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# Formulation Development, Optimization, and Characterization of Entrectinib-Loaded Supersaturable Self-Nanoemulsifying Drug Delivery Systems

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**Abstract**
Entrectinib is a novel potent anticancer drug with poor aqueous solubility. A supersaturable self-nanoemulsifying drug delivery system of entrectinib is developed using a super saturation promoter. The components of the isotropic mixture of SNEDDS were selected based on solubility and emulsification study. The optimum composition was identified using phase diagrams and further optimized by mixture design. The supersaturated SNEDDS was prepared using HPMC K4M as precipitation inhibitor. The droplet of sSNEDDS ranges from 118.42 ± 1.26 to 128.34 ± 0.63 nm with PDI values range from 0.112 to 0.204, which is significantly smaller than that observed with plain SNEDDS. The percent transmittance of the diluted formulation was found to be 98.78 ± 0.74. The viscosity was found to be 528 ± 32 centipoises indicating the good flow ability. FTIR and DSC studies indicated the amorphization of the drug. The dissolution profile of sSNEDDS indicated the faster release of drug compared to both pure drug suspension and SNEDDS formulation. The drug release rate is directly proportional to the concentration of the drug. The drug release from the insoluble matrix is a square root of time-dependent Fickian diffusion process. The formulation was found to be stable and transparent at all pH values and the percent transmittance was more than 95%. No significant difference was observed with all the samples exposed at different storage conditions. This study demonstrated the feasibility of stabilizing and improving the in vitro performance of SNEDDS by incorporating HPMC K4M as precipitation inhibitor.

**Keywords** Entrectinib · Super saturation · Precipitation inhibitor · Optimization · Simplex-lattice design · Self-emulsification

**Abbreviations**

| | |
|---|---|
| NBDDS | nano-based drug delivery system |
| SNEDDS | self-nanoemulsifying drug delivery system |
| sSNEDDS | supersaturable self-nanoemulsifying drug delivery system |
| PDI | polydispersity index |
| HPMC | hydroxy propyl methyl cellulose |
| FTIR spectroscopy | Fourier transformed infrared spectroscopy |
| DSC | differential scanning calorimetry |
| TEM | transmission electron microscope |
| FGFR | fibroblast growth factor receptor |
| US FDA | United States Food and Drug Administration |
| BCS | biopharmaceutical classification systems |
| GRAS | generally recognized as safe |
| GIT | gastro intestinal tract |

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## 1 Introduction

Entrectinib is a novel small molecule with potent anticancer activity. It acts by inhibiting tyrosine receptor kinases, which are overexpressed in cancer cells. Inhibition of the tropomyosin-related kinase (TRK) proteins A, B, and C, receptor tyrosine kinase (ROS1), and anaplastic lymphoma kinase (ALK) protein leads to inhibition of downstream signaling pathways, which in turn suppresses cell proliferation and

apoptosis. It is interesting to note that entrectinib is CNS active and could cross the blood-brain barrier to inhibit the tumor growth and is reported to have anticancer activity in progressive and metastatic solid tumors [1–3]. Entrectinib was first time approved in May 2017 by USFDA with breakthrough designation for the treatment of adult and pediatric patients with NTRK fusion–positive solid tumors [4]. The recommended dose of entrectinib was 600 mg/day for adults and 300 mg /day for children aged 12 years or older [5].

Entrectinib is a crystalline and non-hygroscopic solid with poor aqueous solubility. It is considered a BCS class II compound with low solubility and moderate permeability. Entrectinib is a lipophilic, basic molecule with strong pH-dependent solubility. It exhibits higher solubility in acidic media compared to neutral media. The solubility of entrectinib is more than 40 mg/ml in 0.07 M HCl (pH 1.2), 0.03 mg/ml at pH 5.4, and 0.002 mg/ml at pH 6.4. Its solubility is significantly higher in fed state than fasted state. Peak plasma concentration was found to be 2–4 h in the fasted state compared to 5–7 h in the fed state. Such food effects can cause difficulty during therapy and lead to wide variation in bioavailability of entrectinib [6, 7]. The mean terminal half-life (t1/2) is approximately 21 h in fed state. In addition, the plasma protein binding of entrectinib in humans is about 99.5% [8]. In order to increase the intrinsic solubility and to decrease the pharmacokinetic variability associated with existing capsule formulation, it is essential to develop an alternative formulation of entrectinib with improved characteristics.

In recent years, different formulation strategies were employed to enhance the oral bioavailability of poorly soluble drugs. Various traditional methods like salt formation, co-solvency, micronization, complexation, and use of permeation enhancers have been tested to increase the oral bioavailability. However, all these techniques have shown limited utility in drug delivery. Among various approaches, nano-based drug delivery systems (NBDDS) have the tremendous prospective to increase the bioavailability of poorly soluble drugs [9]. NBDDS have grasped much research interest in current years considering the potential benefits including improving the solubility of lipophilic drugs, increasing the permeability, improving drug stability, controlling drug distribution and elimination, and targeting drug delivery to the specific site. Several NBDDS like nanoemulsions, nanocrystals, nanosponges, nanobubbles, liposomes, lipid nanoparticles, polymeric micelles, polymeric nanoparticles, and inorganic nanocarriers have been developed [10].

Among various nanocarriers, lipid-based nanocarriers are deliberated to be a favourable approach to increase the oral bioavailability of hydrophobic drug substances. Encapsulation or solubilization of drug in lipid excipients may increase the dissolution and bioavailability. Lipid-based nanocarriers offer a variety of options like emulsions, vesicular systems, and lipid particulate systems. These formulations can uphold the drugs in solution state within the gastro intestinal tract (GIT). The availability of novel lipid excipients with generally recognized as safe (GRAS) status has helped the progress of lipid-based nanocarriers [11, 12]. Different types of lipid-based systems consisting of simple oil solution to complex mixtures of oil, surfactants, co-surfactants, and polymers have been developed in recent years. Lipid-based systems can be tailored by changing the composition and concentration of excipients to make them suitable for wide variety of drugs and can be applied to different dosage forms to various routes of administration [13].

Self-nanoemulsifying drug delivery system (SNEDDS) is an effective, smart, and more adequate formulation approach for poorly soluble drugs, compared to wide range of lipid-based systems. SNEDDS can enhance the oral bioavailability by improving the drug solubility, dissolution behaviour in GIT, and gut permeability [14, 15]. SNEDDS is an isotropic mixture of active substance with oil (natural or synthetic), surfactant, and co-surfactant. SNEDDS forms a transparent oil-in-water (o/w) nanoemulsion spontaneously when added to aqueous medium as the free energy required for emulsification process is low. Such nanoemulsion with droplet size of around 20–100 nm provide large interfacial area in the gastrointestinal fluids for enhanced absorption and minimum gastric irritation due to limited contact of drug with the gut wall [16–18]. SNEDDS is superior to other lipid-based systems because of their smaller size, high effective surface area, and absence of creaming, flocculation, sedimentation, or coalescence [19]. After oral administration of SNEDDS, lipid components will be digested by gastrointestinal lipases and result in the formation of mixed micelles containing cholesterol, monoglycerides, phospholipids, fatty acids, and bile salts, which interact with active ingredient, and alter its solubility and absorption characteristics [20].

The conventional SNEDDS formulation consists of plenty of surfactants and co-surfactants to prevent precipitation of the drug when added to GI fluids. The higher concentration of surfactants may lead to gastric irritation. In addition, the drug loading capacity of conventional SNEDDS ranges only from 50 to 90% of the equilibrium solubility of drug and this results in more amount of formulation to reach therapeutic level [21]. To overcome the mentioned limitations of conventional SNEDDS by minimizing drug precipitation in GIT and reducing the amount of surfactant, a new class of supersaturable formulation, namely supersaturable SNEDDS, has been developed as thermodynamically stable system containing a precipitation inhibitor and less amount of surfactant [22]. The results of both in vitro and in vivo studies demonstrated the improved characteristics of sSNEDDS compared to conventional SNEDDS. It has been reported various pharmaceutical excipients as precipitation inhibitors in supersaturable SNEDDS. These substances can

inhibit crystal nucleation and growth by interacting with drug molecules and by changing the viscosity and pH of the medium. A variety of polymers have been used as precipitation inhibitors to produce and preserve the supersaturated state of drugs for longer period of time. These polymers were able inhibit the precipitation by retarding the drug nucleation and crystal growth [23, 24].

SNEDDS formulation is usually a mixture of multiple components like oil, surfactant, co-surfactant, and active substance. The composition of these components may affect the final performance characteristics of the product. The traditional approach of setting the formulation by changing the one variable at a time may not be effectual in the preparation of optimized formulation. Competent optimization of such systems can be achieved by statistical design of experiments. Different statistical experimental designs have been used in setting the optimal composition of a formulation. Regular experimental design like factorial designs and Plackett-Burman design does not hold good for the composition setting of SNEDDS. Mixture designs are more appropriate for the optimization of SNEDDS formulation. They are special type of response surface experiments aimed to determine the optimal composition of blend that produces a desired response. In mixture designs, the proportion of different components can be selected as the independent variables. The proportion of components must sum to 100% complicates the regular designs and analysis of such experiments [25, 26].

The main objective of mixture designs is to define the response as a function of the composition of individual components, using a mathematic model based on limited number of experiments. A mixture design specifies the number and composition of the components that requires to set up a desired model. Mixture designs have been successfully used as an effective approach for the optimization of formulation development and to outline the importance of composition of each excipient. Among various mixture designs, simplex-lattice design is the most conventional approach for optimization of composition of a blend. It is an arrangement of equally spaced dots as a simplex. Use of simplex-lattice design was found to be more efficient method for the optimization of SNEDDS composition. These specific designs offer an optimal distribution of variables so that the experiments will spread over the factor space and identify the optimal experimental composition in the factor space [27–29].

Simplex-lattice design was used in this study for the optimization of SNEDDS composition. The association between response variables and influencing factors was described by multiple linear regression analysis of results using mathematical equations. Desirability function was used to set the optimum composition of blend. Regression analysis of obtained results resulted in polynomial equations which describe the relationship between influencing factors and response variables. Optimum levels were determined using Derringer's desirability function. The optimized drug-loaded SNEDDS was then converted to sSNEDDS using a precipitation inhibitor. The developed formulations were characterized for particle size, surface morphology, and thermal analysis. In vitro drug release experiments were carried out to assess the drug release pattern and to understand the absorption characteristics of the developed formulation.

## 2 Materials and Methods

### 2.1 Materials

Entrectinib was procured from Aelida Pharmaceuticals, Haryana, India. Sunflower oil, peppermint oil, oleic acid, castor oil, Capmul®MCM, Captex®300, Captex®2000, Miglynol®812, and Capryol®PGMC were purchased from HI Media Private limited, Mumbai, India. Tween®80, Tween®20, Span®80, Span®20, PEG 600, PEG 400, propylene, acetonitrile, ethanol, and methanol were procured from SD fine chemicals limited, Mumbai, India. Kolliphor®HS15, Kolliphor®PS80, Kolliphor®ELP, Kolliphor®EL, and Kolliphor®RH40 were obtained from BASF, Germany. Lauroglycol, Labrasol, Lutrol E 300, Labrafac, Labrafil M 2125, and Labrafil M 1944 were obtained from Loba Chemie Private Limited, Mumbai, India.

### 2.2 Methods

#### 2.2.1 Saturation Solubility Study

Entrectinib solubility in different vehicles was determined by adding excess quantity of drug in 5 ml of selected vehicle. The drug samples with different vehicles were mixed with continuous stirring for 48 h to enable solubilization and establish equilibrium. Then, the individual samples were centrifuged at 9000 × g for 10 min. Then, the supernatant was collected and diluted with methanol. Entrectinib concentration of the diluted samples was determined using UV spectrophotometer (Labindia UV-3000+) at a wavelength of 262 nm.

#### 2.2.2 Selection of Surfactant

Surfactant was selected based on the ability to emulsify the selected oil. Emulsification ability can be assessed by measuring the number of inversions needed to produce an even emulsion. Same quantity of surfactant and selected oil was taken in a beaker and mixed thoroughly at 40 °C to get a homogeneous mixture. 0.2 ml of this mixture was added to 100 ml distilled water. The number of inversions required to produce an even emulsion was recorded. The obtained

nanoemulsions were stored in a stable position. The percent transmittance of the settled emulsion was measured at 638.2 nm against a reference blank solution.

#### 2.2.3 Selection of Co-surfactant

Co-surfactant was selected based on the ability to expand the emulsification ability of selected surfactant towards the selected oil. One millilitre of $S_{mix}$ (1:1 surfactant:co-surfactant) was added to 1 ml of selected oil and heated at 40 °C to get a homogeneous mixture. 0.2 ml of this mixture was added to 100 ml distilled water. The number of inversions required to produce an even emulsion was recorded. The obtained nanoemulsions were stored in a stable position. The percent transmittance of the settled emulsion was measured at 638.2 nm against a reference blank solution.

#### 2.2.4 Construction of Phase Diagram

Aqueous titration method was used to identify the emulsification region and to construct the phase diagrams. Three phase diagrams were developed for the selected $S_{mix}$ of different compositions (1:1, 1:2, and 1:3). The selected oil and specific $S_{mix}$ were mixed uniformly in various proportions and titrated with distilled water until a transparent solution is obtained. The volume of water required to form a clear slightly bluish nanoemulsion was noted. The mass percent of oil, $S_{mix}$, and water recorded. The obtained data was entered into Origin pro V 8.0 software to obtain a phase diagram. The obtained diagrams were compared for difference in emulsification region.

#### 2.2.5 Formulation Development

Optimization techniques are capable of offering efficient and cost-effective method for the prediction of optimum composition of SNEDDS based on statistical analysis of results obtained from less number of experiments.

**Design of Experiments** Mixture designs are distinct type of experiments in which the final product is made up of several components. The mixture's components are expressed as a fraction equates to 1 (100%). In these situations, the response will be a function of the proportions of several components of the blend. Statistical mixture designs can be efficiently used to develop and optimize such formulations. The main aim of the mixture design is to model the mixture proportions mathematically to predict the responses for any mixture and to calculate the effect of each factor alone or in combination with other factors [27–29].

Among various mixture designs, simplex-lattice design is the most conventional approach for optimization of composition of SNEDDS. It is a type of mixture design and can be used for 2–30 components. A simplex-lattice design with degree of $m$ contains $m+1$ points of uniformly spaced values between 0 and 1 for each variable. If $m=3$, then the probable elements are 0, 1/3, 2/3, and 1. If $m=4$, then the probable values are 0, 1/4, 2/4, 3/4, and 1. These variables include the pure components and sufficient between them to draw an equation. The estimate of pure error can be obtained from replication of experiments, which is necessary to test the lack of fit of the design [30]. Three components in the SNEDDS formulation, including amount of oil phase (A), amount of surfactant (B), and amount of co-surfactant (C), were designated as independent variables. Stat-Ease Design-Expert® V 8.0 software was used for the design, computation, and evaluation of three component simplex-lattice design. The range of each component for the design was designated based on the emulsification region obtained from the phase diagram.

$$16\% \le A \ge 48\%$$

$$26\% \le B \ge 44\%$$

$$24\% \le C \ge 60\%$$

$$A + B + C = 100\%$$

The response parameters were droplet size ($Y_1$), polydispersity index ($Y_2$), and the percent drug release at 15 min ($Y_3$). The experimental compositions as per the design and obtained responses are as presented in Table 1. The experimental results were evaluated by multiple linear regression analysis. The best fitting polynomial model as described by Eq. 1.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1 X_2 X_3 \quad (1)$$

where

$$X1 + X2 + X3 = 1$$

**Model Verification and Optimization** The optimum composition of SNEDDS was determined using Derringer's desirability function built on the criteria of obtaining particles minimum and uniform droplet size and maximum drug release at 15 min. Confirmation experiments with optimized variables were prepared in triplicate and the results were analyzed as per the optimized prediction profiler. The experimental results obtained for optimized batches were compared with the model predicted responses.

**Preparation of SNEDDS Formulation** Entrectinib-loaded SNEDDS was obtained by dissolving the specified quantity of drug in the isotropic mixture of oil and $S_{mix}$. Then, the mixture is vortexed and subjected to sonication for 5 min to get a transparent solution. The obtained solution was

**Table 1** The experimental composition and results of simplex-lattice design

| Expt. | Amount of oil | Amount of surfactant | Amount of co-surfactant | Droplet size (nm) | Polydispersity index | Drug release at 15 min (%) |
|---|---|---|---|---|---|---|
| 1 | 0 | 0.5 | 0.5 | 156.28 | 0.162 | 21.26 |
| 2 | 0.666667 | 0.166667 | 0.166667 | 386.56 | 0.426 | 14.86 |
| 3 | 0.5 | 0.5 | 0 | 378.12 | 0.298 | 16.43 |
| 4 | 0 | 1 | 0 | 159.48 | 0.242 | 18.34 |
| 5 | 0 | 0 | 1 | 148.76 | 0.186 | 14.56 |
| 6 | 0.5 | 0 | 0.5 | 300.56 | 0.212 | 16.38 |
| 7 | 0 | 1 | 0 | 165.93 | 0.258 | 19.82 |
| 8 | 0.166667 | 0.166667 | 0.666667 | 207.34 | 0.242 | 18.48 |
| 9 | 0.5 | 0.5 | 0 | 382.46 | 0.309 | 15.88 |
| 10 | 1 | 0 | 0 | 438.56 | 0.512 | 12.78 |
| 11 | 0.333333 | 0.333333 | 0.333333 | 286.74 | 0.382 | 18.12 |
| 12 | 1 | 0 | 0 | 442.18 | 0.498 | 13.12 |
| 13 | 0 | 0 | 1 | 156.49 | 0.178 | 14.06 |
| 14 | 0.166667 | 0.666667 | 0.166667 | 246.54 | 0.316 | 18.92 |

stored at a temperature of 37 ± 0.5 °C for a period of 24 h to attain equilibrium.

**Preparation of Placebo Formulation** The placebo formulation was obtained by mixing the components of SNEDDS without adding the drug. Then, the mixture is vortexed and subjected to sonication for 5 min to get a transparent solution. The obtained solution was stored at a temperature of 37 ± 0.5 °C for a period of 24 h to attain equilibrium.

**Selection of a Precipitation Inhibitor** In vitro precipitation experiments were carried out to estimate the concentration-time profile and supersaturated state of the drug. Various polymers like PVP K30, Eudragit L100, Poloxamer 407, and HPMC K4M were used to main the stable super saturation state. One hundred milligrams of optimized formulation with selected polymer was added to simulated gastric fluid (100 ml) and homogenized with continuous stirring. One millilitre of each sample was withdrawn from the saturated solutions without volume replacement at specified time intervals. The samples were centrifuged at 12000 × g for 10 min. The supernatant solution was collected and suitably diluted with methanol. Entrectinib concentration of the diluted samples was determined using UV-spectrophotometer (Labindia UV-3000+) at a wavelength of 262 nm.

**Preparation of Supersaturable SNEDDS of Entrectinib** Supersaturable SNEDDS of entrectinib was obtained by a simple admixture method as reported elsewhere. The selected precipitation inhibitor (equivalent to 5% w/w of the formulation) was incorporated into the prepared formulation. The formulations were vigorously vortexed for 5 min to get a uniform emulsion. Then, the final formulations were maintained stable at 37 ± 0.5 °C for 24 h to attain equilibrium.

## 2.3 Characterization of SNEDDS and sSNEDDS Formulations

### 2.3.1 Droplet Size and Zeta Potential

Malvern particle size analyzer (Mastersizer® 300) equipped with MAS OPTION software was used to determine the average size of droplets. The diluted sample was used for the measurement of droplet size. The average droplet size and polydispersity index were calculated using cumulative analysis of triplicate results. Zeta potential values of the respective samples were obtained using an additional electrode on the same instrument.

### 2.3.2 TEM

The formulation was suitably diluted using distilled water. One drop of diluted and homogenized sample was placed on a film coated copper grid. Two percent w/v aqueous solution of phosphotungstic acid was used for staining the slides. Then, the sample was allowed to stand for a minute, and the excess solution was removed for contrast enhancement. The samples were observed for morphological structure under a transmission electron microscope (JEM-F200, JEOL, Tokyo, Japan) at 7200 × magnification.

### 2.3.3 Self-Emulsification Time

All the formulations were evaluated for emulsification time as reported elsewhere [31]. One millilitre of formulation was mixed with 200 ml of distilled water under agitation using magnetic stirrer. The time required for emulsification was recorded.

#### 2.3.4 Transmittance Percentage

The percent transmittance of diluted samples was determined using UV spectrophotometer at 630 nm against reference blank solution [32].

#### 2.3.5 Determination of Viscosity

The viscosity of the final formulations was measured using a Brookfield rotational viscometer (DV2T) using C16-1 spindle at 10 rpm. The type of emulsion can be identified based on the viscosity values. If the viscosity is high, then it can be without type emulsion and vice versa [33].

#### 2.3.6 FTIR Spectroscopy

FTIR spectra of individual components, physical mixture, and optimized formulation were recorded using potassium bromide disk method. Two milligrams of the sample was mixed with spectra grade potassium bromide (150 mg) over a range of 400–4000 $cm^{-1}$. The mixture was pressed into a 12-mm diameter disk using hydraulic press.

#### 2.3.7 DSC Thermogram

Thermal analysis of pure entrectinib, SNEDDS formulation, and sSNEDDS formulation was performed to using a differential scanning calorimeter (DSC 2500, TA instruments). Five milligrams of samples was taken in standard aluminium plates and the thermograms were recorded from 30 to 400 °C at a heating rate of 10 °C/min under an inert atmosphere using empty plate as reference.

#### 2.3.8 Drug Release Study

The drug dissolution pattern of entrectinib formulations was studied using a USP II paddle apparatus under sink conditions. Formulations (≈ 10 mg of drug) were added to 900 ml of phosphate buffer (pH 6.8). At specified time intervals, 2 ml of samples was withdrawn and passed through a 0.22-µm syringe filter. The sample was then collected and diluted suitably with methanol. The concentration of entrectinib was determined using UV-spectrophotometer (Labindia UV-3000+) at a wavelength of 262 nm. All the results were obtained in triplicate. The dissolution profile was plotted and compared with each other. The drug release data was further analyzed using different kinetic models to predict the drug release mechanism.

#### 2.3.9 Dilution and pH Stability

The effect of dilution and pH stability of both the formulations was evaluated by diluting the samples 1000 folds in glass vials with distilled water, phosphate buffer (pH 6.8), and acid buffer (pH 1.2). The diluted samples were observed for any sort of instability after 24 h.

#### 2.3.10 Thermodynamic Stability

The influence of changes in temperature on phase separation of prepared formulations was assessed by exposing to six cooling (4 °C) and heating cycles (40 °C) and freeze thaw cycles (−21 °C and +25 °C) for 2 days.

#### 2.3.11 Stability Study

The physical and chemical stability of the final formulations was assessed by conducting the accelerated stability studies following ICH guidelines. Both the formulations were stored at different storage conditions for 6 months and changes in the critical quality attributes.

## 3 Results and Discussion

SNEDDS forms nanoemulsions instantaneously when mixed with intestinal fluids and the drug will be presented in the dissolved state. The enhanced drug dissolution and absorption can be attributed to the small droplet size which provides large effective surface area [34]. In order to prepare an efficient SNEDDS formulation of entrectinib, selection of suitable oil phase, surfactant mixture, and proper droplet size is essential. The selection of oil phase primarily based on solubilization potential, followed by emulsification ability, whereas the selection of surfactant mixture primarily based emulsification efficiency and drug solubility would be secondary.

The results of solubility study of entrectinib are displayed in Fig. 1. Drug loading capacity is an important parameter to be considered while selecting the components of SNEDDS. The solubilization potential and extensive emulsification region in the phase diagram are the major factors in selecting the components. Among different oils studied, Capmul®MCM have shown maximum solubilization potential. Capmul®MCM is a semisynthetic glyceryl caprylate, obtained by the esterification of glycerine with specific medium/long-chain fatty acids. The higher solubility of entrectinib in Capmul®MCM is due to lipophilic nature of esterified medium-chain glycerides [35]. Capmul®MCM was selected as oil of choice on the basis of maximum

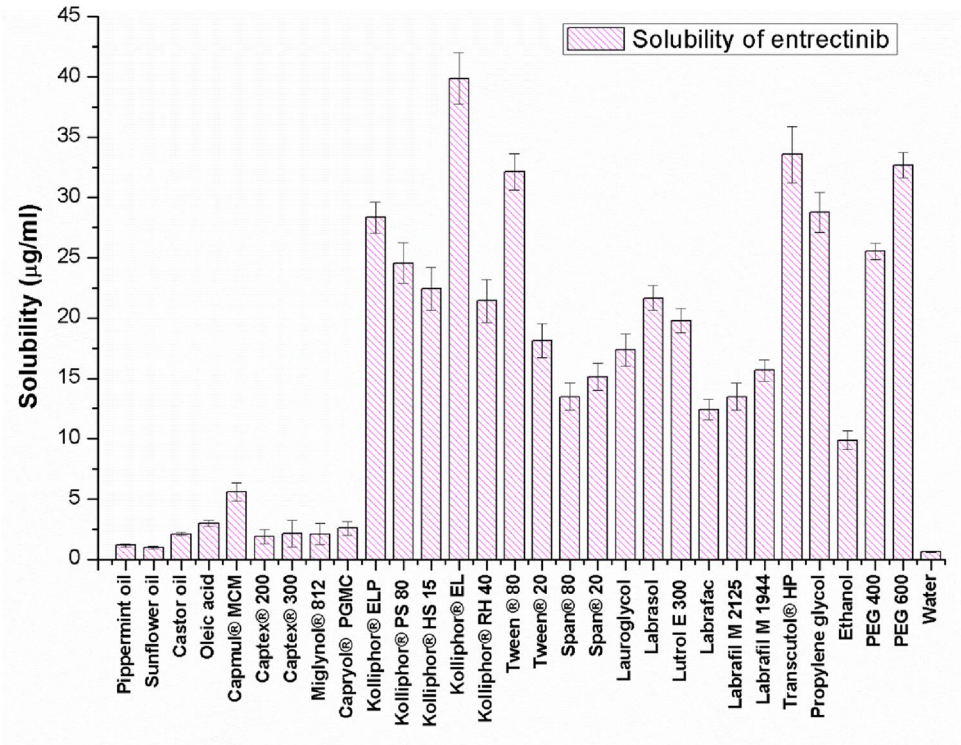


**Fig. 1** Solubility of entrectinib in different vehicles

solubilization of drug of interest. The selected oil should be able to present the drug in its dissolved state in GIT so as to have better permeation through GIT.

Surfactant is the second major component in the formulation of SNEDDS and its selection is critical. The different characteristics of surfactant like viscosity, HLB value, cloud point, and affinity towards oil phase will have a great influence on droplet size emulsification characteristics. The selected surfactant should have sufficient lipophilicity to provide the accurate curvature at the interface. The surfactant should be able to reduce the interfacial tension so as to provide ease of dispersion. In selecting the surfactant, its emulsification ability, HLB value, and solubilization potential are the three important features needs to be considered. Among different class of surfactants, non-ionic surfactants are widely used in SNEDDS formulations because of their minimal toxicity and their ability to stabilize the formulation over a wide range of pH and ionic strength. The non-ionic surfactants with HLB values greater than 12 are highly endorsed because of their ability to form spontaneous emulsions with minimum droplet size. Some of the surfactants might cause GI irritation after oral administration. Hence, the orally acceptability and regulatory status (like GRAS – generally regarded as safe) needs to be considered while selecting the surfactant. The amount of surfactant in the final formulation should be maintained as low as possible.

In this study, different surfactants namely Kolliphor® EL, Kolliphor® RH, Kolliphor® HS15, Kolliphor® Kolliphor® ELP, Kolliphor® PS 80, Tween®20, Tween®80, Span®20, Span®80, Lauroglycol, Labrasol, Lutrol E 300, Labrafac, Labrafil M 2125, and Labrafil M 1944 were tested for emulsification of selected oil. The amount of oil emulsified by different surfactants is as shown in Fig. 2. The percentage transmittance and number of inversions required for emulsification for each combination is noted and is as shown in Fig. 3. Emulsification study revealed that Kolliphor® EL has good potential for emulsification. Among various surfactants screened, maximum solubility was observed in Kolliphor® EL with 39.872 mg/ml. High solubility in Kolliphor® EL can be ascribed to its amphiphilic character and higher HLB value [36]. Hence, in the present study, Kolliphor® EL was the surfactant of choice for the preparation of entrectinib SNEDDS.

In the formulation of SNEDDS, a single surfactant may not be sufficient to reduce the interfacial tension as required. The addition of another surfactant (co-surfactant) is essential to enhance the solubility and dispersibility of surfactant in the oil phase. The addition of co-surfactant can promote stability and homogeneity of emulsions. Moreover, use of co-surfactants can reduce the local irritation caused by surfactants and dose variability. The weight ratio of surfactant/co-surfactant also will have a crucial role on droplet size and the extent of emulsification region. Commonly used co-surfactants comprise propylene glycol, ethanol, polyethylene glycols (PEG 600 and PEG 400), and Transcutol®HP. Among co-surfactants, Transcutol® HP and PEG 600 exhibited maximum solubility with 33.56 ± 0.762 mg/ ml and 32.67 ± 0.267 mg/ml respectively.

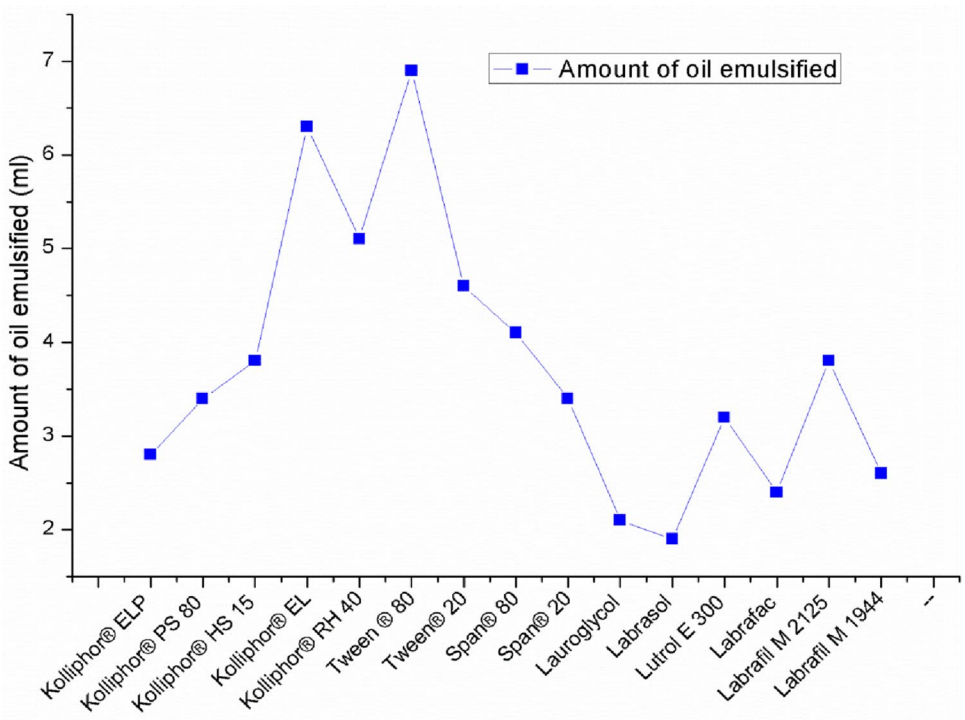


**Fig. 2** Amount of oil emulsified by different surfactants

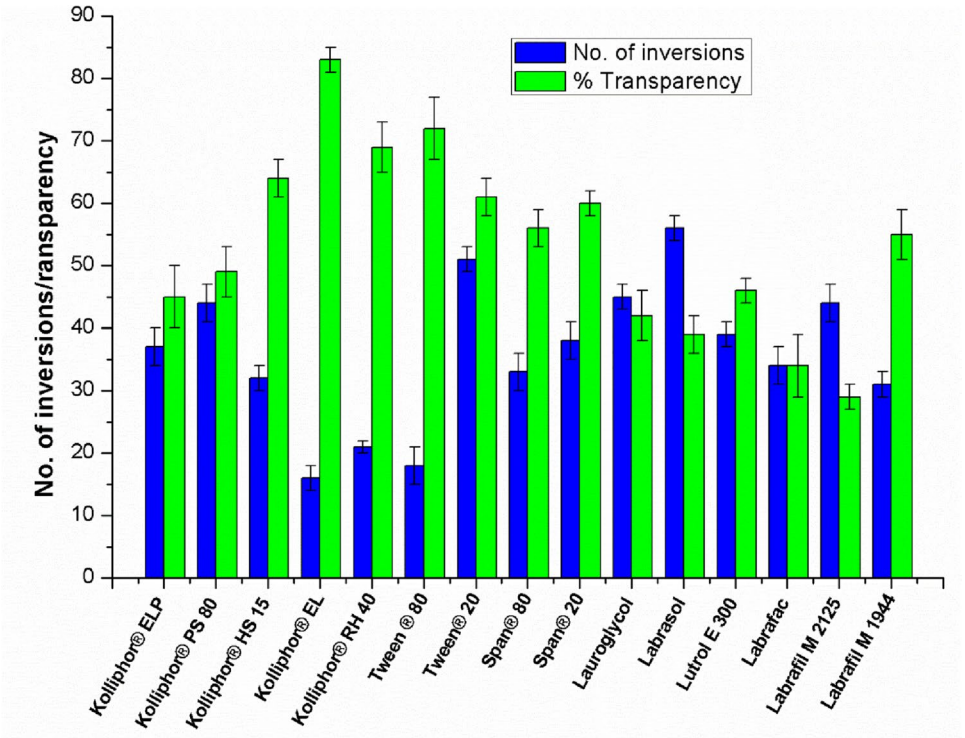


**Fig. 3** Number of inversions and percent transmittance with different surfactants

Five co-surfactants, namely propylene glycol, ethanol, poly ethylene glycols (PEG 400 and PEG 600), and Transcutol® HP, were individually added to the surfactant in a fixed ratio of 1:1. The combination of surfactants has shown better emulsification potential compared to surfactant alone. The number of inversions and percent transparency of different co-surfactants is as shown in Fig. 4. It is evident from the data that Transcutol® HP has shown highest emulsification of oil. In addition, the combination resulted in higher values of % transparency and ease of emulsification compared to

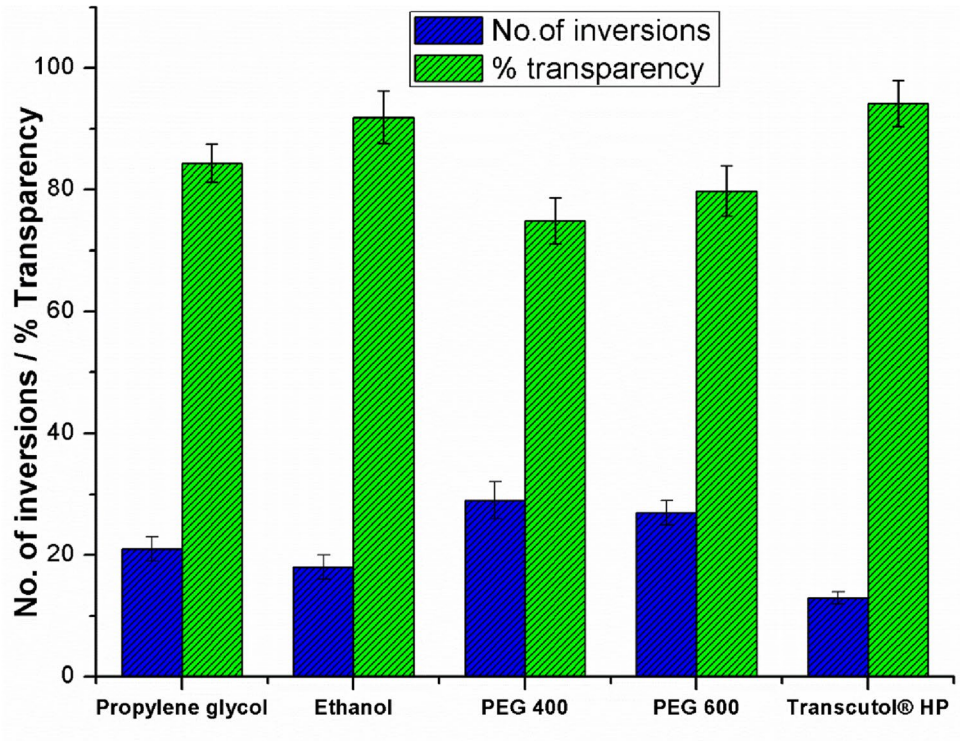


**Fig. 4** Number of inversions and percent transmittance with different co-surfactants

the surfactant alone. This indicated the importance of co-surfactant for the preparation of SNEDDS. Based on the results of emulsification study, Transcutol®HP was chosen as co-surfactant.

Emulsification region of a three component system can be identified easily from ternary phase diagrams. Each apex of the phase diagram represents 100% of the respective component. The shaded area determines the composition of a three component system. The phase diagrams were built for the three components, namely oil, $S_{mix}$, and water, with different mass ratios of $S_{mix}$. The emulsification region was broad with $S_{mix}$ ratio of 1:1. It is evident from the diagrams that decrease in $S_{mix}$ ratio resulted in decreased emulsion region as shown in Fig. 5. Based on ternary phase diagrams, the range of components was selected as follows: 20% ≤ Capmul®MCM ≤ 41%, 18% ≤ Kolliphor® EL ≤ 30%, 30% ≤ Transcutol® HP ≤ 50%. The range of oil, surfactant, and co-surfactant was further optimized by simplex-lattice design.

A systemic approach for the development of a formulation is essential to reduce the variation in the final characteristics of the product. The amount of oil (A), amount of surfactant (B), and amount of co-surfactant (C) were found to have influence on the droplet size, polydispersity index,

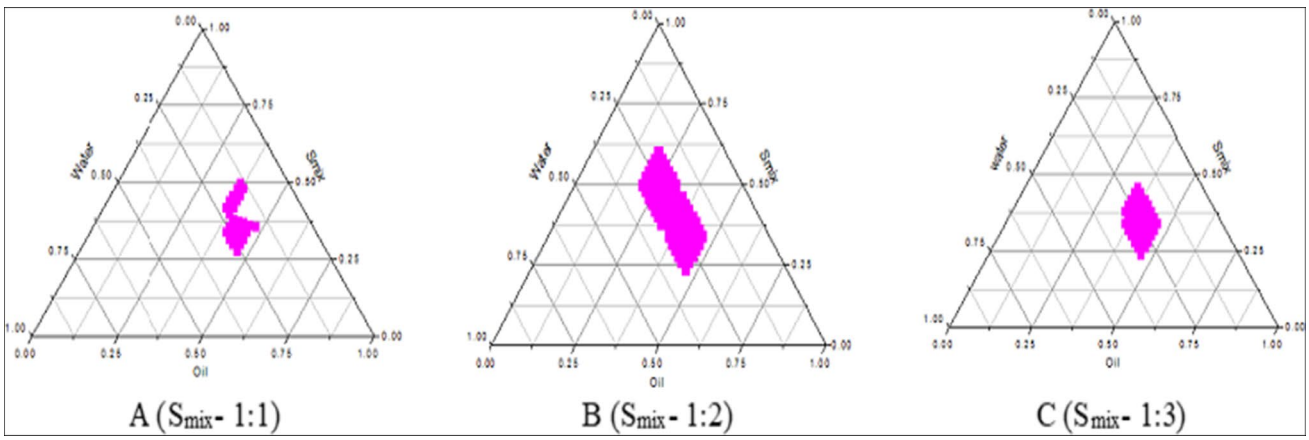


**Fig. 5** Phase diagrams to depict the emulsification region for different ratio of $S_{mix}$

and drug release at 15 min. Among different strategies, statistical design of experiments was proven to be an effective approach. Different kind of designs can be adopted based on the nature of factors. Among various designs, simplex-lattice design was found to be more appropriate to optimize the composition of mixture components. Based on simplex-lattice design, fourteen trial experiments which consist of six simplex points were arbitrarily arranged. The experiments were performed as per the design and the obtained results are presented in Table 1. The obtained results were analyzed using multiple linear regression analysis and mathematical equations were generated to correlate each dependent variable. The results were evaluated with analysis of variance (ANOVA), regression coefficients ($R^2$), 3-dimensional response surface, and contour plots.

The range of droplet size ($Y_1$) for all batches was 148.76–442.18 nm. Similarly, the range for polydispersity index ($Y_2$) was 0.162–0.512 and the % release of drug at 15 min ($Y_3$) was found to be in the range of 12.78–21.26 %. Mathematical equations were generated for each response and are presented in Table 2. The mathematical models developed for the responses $Y_1$ and $Y_3$ were based on quadratic model, whereas the model developed for $Y_2$ was based on super cubic model. These equations represent the quantitative effect of amount of Capmul® MCM, Kolliphor® EL, and Transcutol® HP and their interactive effect on droplet size ($Y_1$), polydispersity index ($Y_2$), and the percent drug release after 15 min ($Y_3$). The magnitude of coefficients of A, B, and C indicates the influence of individual factors on response variables. The coefficients with more than one factor term indicate the interactive effect. The polynomial equations obtained for all the responses were found to be statistically significant, as indicated by ANOVA values of different parameters as shown in Table 3. The practical values obtained for all the responses were in good agreement with the theoretically predicted values as indicated in Fig. 6.

Droplet size plays important role in the absorption and distribution. The droplet size depends on the composition of SNEDDS formulation. Increase in proportion of surfactants usually reduces the interfacial tension and produces smaller droplet size. The quadratic model obtained for $Y_1$ was found to be significant with model *F*-value of 4054.78. This model revealed that the amount of Capmul® MCM, Kolliphor® EL, and Transcutol® HP has significant positive effect on droplet size. It is evident from the equation that the effect of variable A is more significant than B and C on $Y_1$. The resultant model for $Y_1$ has shown good correlation coefficient (0.9991). The influence of individual variables was further elucidated using respective contour and 3D response surface plots (Fig. 7a and b).

Polydispersity (PDI) is an important parameter used to describe the size distribution of nanocarriers systems. Usually the PDI values falls between 0 and 1. PDI values less than 0.05 indicate a highly monodisperse system. PDI values greater than 0.7 can be observed with highly heterogeneous sample. PDI values of less than 0.2 usually considered acceptable for polymer-based nanocarriers, whereas for the lipid-based systems, PDI values of less than 0.3 is acceptable. For effective drug delivery, we need to have carrier systems having uniform size so that we can predict their behaviour in vivo. The polydispersity index of the prepared SNEDDS was found to be in the range of 0.162–0.512 (Table 1). The super cubic model developed for polydispersity index ($Y_2$) was found to be significant with model *F*-value of 225.32. This model revealed that the amount of Capmul® MCM, Kolliphor® EL, and Transcutol® HP has significant positive effect on polydispersity index. It is evident from the equation that the effect of variable A is more significant than B and C on $Y_2$. The resultant model for $Y_2$ have shown good correlation coefficient (0.9948). The influence of individual variables was further elucidated using respective contour and 3D response surface plots (Fig. 7c and d).

The percent drug release at 15 min ($Y_3$) from the developed formulations ranged between 12.78 and 21.26. The quadratic model obtained for $Y_3$ was found to be significant with model *F*-value of 61.61. This model revealed that the amount of Capmul® MCM, Kolliphor® EL, and Transcutol® HP has significant positive effect on $Y_3$. It is evident from the equation that the effect of variable B is more significant than C and A on $Y_3$. The resultant model for $Y_3$ has shown good correlation coefficient (0.9647). The influence of individual variables was further elucidated using respective contour and 3D response surface plots (Fig. 7e and f).

Derringer's desirability approach was used for factor optimization. It is based on the conversion of all the responses from different scales to a scale-free value. The values of the responses were transformed into the desirability scale. The criteria selected for the approach were based on minimization of droplet size and PDI, while maximizing the percent

**Table 2** Polynomial equations for the responses

| Response | Polynomial equation |
|---|---|
| $Y_1$ - Droplet size | 441.81A+162.82B+151.39C+317.33AB |
| $Y_2$ - Polydispersity index | 0.51A+0.25B+0.18C-0.29AB-0.52AC-0.22BC+5.19ABC |
| $Y_3$ - Percent drug release at 15 min | 12.83A+ 19.01B+14.46C+9.68AC+17.27BC |

**Table 3** ANOVA table of all the three polynomial models

| Source of variations | Sum of squares | Degrees of freedom | Mean square values | *F*-value | *P*-value Prob >*F* | |
|---|---|---|---|---|---|---|
| *$Y_1$- Droplet size* | | | | | | |
| Model | 164685.8 | 3 | 54895.27 | 4054.784 | < 0.0001 | Significant |
| Linear mixture | 155346 | 2 | 77672.98 | 5737.236 | < 0.0001 | |
| AB | 9339.857 | 1 | 9339.857 | 689.8791 | < 0.0001 | |
| Residual | 135.384 | 10 | 13.5384 | | | |
| Lack of fit | 68.73627 | 6 | 11.45604 | 0.687558 | 0.6758 | Not significant |
| Pure error | 66.6477 | 4 | 16.66193 | | | |
| Cot total | 164821.2 | 13 | | | | |
| *$Y_2$ - Polydispersity index* | | | | | | |
| Model | 0.169341 | 6 | 0.028223 | 225.3174 | < 0.0001 | Significant |
| Linear mixture | 0.136159 | 2 | 0.068079 | 543.5017 | < 0.0001 | |
| AB | 0.007022 | 1 | 0.007022 | 56.06213 | 0.0001 | |
| AC | 0.014293 | 1 | 0.014293 | 114.1049 | < 0.0001 | |
| BC | 0.002553 | 1 | 0.002553 | 20.38008 | 0.0028 | |
| ABC | 0.029177 | 1 | 0.029177 | 232.927 | < 0.0001 | |
| Residual | 0.000877 | 7 | 0.000125 | | | |
| Lack of fit | 0.000558 | 3 | 0.000186 | 2.337313 | 0.215 | Not significant |
| Pure error | 0.000319 | 4 | 7.96E-05 | | | |
| Cot total | 0.170218 | 13 | | | | |
| *$Y_3$ - Drug release at 15 min* | | | | | | |
| Model | 84.17748 | 4 | 21.04437 | 61.61247 | < 0.0001 | Significant |
| Linear mixture | 56.24926 | 2 | 28.12463 | 82.34165 | < 0.0001 | |
| AC | 6.047102 | 1 | 6.047102 | 17.70435 | 0.0023 | |
| BC | 19.26025 | 1 | 19.26025 | 56.38904 | < 0.0001 | |
| Residual | 3.074042 | 9 | 0.34156 | | | |
| Lack of fit | 1.644792 | 5 | 0.328958 | 0.920646 | 0.5472 | Not significant |
| Pure error | 1.42925 | 4 | 0.357313 | | | |
| Cot total | 87.25152 | 13 | | | | |

drug release at 15 min. The maximum desirability function was obtained with the response values at A: 0 (20%), B: 0.555(24.6 %) and C: 0.445 (55.4%) with the resultant D value of 0.986. Three batches confirmation experiments were performed to validate the selected model. The obtained results are as shown in Table 4. The obtained results were in fine agreement with the predicted result, indicating the success of simplex-lattice design for the optimization of composition of SNEDDS.

Supersaturable self-nanoemulsifying drug delivery system (sSNEDDS) consists of a polymeric precipitation inhibitor which generates and maintains the drug in a meta stable supersaturated state by preventing the precipitation. sSNEDDS formulations can have added benefit over the conventional SNEDDS in improving the bioavailability of weekly soluble drugs. The precipitation inhibition mechanisms of various polymers like HPMC, PVP, Eudragits, and poloxamers to maintain the super saturation state of the drug comprise the inhibition of crystal growth and nucleation. These polymers are also known to increase the solubility of drugs. At higher concentrations, these polymers increase the viscosity and result in kinetic stabilization of the supersaturated state by restricting the movement of drug particles. Inhibitory effects of these polymers remain highly dependent on the combination of drug and polymer. Hence, it is important to screen for a suitable polymer.

Four different polymers, namely PVP K30, HPMC K4M, Poloxamer 407, and Eudragit L100, were tested as precipitation inhibitors to determine the degree of super saturation under non-sink conditions. Individual polymers (equivalent to 5% w/w of formulation) were added to different samples of SNEDDS formulation. The formulations were then suspended in 100 ml of selected medium. The drug is expected to exist in any of the three states, namely, as (a) free drug, (b) solubilized form, and (c) precipitated form in selected medium. The drug can be dynamically changed from one form to another. The drug concentration-time profiles with or without polymers are as shown

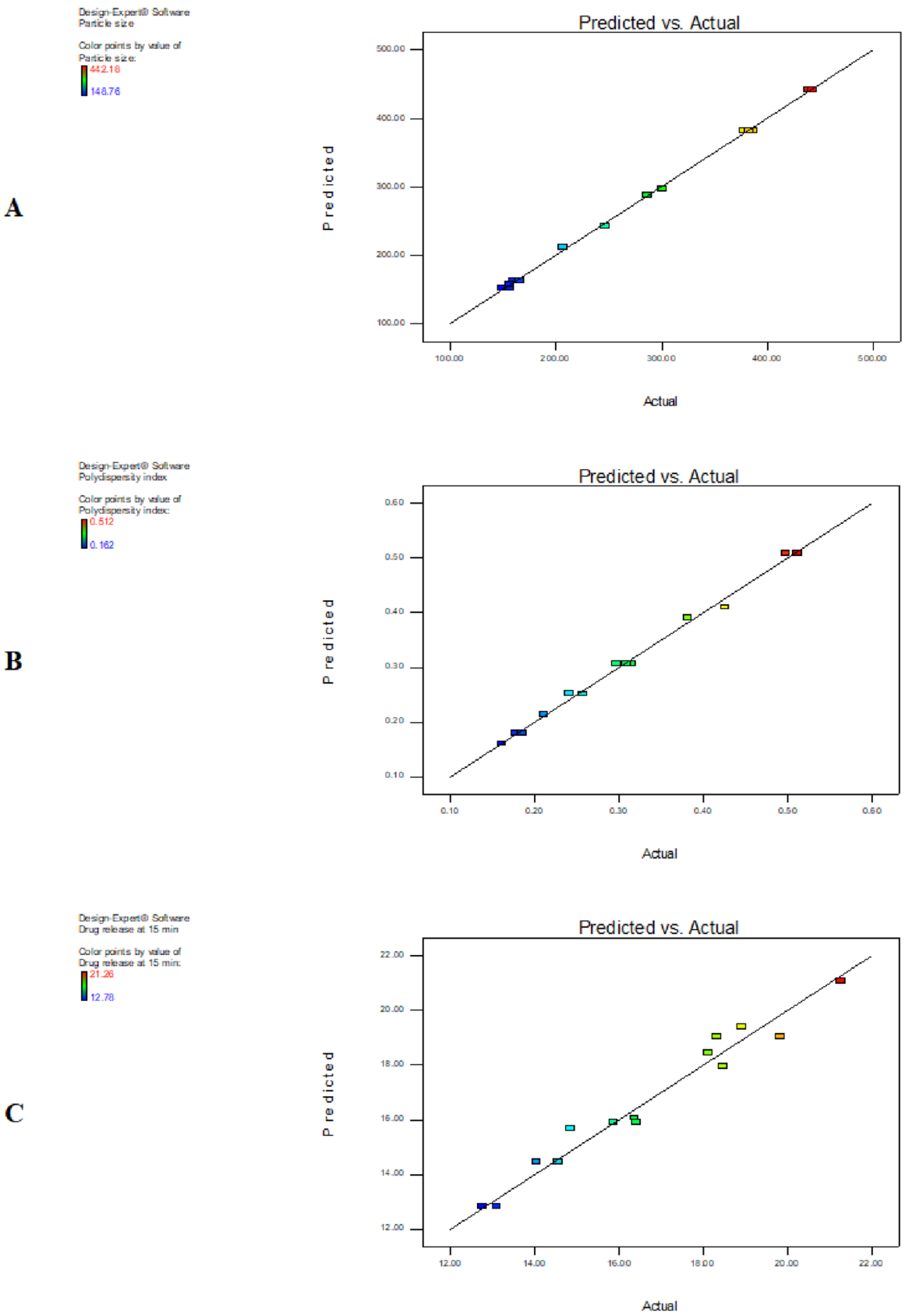


**Fig. 6** 2D plots illustrating the obtained versus predicted values for the responses (**A**), droplet size (**B**), polydispersity index (**C**) percent drug release at 15 min

in Fig. 8. Significant higher concentration of drug with the addition of polymers indicates the inhibition of precipitation. The concentration of entrectinib in the test medium was calculated to be 1000 µg/ml (10mg entrectinib in 100 ml medium). In the case of plain SNEDDS formulation, the concentration of entrectinib rapidly declined to about 312 µg/ml and 241µg/ml at 15 and 30 min, respectively. When the polymers are included in the formulation, higher concentration was observed than that of SNEDDS formulation. It is evident from the results that HPMC K4M was more effective to maintain the drug in the supersaturated state than other inhibitors.

A series of sSNEDDS formulations with different concentrations of HPMC K4M (0.5%, 1%, 2%, and 5%) were prepared to study the influence of amount of polymer on the degree of supersaturate state. As the concentration of polymer increases, the precipitation inhibition effect was increased. No significant difference was noted when the amount of the polymer increases from 2 to 5%. As the concentration of HPMC K4M increases, the mean self-emulsification time was increased. The self-emulsification time was less than 1 min demonstrating the high emulsification efficiency. Considering the influence of concentration of polymer, 2% HPMC K4M as precipitation inhibitor was used for the further studies.

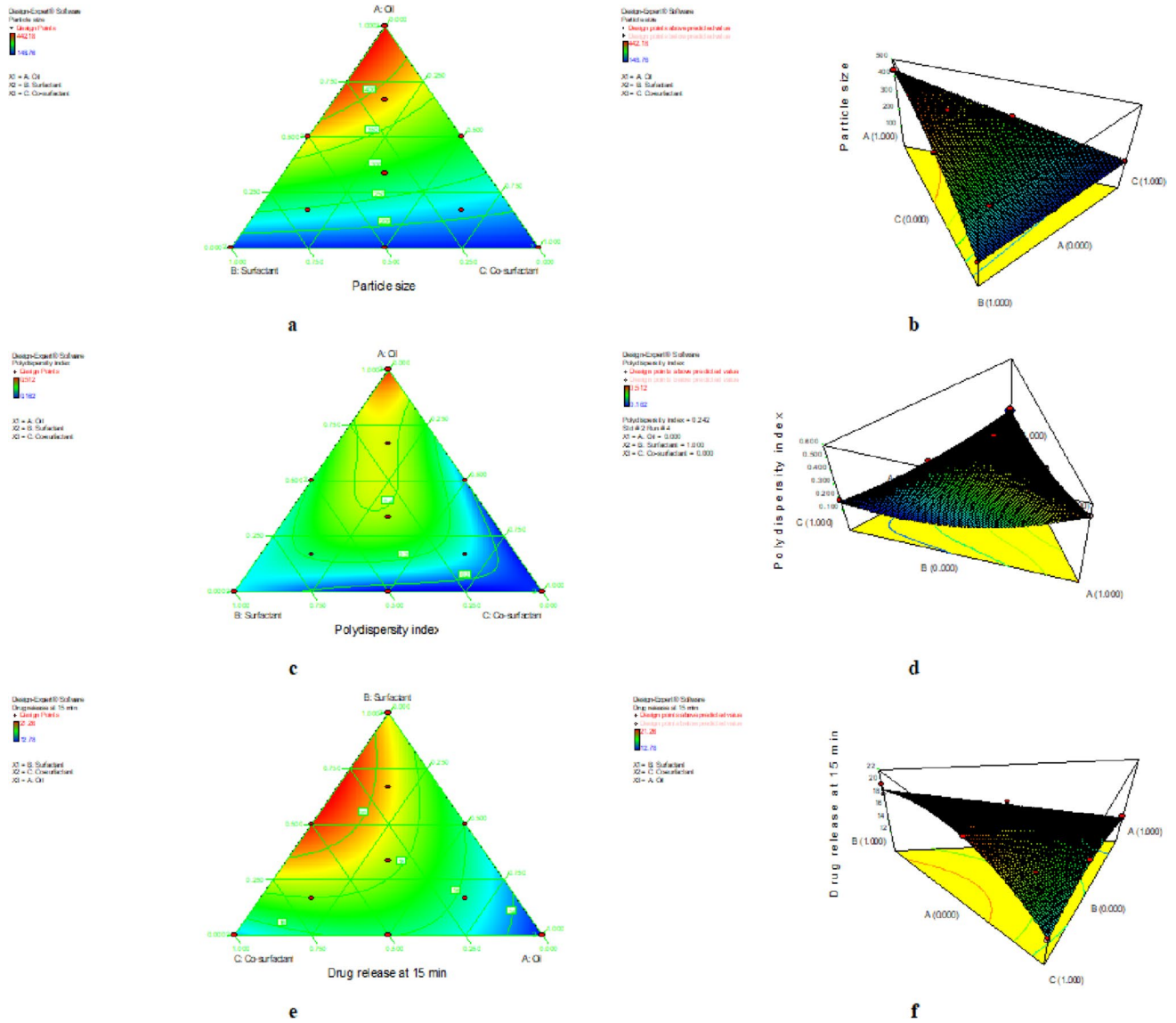


**Fig. 7** Contourand 3D response surface plots (**a**)contour plot showing the effect of variables on particle size (**b**) 3-D response surface plot showingthe effect of variables on particle size (**c**)contour plot showing the effect of variables on polydispersity index (**d**) 3-D response surface plot showingthe effect of variables on polydispersity index (**e**) contour plot showing the effect of variables on drug release at15 min (**f**) 3-D response surface plotshowing the effect of variables on drug release at 15 min

**Table 4** Optimum conditions obtained by derringer's desirability approach

| Independent variable | Coded values | Estimated values | | | Results obtained | | | |
|---|---|---|---|---|---|---|---|---|
| | | Droplet size ($Y_1$) | PDI ($Y_2$) | Percent drug release at 15 min ($Y_3$) | Trial | Droplet size ($Y_1$) | PDI ($Y_2$) | Percent drug release at 15 min ($Y_3$) |
| A – Amount of oil | 0.000 | 158.18 | 0.164 | 21.253 | S1 | 150.53 | 0.171 | 22.34 |
| B – Amount of surfactant | 0.555 | | | | S2 | 154.86 | 0.212 | 21.76 |
| C – Amount of co-surfactant | 0.445 | | | | S3 | 152.32 | 0.152 | 20.65 |

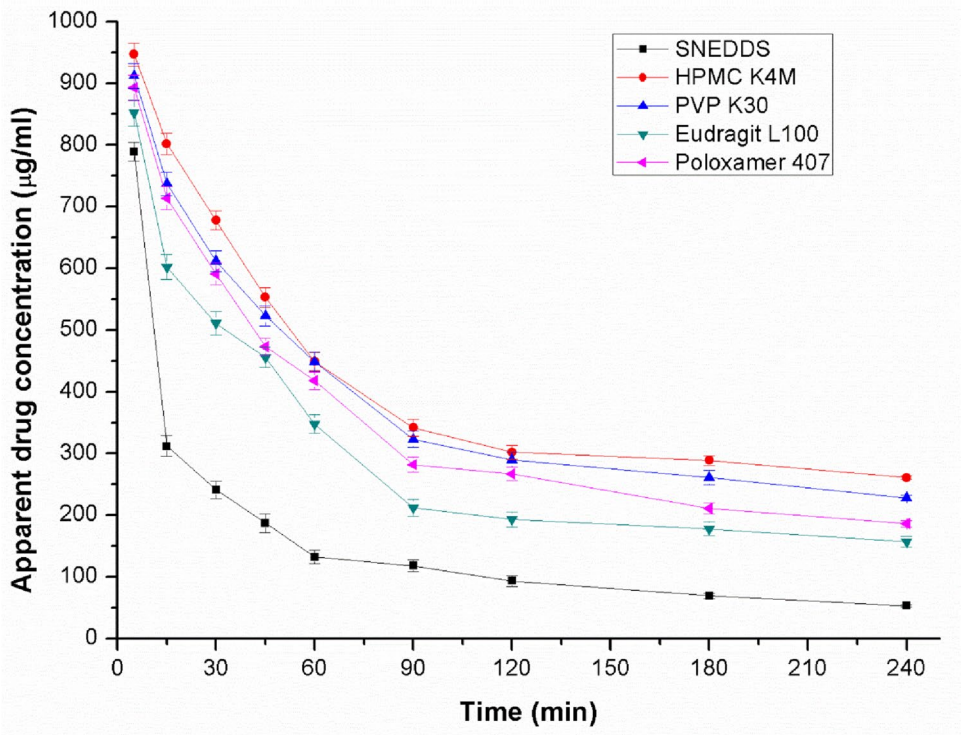


**Fig. 8** The drug concentration-time profiles with various polymers

The droplet size and PDI for plain SNEDDS (S1–S3) was found to be in the range of 159.53 ± 0.76 to 164.84 ± 1.87 nm and 0.151 to 0.212, respectively, whereas the droplet size of sSNEDDS (F1–F4) ranges from 118.42 ± 1.26 to 128.34 ± 0.63 nm with PDI values ranges from 0.112 to 0.204. Significant difference in droplet size of both the formulations was observed. Addition of HPMC K4M might have resulted in smaller droplet size by forming a physical barrier around the oil droplets to prevent aggregation. The zeta potential values of sSNEDSS were noted to be higher compared to plain SNEDDS, indicating the more stability of sSNEDDS. The droplet size, PDI, and zeta potential values of both the formulations are presented in Table 5.

TEM images (Fig. 9) revealed the spherical shape of the nano droplets of both the formulations (SNEDDS and sSNEDDS) and the particle size observed was similar to the results obtained by dynamic light scattering method. The

**Table 5** Results of droplet size, PDI, and zeta potential

| Formulation | Average droplet size (nm) | PDI | Zeta potential (mV) |
|---|---|---|---|
| SNEDDS | | | |
| S1 | 150.53 ± 2.28 | 0.171 ± 0.005 | -20.92 ± 1.18 |
| S2 | 154.86 ± 2.64 | 0.212 ± 0.005 | -21.14 ± 2.36 |
| S3 | 152.32 ± 1.92 | 0.152 ± 0.005 | -20.36 ± 0.86 |
| sSNEDDS | | | |
| F1 | 122.34 ± 1.12 | 0.212 ±0.005 | -20.83 ±2.1 |
| F2 | 134.23 ± 3.24 | 0.186 ±0.005 | -21.23 ±1.6 |
| F3 | 128.46 ± 2.56 | 0.173±0.005 | -22.34 ±1.2 |
| F4 | 131.24 ± 3.13 | 0.234±0.005 | -21.65 ±1.7 |

All the results presented in the table are average of three experiments and values are presented as mean± SD., $n$=3

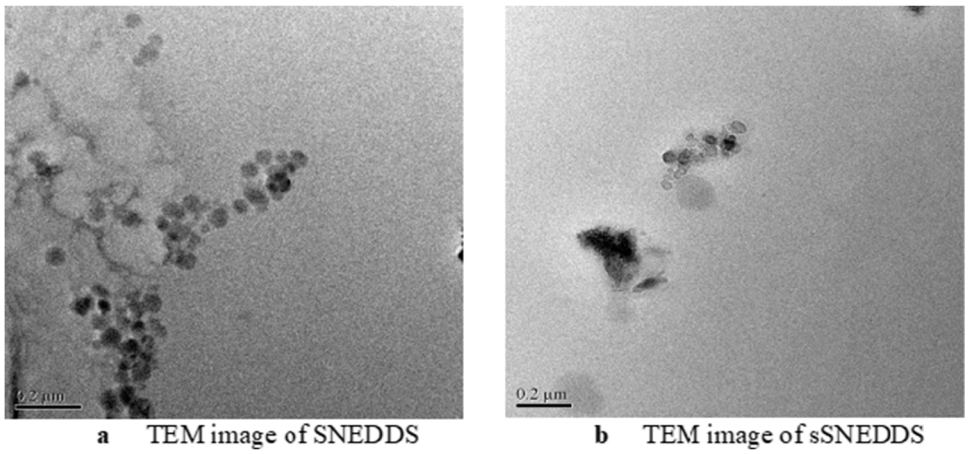


**Fig. 9** TEMimages (**a**) entrectinib loaded SNEDDS-formulation (**b**) entrectinib loadedsSNEDDS formulation

**a** TEM image of SNEDDS **b** TEM image of sSNEDDS

final optimized formulation formed spontaneous nanoemulsion within 15 s when added to physiological fluid. The percent transmittance of the diluted sSNEDDS formulation was found to be 98.78 ± 0.74. The viscosity of the final sSNEDDS formulation was noted to be 528 ± 32 centipoises at 25 °C, indicating the free flowing property of the final formulation.

FTIR spectra of entrectinib, Capmul® MCM, Kolliphor® EL, Transcutol®HP, HPMC K4M, physical mixture, SNEDDS, and sSNEDDS were recorded to identify any kind of interaction between excipients and drug. IR spectra of drug and excipients indicated the main individual distinct peaks as shown in Fig. 10. The prominent characteristic peaks of entrectinib corresponding to the structural groups in the FTIR spectrum at 3430, 3313, 2945, 2865, 1606, and 1573 $cm^{-1}$ reveal the identity of the drug. The characteristic peaks of the drug were observed at same wave numbers in the FTIR spectra of physical mixture demonstrating the absence of any specific interactions between the drug and excipients, whereas in both the formulations, the distinctive peaks of the drug were disappeared, indicating the complete encapsulation of drug in the matrix.

DSC thermograms of entrectinib, Capmul® MCM, Kolliphor® EL, Transcutol®HP, HPMC K4M, physical mixture, SNEDDS, and sSNEDDS are as shown in Fig. 11. Entrectinib has shown a distinct endothermic

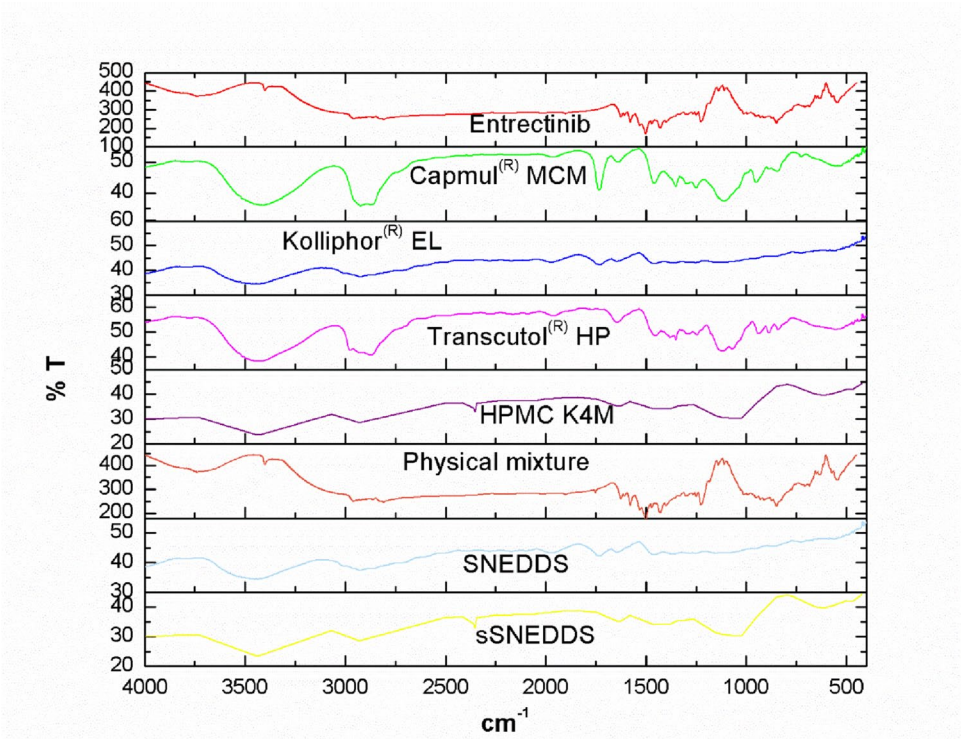


**Fig. 10** FTIR spectra of entrectinib, Capmul®MCM, Kolliphor® EL, Transcutol®HP, HPMC K4M, physical mixture, SNEDDS, and sSNEDDS

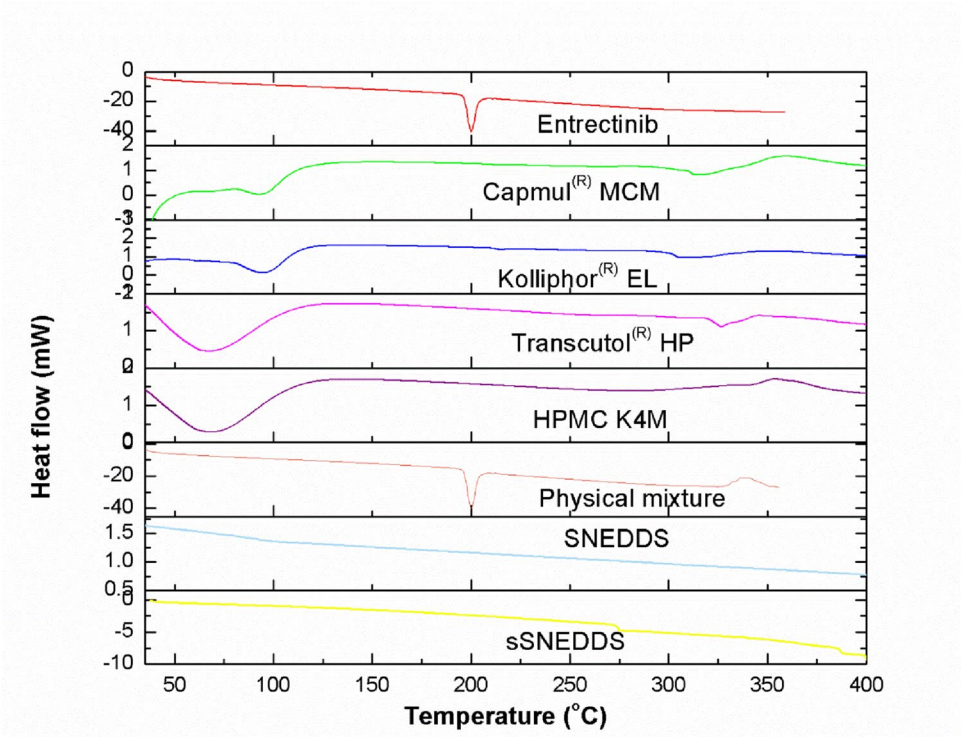


**Fig. 11** DSC thermograms of entrectinib, Capmul®MCM, Kolliphor® EL, Transcutol®HP, HPMC K4M, physical mixture, SNEDDS, and sSNEDDS

peak at 200.32 °C corresponds to its melting point. The characteristic peak of the drug has not been altered in the thermogram of physical mixture demonstrating the absence of any specific interactions between the drug and excipients. However, the characteristic endothermic of the drug was not observed in the thermogram of both the formulations. This confirms the amorphization of drug in both the formulations.

The dissolution profiles of pure drug suspension, SNEDDS formulation, and sSNEDDS formulation are as shown in

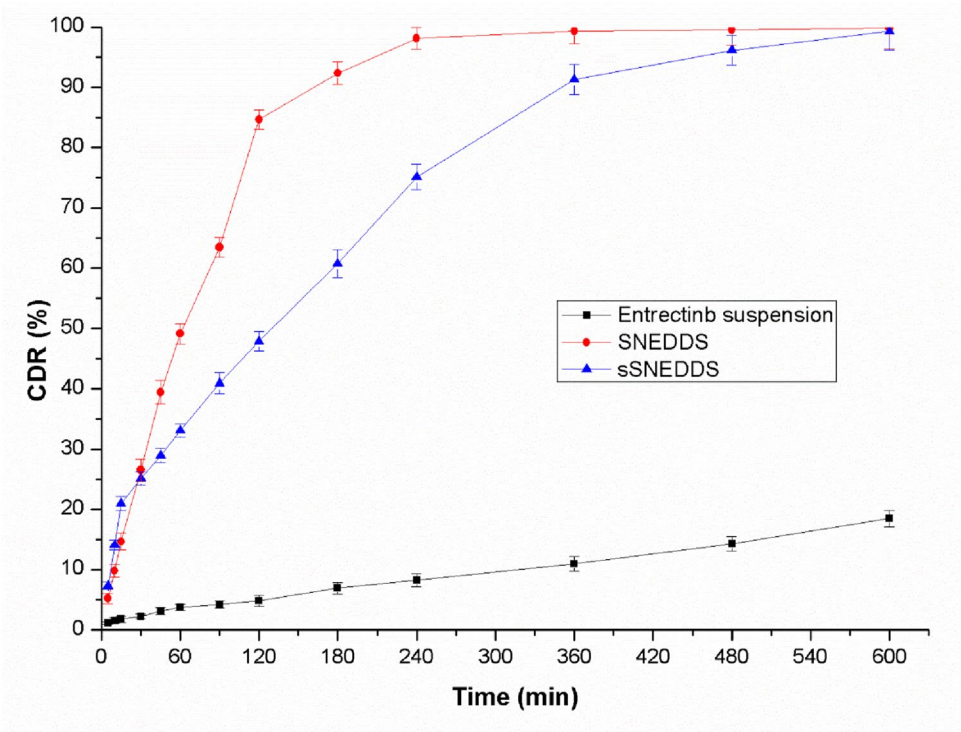


**Fig. 12** Dissolution profile of entrectinib from sSNEDDS formulation

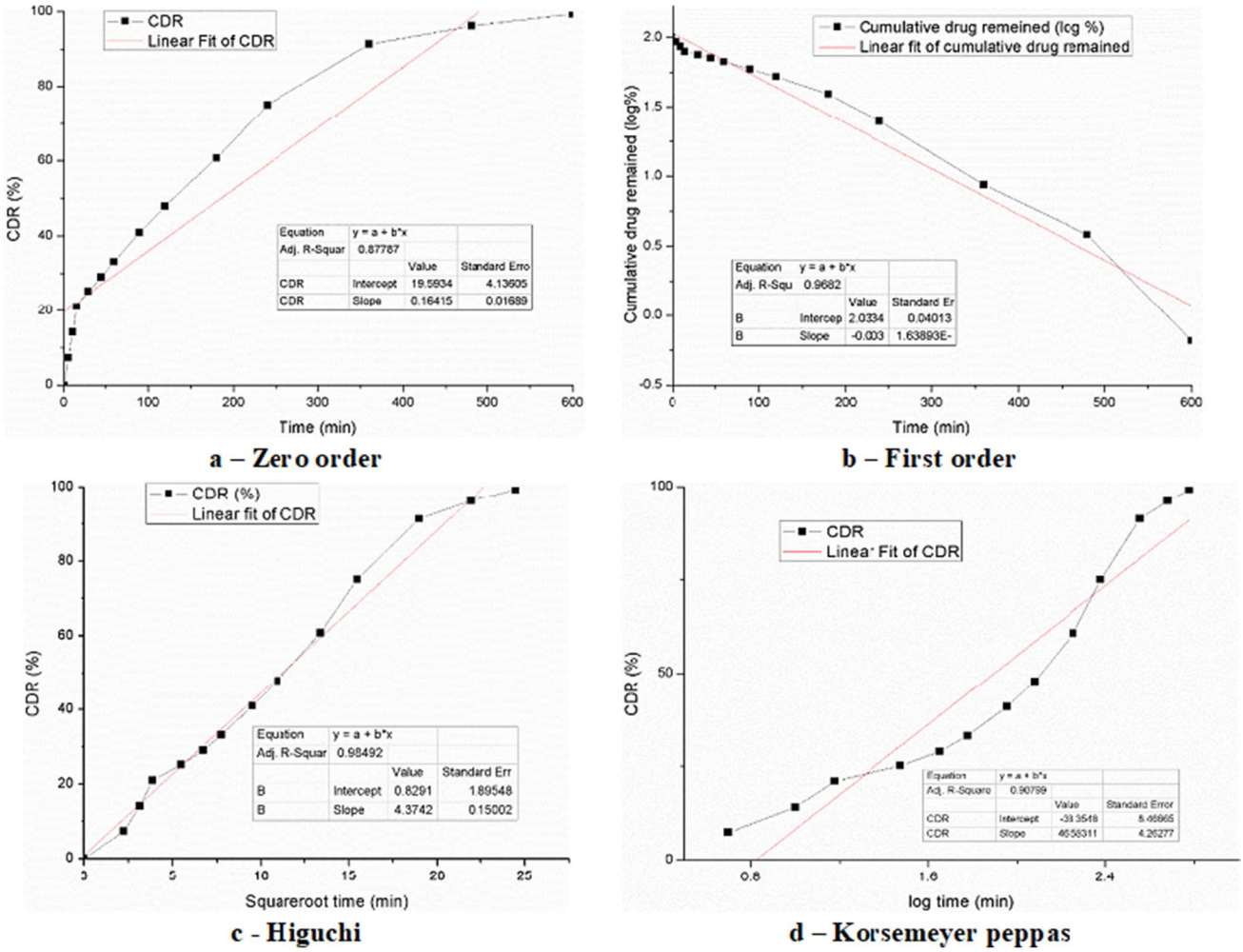


**Fig. 13** Drugrelease kinetics curves (**a**) zeroorder (**b**) first order (**c**) Higuchi model (**d**) Korsemeyer peppas model

Fig. 12. The dissolution profile of sSNEDDS indicated the faster release of drug (7.34 ± 1.8% within 5 min) in comparison with pure drug suspension and SNEDDS formulation. Significant increase in dissolution was observed with both the formulations. The rapid initial release of the drug from sSNEDDS formulation can be attributed to the low surface free energy of the system which results in quick emulsification by forming an interface between the oil droplets and dissolution medium. The enhanced dissolution form both the formulations can be ascribed to the greater surface area of the nanosized droplets and to the physical transformation of drug from low water-soluble crystalline state to the freely soluble amorphous state.

The dissolution data of the sSNEDDS formulation was fitted into different kinetic equations to understand the drug release pattern and mechanism. The drug release kinetics curves of different models are as shown in Fig. 13. The regression coefficient and slope of the curves are as shown in Table 6. It is obvious from the obtained results that the regression coefficient value of first-order kinetics is close to unity. Hence, the rate of drug release from the sSNEDDS follows dose-dependent kinetics (i.e., the drug release rate is directly proportional to the concentration). To further comprehend the mechanism of drug release, the data was transformed to other kinetic models such as the Korsmeyer-Peppas and Higuchi models. The regression coefficient value is closer to unity in the case of Higuchi model (0.98492), which indicates the Fickian diffusion process.

The sSNEDDS formulation was diluted 100, 500, and 1000 folds with distilled water, pH 6.8 phosphate buffer, and

**Table 6** Drug release kinetics data of entrectinib SSNEDDS

| Model | $R^2$ | $N$ |
|---|---|---|
| Zero-order | 0.87787 | 0.16415 |
| First-order | 0.9682 | -0.0032 |
| Higuchi | 0.98492 | 4.3742 |
| Korsmeyer-Peppas | 0.90799 | 46.583 |

**Table 7** Stability data of entrectinib sSNEDDS

| Parameter | Temperature (°C) | 0 days | 90 days | 180 days |
|---|---|---|---|---|
| Average droplet size (nm) | 4 ± 1 °C | 128.46 ± 2.56 | 133.56 ± 2.12 | 135.64 ± 4.12 |
| | 25 ± 2 °C | 128.46 ± 2.56 | 137.34 ± 3.14 | 138.78 ± 3.78 |
| | 40 ± 2 °C | 128.46 ± 2.56 | 138.56 ± 2.86 | 139.12 ± 3.12 |
| Zeta potential (mV) | 4 ± 1 °C | −22.34 ± 1.2 | −24.36 ± 1.9 | −24.76 ± 2.1 |
| | 25 ± 2 °C | −22.34 ± 1.2 | −23.12 ± 2.8 | −24.12 ± 2.5 |
| | 40 ± 2 °C | −−22.34 ± 1.2 | −24.56 ± 3.1 | −24.98 ± 2.9 |
| Polydispersity index | 4 ± 1 °C | 0.173 ± 0.005 | 0.198 ± 0.005 | 0.208 ± 0.005 |
| | 25 ± 2 °C | 0.173 ± 0.005 | 0.206 ± 0.005 | 0.214 ± 0.005 |
| | 40 ± 2 °C | 0.173 ± 0.005 | 0.212 ± 0.005 | 0.218 ± 0.005 |

pH 1.2 0.1 N HCl to study the influence of dilution medium and robustness to dilution. in all the cases, the formulation was found to be stable and transparent at all pH values and the percent transmittance was more than 95%. Any sort of precipitation was not observed even after dilution, indicating the dilution stability of sSNEDDS formulation. Thermodynamic stability of the sSNEDDS formulation was assessed by exposing the diluted sample at different heating cycles. Any kind of separation or precipitation was not observed when stored at different conditions. Stability studies were performed to assess the influence of stress conditions on the quality of drug product. The samples of drug product were exposed to different temperature conditions and monitored the critical parameters at different time intervals. The influence of different storage conditions on important characteristics of the optimized formulation was monitored for 6 months. Significant difference was not observed when exposed at different storage conditions as presented in Table 7.

$n = 3$ ($P < 0.05$)

## 4 Conclusions

A supersaturable self-nanoemulsifying drug delivery system of entrectinib was prepared by using a super saturation promoter. The components of the SNEDDS formulation were optimized using phase diagram and simplex-lattice design. The droplet size of the sSNEDDS ranges from 166.78 ± 3.14 to 178.86 ± 1.24 nm with uniform size distribution. The droplet size of sSNEDDS was significantly smaller than that observed with plain SNEDDS formulation. The dissolution profile of sSNEDDS indicated the faster release of drug compared to both pure drug suspension and SNEDDS formulation. The drug release from the sSNEDDS formulation follows Fickian diffusion process in which the release of drug from the insoluble matric as a square root of time-dependent process. The formulation was found to be stable and transparent at all pH values and the percent transmittance was more than 95%. Any kind of separation or precipitation was not observed at different temperature cycles. No significant difference was observed with all the samples exposed at different storage conditions. Overall, this study demonstrated the feasibility of stabilizing and improving the in vitro performance of SNEDDS of entrectinib by using HPMC K4M as precipitation inhibitor.

**Availability of Data and Material** Will be made available on request.

**Author Contribution** MRR carried out the entire research and prepared the manuscript. KSG guided the work and reviewed the manuscript.

## Declarations

**Ethics Approval and Consent to Participate** Not applicable as no animal or humans are used in this study.

**Consent for Publication** This work is original and not published or under consideration in any other journal.

**Conflict of Interest** The authors declare that they have no competing interests

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