatability Studies by FT-IR Spectroscopy:** Fourier transform infrared spectra were taken by scanning 400 to 4000 $cm^{-1}$ range and resolution was 1 $cm^{-1}$. The major peaks recorded in spectra were compared with the standard spectra of a pure drug (Gefitinib). It concludes that the spectrum of Gefitinib and the combination of the drug with additives showed all characteristic peaks of Gefitinib were present in the combined spectrum. It indicates the compatibility of a pure drug (Gefitinib) and additives.

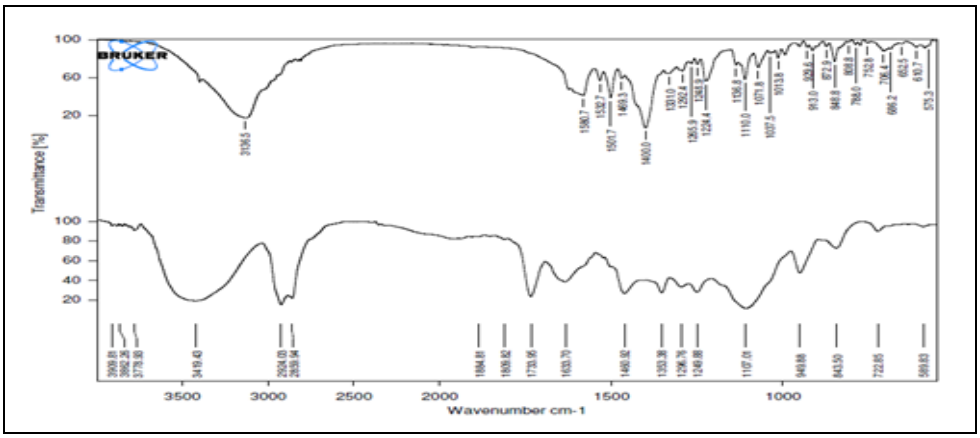



**FIG. 7: DRUG-EXCIPIENTS COMPATIBILITY OF GEFITINIB AND MATERIALS PK15LA USED IN FORMULATION**

## Interpretation of IR Spectra of Gefitinib and Formulation Materials PK15LA:

**TABLE 5: INTERPRETATION DATA OF GEFITINIB AND FORMULATION MATERIALS PK15LA**

| Absorption ($cm^{-1}$) | Group | Compound Class | Gefitinib | Formulation (PK15LA) |
|---|---|---|---|---|
| 1550-1500 | N-O stretching | Nitro compound | 1532.7 | 1528.4 |
| 1420-1330 | O-H bending | Alcohol | 1469.3, 1331.0 | 1460.92, 1353.38 |
| 1275-1200 | C-O stretching | Alkyl aryl ether | 1292.4, 1248.9 | 1296.76, 1249.88 |
| 1150-1085 | C-O stretching | Aliphatic ether | 1110.0 | 1107.01 |
| 995-985 | C=C bending | alkene | 929.6 | 949.88 |
| 850-550 | C- Cl stretching | Halo compound | 848.8, 752.8, 575.3 | 843.50, 722.85, 589.83 |

**Pseudo Ternary Phase Diagram:** From the pseudo ternary phase diagram, it was found that the formulations containing Peceol as oil phase, Kolliphor HS 15 as a surfactant, Labrasol as co-surfactant showed good nano emulsifying property.

For $S_{mix}$ 4:1 ratio formulations PK15LA41 of 9:1 to 4:6, 2:8 showed milky white emulsion (MWE), 1:9 showed clear transparent emulsion (CTE), 3:7 showed bluish-white emulsion (BWE).

For $S_{mix}$ 3:1 ratio formulations PK15LA31 of 9:1 to 4:6, 2:8 showed milky white emulsion (MWE), 1:9 showed clear transparent emulsion (CTE), 3:7 showed bluish-white emulsion (BWE).

**TABLE 6: GLOBULE SIZE AND ZETA POTENTIAL OF 4:1**

| Formulation | Globule size (d.nm) | PDI | Zeta potential (mV) | Remarks |
|---|---|---|---|---|
| PK15LA9:1 (4:1) | 440.4 | 0.650 | -53.9 | MWE |
| PK15LA8:2 (4:1) | 211.5 | 0.391 | -47.6 | MWE |
| PK15LA7:3 (4:1) | 326.6 | 0.539 | -50.8 | MWE |
| PK15LA6:4 (4:1) | 235.4 | 0.417 | -48.2 | MWE |
| PK15LA5:5 (4:1) | 320.1 | 0.644 | -42.9 | MWE |
| PK15LA4:6 (4:1) | 366.2 | 0.617 | -42.7 | MWE |
| PK15LA3:7 (4:1) | 229.4 | 0.194 | -38.8 | BWE |
| PK15LA2:8 (4:1) | 241.9 | 0.405 | -34.4 | MWE |
| PK15LA1:9 (4:1) | 184.9 | 0.123 | -30.9 | CTE |

**FIG. 8: PHYSICAL APPEARANCE OF PK15LA 4:1 WITH WATER TITRATION METHOD**

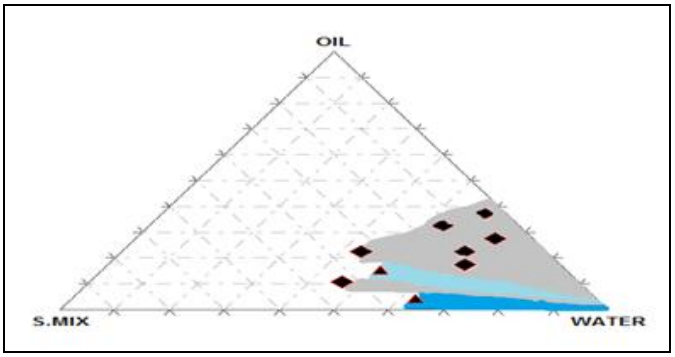



**FIG. 9: PSEUDO TERNARY PHASE DIAGRAM OF PK15LA 4:1**

**TABLE 7: GLOBULE SIZE AND ZETA POTENTIAL OF 3:1**

| Formulation | Globule size (d.nm) | PDI | Zeta potential (mV) | Remarks |
|---|---|---|---|---|
| PK15LA9:1 (3:1) | 191.2 | 0.306 | -31.6 | MWE |
| PK15LA8:2 (3:1) | 219.5 | 0.165 | -31.9 | MWE |
| PK15LA7:3 (3:1) | 417.8 | 0.602 | -49.2 | MWE |
| PK15LA6:4 (3:1) | 178.0 | 0.482 | -35.3 | MWE |
| PK15LA5:5 (3:1) | 255.2 | 0.288 | -38.1 | MWE |
| PK15LA4:6 (3:1) | 213.7 | 0.299 | -51.9 | MWE |
| PK15LA3:7 (3:1) | 242.1 | 0.253 | -47.6 | BWE |
| PK15LA2:8 (3:1) | 259.7 | 0.200 | -18.9 | MWE |
| PK15LA1:9 (3:1) | 163.4 | 0.386 | -17.3 | CTE |

**FIG. 10: PHYSICAL APPEARANCE OF PK15LA 3:1 WITH WATER TITRATION METHOD**

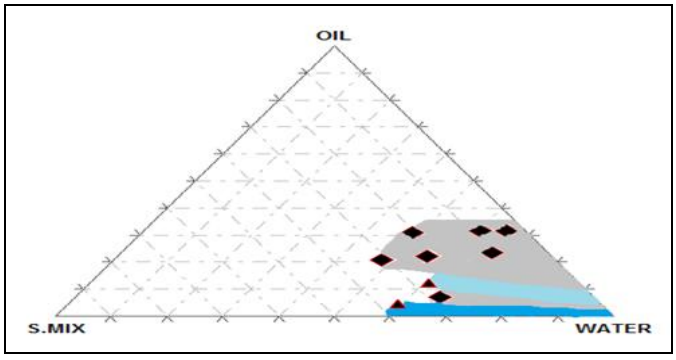



**FIG. 11: PSEUDO TERNARY PHASE DIAGRAM OF PK15LA 3:1**


**FIG. 12: FORMULATION OF GEFITINIB LIQUID SEDDS**

**TABLE 8: COMPOSITION OF PREPARED GEFITINIB SEDDS FORMULATIONS**

| S. no. | Formulation | API (Gefitinib) w/w% | Peceol w/w% | Kolliphor HS 15 w/w% | Labrasol w/w% | Total |
|---|---|---|---|---|---|---|
| 1 | PK154LA1 1:9 | 40 mg | 200 mg | 1440 mg | 360 mg | 2 ml |
| 2 | PK154LA1 2:8 | 40 mg | 400 mg | 1280 mg | 320 mg | 2 ml |
| 3 | PK153LA1 1:9 | 40 mg | 200 mg | 1350 mg | 450 mg | 2 ml |
| 4 | PK153LA1 2:8 | 40 mg | 400 mg | 1200mg | 400 mg | 2 ml |

**Evaluation of Gefitinib Liquid Self Emulsifying Drug Delivery Formulations:**

**Self Emulsification Time:** The liquid SEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation.

From the results obtained in **Table 9**, it was clear that the formulations were self-emulsified within 29 ± 1.05 to 36 ± 1.50 seconds and indicates the ability for rapid emulsification.

**TABLE 9: SELF EMULSIFICATION TIME VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Self emulsification time (sec) | Remarks |
|---|---|---|
| PK154LA1 1:9 | 29 ± 1.05 sec | Good |
| PK154LA1 2:8 | 35 ± 1.25 sec | Good |
| PK153LA1 1:9 | 30 ± 1.25 sec | Good |
| PK153LA1 2:8 | 36 ± 1.50 sec | Good |

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

**Dispersibility Test:** The formulations were visually estimated using the grading system previously mentioned and the results were shown in **Table 10**. Perceptible observations showed that all Gefitinib SEDDS formulations were found to be grade A. The rapid self-emulsification of the investigated formulations can be attributed to their low oil content (200-400% w/w).

**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 exhibited no phase separation even after 24 h as shown in **Table 11** indicates that emulsified oil globules are without phase separation.

**TABLE 10: DISPERSIBILITY TEST VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Observation | Grade |
|---|---|---|
| PK154LA1 1:9 | Rapidly forming emulsion having a clear or bluish appearance within 1 min | A |
| PK154LA1 2:8 | Rapidly forming emulsion having a clear or bluish appearance within 1 min | A |
| PK153LA1 1:9 | Rapidly forming emulsion having a clear or bluish appearance within 1 min | A |
| PK153LA1 2:8 | Rapidly forming emulsion having a clear or bluish appearance within 1 min | A |

**TABLE 11: ROBUSTNESS TO DILUTION VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Distilled water | 0.1N HCl | 6.8 Phosphate buffer |
|---|---|---|---|
| PK154LA1 1:9 | Passed | Passed | Passed |
| PK154LA1 2:8 | Passed | Passed | Passed |
| PK153LA1 1:9 | Passed | Passed | Passed |
| PK153LA1 2:8 | Passed | Passed | Passed |

**Thermodynamic Stability Studies:** No phase separation is observed for formulations PK154LA1 1:9 and PK153LA1 1:9 and indicates stable formulations under the effect of temperature.

Phase separation is observed for formulations PK153LA1 2:8 and PK154LA1 2:8 thus indicates unstable under the effect of temperature. The values are represented in **Table 12**.

**TABLE 12: THERMODYNAMIC STABILITY STUDY VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Freeze thaw cycles (2 cycles NLT 48 h) | Centrifugation (3500 rpm for 30 min) |
|---|---|---|
| PK154LA1 1:9 | Passed | Passed |
| PK154LA1 2:8 | Failed | Failed |
| PK153LA1 1:9 | Passed | Passed |
| PK153LA1 2:8 | Failed | Failed |

**Drug Loading Efficiency:** The drug loading efficiency of Gefitinib liquid SEDDS formulations was found in the range of 98.735 ± 0.43% for F1 to 94.567 ± 0.65% for F4, indicating uniform drug dispersion in formulations shown in **Table 13**.

It was also observed that the formulations F1 and F3 have the highest drug content, due to a higher concentration of surfactant and co-surfactant in these two formulations and possess high solubilization capacity to solubilize 40 mg dose of Gefitinib.

**TABLE 13: DRUG LOADING EFFICIENCY VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Drug loading efficiency |
|---|---|
| PK154LA1 1:9 | 98.735 ± 0.43% |
| PK154LA1 2:8 | 94.387 ± 0.54 % |
| PK153LA1 1:9 | 96.267 ± 0.52% |
| PK153LA1 2:8 | 94.567 ± 0.65% |

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 14: PERCENTAGE TRANSMITTANCE VALUES FOR GEFITINIB LIQUID SEDDS**

| Formulation | Distilled water | 0.1N HCl | 6.8 phosphate buffer solution |
|---|---|---|---|
| PK154LA1 1:9 | 98.53 ± 0.45 | 98.79 ± 0.67 | 98.25 ± 0.79 |
| PK154LA1 2:8 | 97.16 ± 0.94 | 97.46 ± 0.71 | 97.24 ± 0.64 |
| PK153LA1 1:9 | 98.43 ± 0.52 | 98.52 ± 0.66 | 98.07 ± 0.39 |
| PK153LA1 2:8 | 95.10 ± 0.57 | 96.82 ± 0.75 | 95.47 ± 0.96 |

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

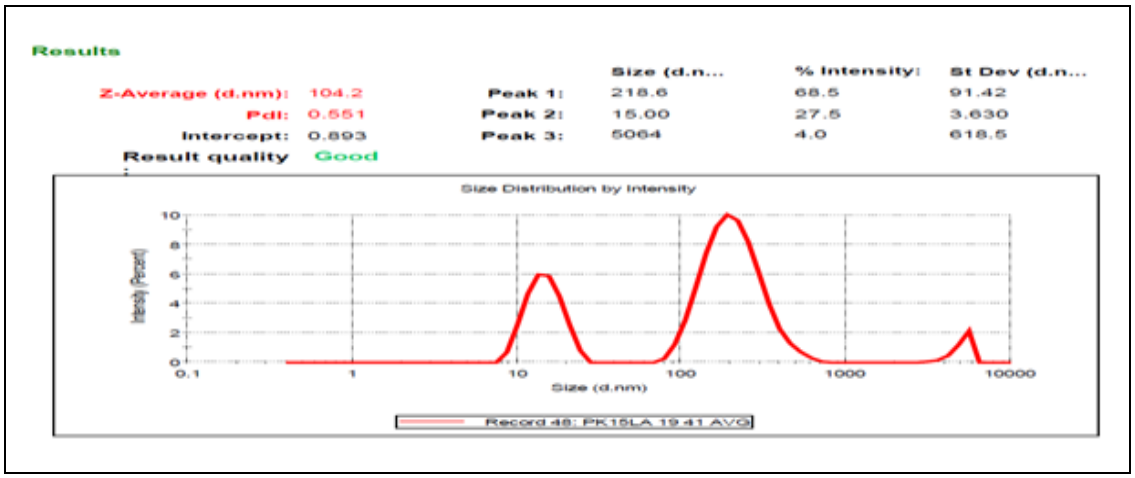
## Determination of Globule Size and Zeta Potential:

**TABLE 15: GLOBULE SIZE AND ZETA POTENTIAL VALUES FOR GEFITINIB LIQUID SEDDS**

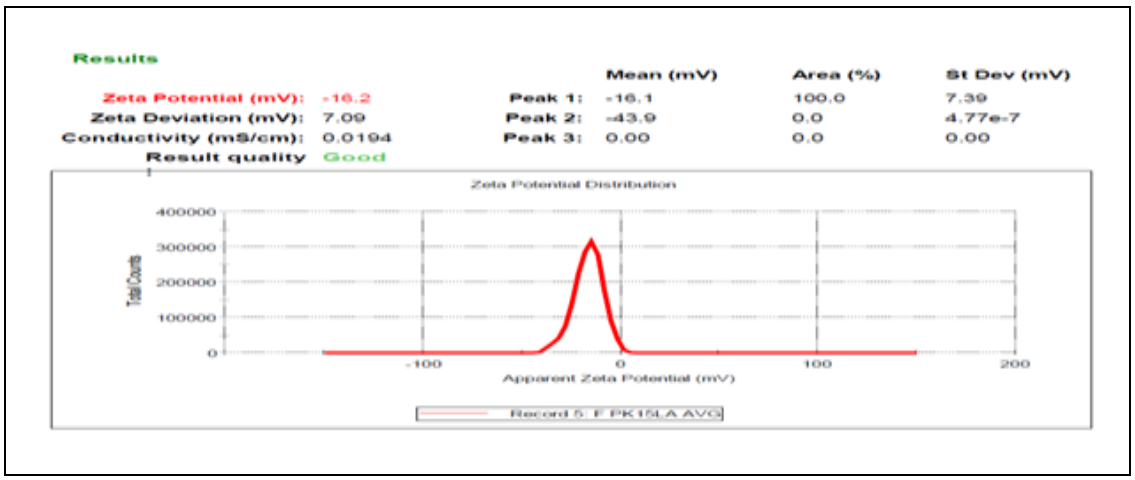
| Formulation | Globule size (d.nm) | PDI | Zeta potential (mV) |
|---|---|---|---|
| PK154LA1 1:9 | 104.2 | 0.551 | -16.2 |
| PK154LA1 2:8 | 202.6 | 0.495 | -28.4 |
| PK153LA1 1:9 | 184.1 | 0.603 | -27.9 |
| PK153LA1 2:8 | 241.7 | 0.354 | -23.6 |

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

## Globule Size of PK154LA1 1:9




## Zeta Potential of PK154LA1 1:9:

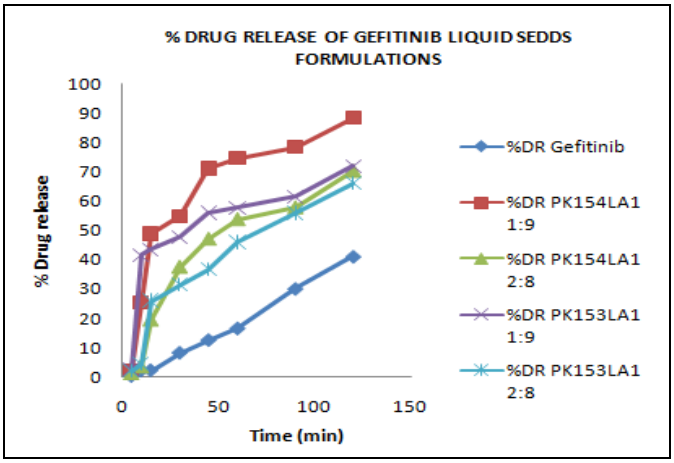



***In-vitro* Drug Release Studies:** The pure drug Gefitinib percentage drug release was 41.139 ± 0.32 % at the end of 120 min. When compared to pure drug release, the F1 formulation showed 88.253 ± 0.20% drug release at the end of release time. So, finally, F1 formulation was optimized, it shows good drug release and optimized SEDDS formulation F1 has enhanced solubility and dissolution rate of poorly aqueous soluble drug (Gefitinib) by 2.14 times.

**TABLE 16: DISSOLUTION DATA FOR PURE DRUG AND SEDDS FORMULATIONS OF GEFITINIB**

| Time (min) | % Drug released (Gefitinib) | % Drug released PK154LA1 1:9 | % Drug released PK154LA1 2:8 | % Drug released PK153LA1 1:9 | % Drug released PK153LA1 2:8 |
|---|---|---|---|---|---|
| 5 | 0.18 ± 0.40 | 2.356 ± 0.23 | 1.287 ± 0.15 | 2.999 ± 0.43 | 2.070 ± 0.30 |
| 10 | 2.074 ± 0.35 | 25.312 ± 0.37 | 3.551 ± 0.32 | 41.725 ± 0.31 | 4.491 ± 0.29 |
| 15 | 2.173 ± 0.36 | 48.893 ± 0.24 | 19.547 ± 0.41 | 43.463 ± 0.26 | 25.942 ± 0.26 |
| 30 | 8.176 ± 0.21 | 58.841 ± 0.40 | 37.291 ± 0.24 | 47.699 ± 0.24 | 31.288 ± 0.37 |
| 45 | 12.527 ± 0.30 | 71.061 ± 0.36 | 47.051 ± 0.34 | 56.001 ± 0.37 | 36.778 ± 0.33 |
| 60 | 16.257 ± 0.28 | 74.55 ± 0.24 | 53.358 ± 0.40 | 57.772 ± 0.42 | 45.879 ± 0.46 |
| 90 | 30.112 ± 0.38 | 78.27 ± 0.31 | 57.755 ± 0.51 | 61.380 ± 0.12 | 55.779 ± 0.52 |
| 120 | 41.139 ± 0.32 | 88.253 ± 0.20 | 70.188 ± 0.52 | 71.819 ± 0.29 | 65.949 ± 0.51 |

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




**GRAPH 2: COMPARISON OF PURE DRUG RELEASE WITH FORMULATED GEFITINIB SEDDS**

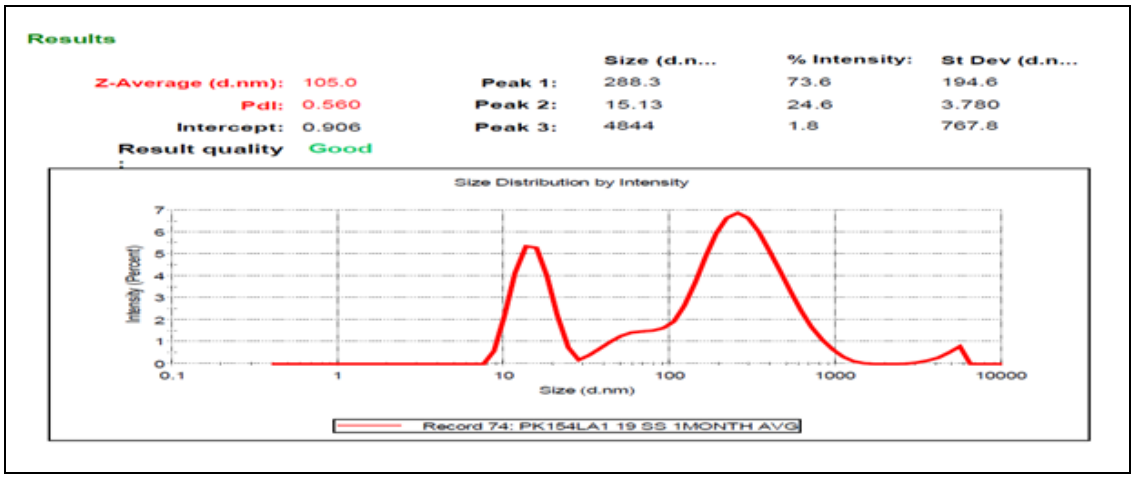
**Accelerated Stability Study:** Accelerated stability study was performed at 40 ± 2 °C /75 ± 5% RH for 1 month on the optimized formulation (F1) and evaluated for drug content, globule size, PDI, zeta potential and dissolution study.

The optimized formulation F1(PK154LA1 1:9) was stable under accelerated conditions for 1 month with respect to drug loading efficiency, globule size, PDI, zeta potential and dissolution study. Drug loading efficiency was found to be 97.975 ± 0.25%. Globule size of F1 was observed to be 105.0 d.nm and zeta potential -18.1 mV. There is no significant change in drug loading efficiency, globule size, PDI, zeta potential and dissolution study. The result of the *in-vitro* dissolution study of F1 formulation (PK154LA1 1:9) at 1 day shows 88.253 ± 0.20% and at accelerated conditions for 1 month shows 88.171 ± 0.36% at end of release time 120 min indicating no change in % drug release after stability study.

**TABLE 17: ACCELERATED STABILITY STUDY VALUES OF GEFITINIB SEDDS F1 PK154LA1 1:9 (OPTIMIZED) FORMULATION AT 1 DAY AND 1 MONTH**

| Formulation | %DR | Globule size (d.nm) | PDI | Zeta potential (MV) | DLE |
|---|---|---|---|---|---|
| F1 (1 day) | 88.253 ± 0.20% | 104.2 | 0.551 | -16.2 | 98.735 ± 0.43% |
| F1 (1 month) | 88.171 ± 0.36% | 105.0 | 0.560 | -18.1 | 97.975 ± 0.25% |

**Globule size of PK154LA1 1:9 at 40 ± 2 °C / 75 ± 5% RH Accelerated Conditions for 1 Month:**



**Zeta potential of PK154LA1 1:9 at 40 ± 2 °C / 75 ± 5% RH Accelerated Conditions for 1 Month:**

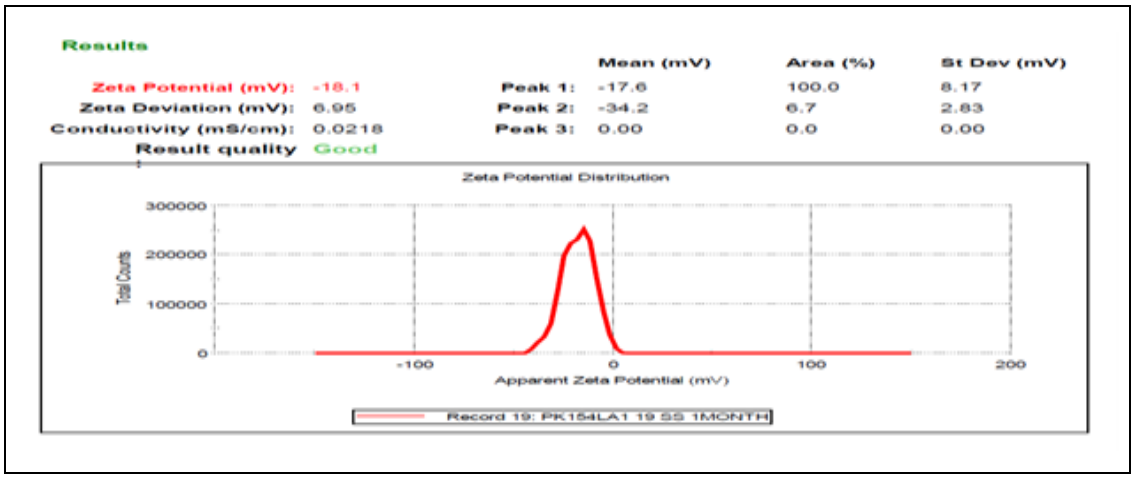
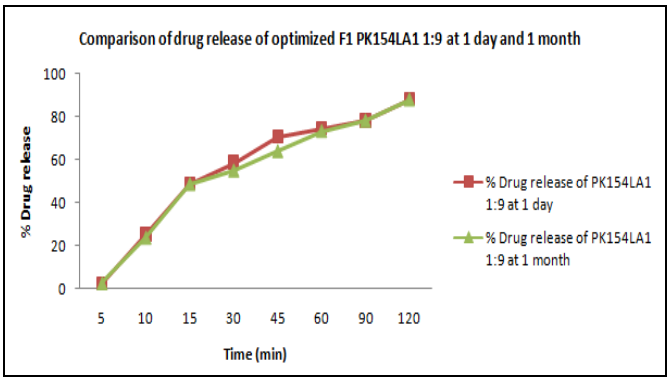



**TABLE 18: DISSOLUTION DATA FOR GEFITINIB SEDDS F1 (OPTIMIZED) FORMULATION AT 1 DAY AND GEFITINIB SEDDS F1 (OPTIMIZED) FORMULATION AT 1 MONTH**

| Time (min) | % Drug released PK154LA1 1:9 at 1 day | % Drug released PK154LA1 1:9 at 1 month |
|---|---|---|
| 5 | 2.356 ± 0.23 | 2.374 ± 0.13 |
| 10 | 25.312 ± 0.37 | 23.672 ± 0.42 |
| 15 | 48.893 ± 0.24 | 48.750 ± 0.32 |
| 30 | 58.841 ± 0.40 | 55.038 ± 0.37 |
| 45 | 71.061 ± 0.36 | 64.081 ± 0.13 |
| 60 | 74.55 ± 0.24 | 73.455 ± 0.20 |
| 90 | 78.27 ± 0.31 | 78.315 ± 0.24 |
| 120 | 88.253 ± 0.20 | 88.171 ± 0.36 |

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




**GRAPH 3: COMPARISON OF OPTIMIZED F1 FORMULATION DRUG RELEASE AT 1 DAY AND 1 MONTH**

## Drug Release Kinetics:

**TABLE 19: REGRESSION COEFFICIENT VALUES OF F1 FORMULATION GEFITINIB (PK154LA1 1:9) SEDDS**

| Kinetics | Zero-order | First-order | Higuchi | Korsmeyer Peppas |
|---|---|---|---|---|
| PK154LA1 1:9 at 1 day | 0.726 | 0.920 | 0.858 | 0.715 |
| PK154LA1 1:9 at stability condition for 1 month | 0.753 | 0.943 | 0.876 | 0.725 |

The drug release data obtained was extrapolated by Zero order, First order, Higuchi, Korsmeyer Peppas to know the mechanism of drug release from the formulation F1. The release rate kinetic data for formulation F1and at the accelerated condition for 1 month was shown in **Table 19**. The release kinetics shows that the release of the drug does not follow any order kinetics in the F1 (PK154LA1 1:9) formulation. SEDDS can be used as a potentiality for improving the solubility and dissolution rate of Gefitinib, indicating that Gefitinib liquid SEDDS are independent of order kinetics.

**CONCLUSION:** Gefitinib 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 2-4
- Low melting point
- Low dose

The optimized formulation F1 exhibited no phase separation or precipitation of drugs during thermo-dynamic stability studies. Self emulsification time was under 1 min. The percentage transmittance of F1 was above 95% showing clear emulsions. Drug loading efficiency was observed to be 98.735 ± 0.43%. Globule size of F1 was observed to be 104.2 d.nm and zeta potential was -16.2 mV.

The optimized formulation (F1) PK154LA1 1:9 was stable under accelerated conditions for 1 month with respect to drug loading efficiency, globule size, PDI, zeta potential and dissolution study. Drug loading efficiency was found to be 97.975 ± 0.25%. Globule size of PK154LA1 1:9 at 1 month was observed to be 105.0 d.nm and PK154LA1 1:9 zeta potential at 1 month was observed to be -18.1 mV.

Optimized formulation F1 has successfully shown drug release for 120 min and the drug release pattern was good. The pure drug Gefitinib percentage drug release was 41.1395 ± 0.32% at the end of 120 min. When compared to pure drug release, the F1 formulation showed 88.253 ± 0.20% drug release at the end of release time. So, finally, F1 formulation was optimized, it shows good drug release and optimized SEDDS formulation F1 has enhanced solubility of poorly aqueous soluble drug (Gefitinib) by 2.14 times.

The result of the *in-vitro* dissolution study of F1 formulation (PK154LA1 1:9) at 7 days shows 88.253 ± 0.20 % and at accelerated conditions for 1 month shows 88.171 ± 0.36% at end of release time 120 min indicating no change in % drug release after stability study. The enhanced *in-vitro* dissolution profile from liquid SEDDS is an indication of improved solubility and dissolution rate of the drug (Gefitinib). Hence formulated Gefitinib SEDDS has the capability for delivering poorly aqueous soluble drug Gefitinib insoluble state in the Gastro-Intestinal Tract.

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**CONFLICTS OF INTEREST:** Nil

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