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Formulation development, optimization and characterization of Pemigatinib-loaded supersaturable self-nanoemulsifying drug delivery systems

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Abstract

Background: Pemigatinib is a small molecule tyrosine kinase inhibitor of fibroblast growth factor receptor inhibitors. The oral bioavailability of Pemigatinib is constricted due to its limited solubility at physiological pH. It is essential to develop a novel formulation of Pemigatinib to improve the intrinsic solubility and to reduce the pharmacokinetic variability. Self-nanoemulsifying drug delivery system is an effective, smart and more adequate formulation approach for poorly soluble drugs. Different from conventional self-nanoemulsifying drug delivery system, a supersaturable self-nanoemulsifying drug delivery system of Pemigatinib was prepared by using a supersaturation promoter.

Results: Among all the oils, Captex® 300 have shown maximum solubility of Pemigatinib. Considering the solubilization potential and emulsification ability Kolliphor®RH 40 was selected as surfactant. Transcutol®HP was selected as co-surfactant. The composition of oil, surfactant and co-surfactant was identified using phase diagrams and further adjusted by simplex-lattice design. HPMC K4M as precipitation inhibitor at 5% concentration resulted in effective supersaturating with increased self-emulsification time. The droplet of sSNEDDS ranges from 166.78 ± 3.14 to 178.86 ± 1.24 nm with PDI 0.212 – 0.256, which is significantly smaller than that observed with plain SNEDDS. TEM images revealed the spherical shape of the nanodroplets. The final optimized formulation formed spontaneous nanoemulsion within 15 secs when added to physiological fluids. The percent transmittance of the diluted formulation was found to be 99.12 ± 0.46. The viscosity was found to be 574 ± 26 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%. Any kind of separation or precipitation was not observed at different temperatures cycles. No significant difference was observed with all the samples exposed at different storage conditions.

Conclusions: This study demonstrated the feasibility of stabilizing and improving the in-vitro performance of self-nanoemulsifying drug delivery systems of Pemigatinib by incorporating HPMC K4M as precipitation inhibitor.

Keywords: Pemigatinib, Precipitation inhibitor, Optimization, Simplex-lattice design, Self-emulsification

Background

Pemigatinib is an orally active small molecule kinase inhibitor of the fibroblast growth factor receptor (FGFR1, FGFR2 and FGFR 3), with potential anticancer activity.

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FGFRs are a group of receptor tyrosine kinases that activate signalling pathways in tumour cells. Pemigatinib was first approved by US FDA on 17 April 2020 for the treatment of advanced or metastatic cholangiocarcinoma. It is marketed under the brand name Pemazyre, with different strengths for oral administration. The maximum daily recommended dose is 13.5 mg for 14 days followed by 7 days off therapy, in a cycle of 21 days [1].

Pemigatinib is a BCS class-II compound, though exhibits BCS class I properties in acidic media. The water solubility is about 0.144 mg/ml with log P value of 2.26. It is diprotic basic compound with pKa values of 3.1 and 5.7. It displays pH-dependent solubility in the pH range from 1.2 to 7.4. It's solubility decrease with increasing pH [2]. Pemigatinib displays concentration reliant permeability. Pemigatinib undergoes extensive first pass metabolism, with only about 1 to 1.4% of the administered dose recovered in unchanged from. The poor solubility of the drug substance is the main inherent factor influence the oral absorption of the drug [3]. In order to improve intrinsic solubility and to reduce the high pharmacokinetic variability observed with the existing tablet formulation, it is essential to develop an alternative formulation of Pemigatinib 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 [4]. 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 [5].

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 [6]. 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 [7].

Self-nanoemulsifying drug delivery systems (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 behavior in GIT and gut permeability [8]. SNEDDS is isotropic mixture of active substance with Oil (natural or synthetic), Surfactant and Co-surfactant. SNEDDS form 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 [9]. SNEDDS are superior to other lipid-based systems because of their smaller size, high effective surface area, and absence of creaming, flocculation, sedimentation, or coalescence. After oral administration of SNEDDS, lipid components will be digested by gastrointestinal lipases and results in the formation of mixed micelles containing cholesterol, monoglycerides, phospholipids, fatty acids and bile salts, which interact with active ingredient, and alters its solubility and absorption characteristics [10].

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 50–90% of the equilibrium solubility of drug and this results in more amount of formulation to reach therapeutic level [11]. 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 [12]. The results of both in-vitro and in-vivo studies demonstrated the improved characteristics of supersaturable SNEDDS compared to conventional SNEDDS. It has been reported that 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 [13, 14].

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 factorials designs and Placket Burman design do not hold good for the composition setting of SNEDDS. Mixture designs are more appropriate for the optimization of SNEDDS formulation [15].

Among various mixture designs, simplex-lattice design is the most conventional approach for optimization of composition of a blend. 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.

Experimental

Materials

Pemigatinib 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, Kolliphor®RH40 were obtained from BASF, Germany. Lauroglycol, Labrasol, Lutrol E 300, Labrafac, Labrafil M 2125, Labrafil M 1944 were obtained from Loba Chemie Private Limited, Mumbai, India.

Determination of saturation solubility

Pemigatinib 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 5 ml methanol. Pemigatinib concentration of the diluted samples was determined using UV-spectrophotometer (Labindia UV-3000 +) at a wavelength of 262 nm [16].

Surfactant screening

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 were 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 [17]. In this study, different surfactants namely Kolliphor® EL, Kolliphor® RH, Kolliphor® HS15, Kolliphor® Kolliphor® ELP, Kolliphor® PS 80, Span®20, Span®80, Tween®20, Tween®80, Lauroglycol, Labrasol, Lutrol E 300, Labrafac, Labrafil M 2125 and Labrafil M 1944 were tested for emulsification of selected oil.

Screening for co-surfactant

Co-surfactant was selected based on the ability to expand the emulsification ability of selected surfactant toward the selected oil. 1 ml 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 [17]. Five co-surfactants namely Propylene glycol, Ethanol, Poly ethylene glycols (PEG 400 and PEG

600) and Transcutol® HP were individually added to the selected surfactant at a fixed ratio of 1:1.

Phase diagram

Aqueous titration method was used to identify the emulsification region and to construct the phase diagrams [18]. 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.

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 [19].

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 and1. If m = 4, then the probable values are 0, 1/4,2/4, ¾ 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 [20]. 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.

$$16\% \leq A \geq 48\%$$
$$26\% \leq B \geq 44\%$$
$$24\% \leq C \geq 60\%$$
$$A + B + C = 100\%$$

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 $X_1 + X_2 + X_3 = 1$.

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

Pemigatinib loaded SNEDDS were obtained by dissolving the specified quantity of drug in the isotropic mixture of oil and S_{mix}. The isotropic mixtures were prepared by phase titrations method. 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 [21].

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 [21].

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	0.5	0	0.5	298.73	0.383	23.38
2	0.5	0.5	0	321.45	0.408	17.12
3	0.66666	0.166667	0.166667	355.34	0.406	19.43
4	0	0.5	0.5	179.92	0.288	19.32
5	0	0	1	165.56	0.242	20.88
6	0.5	0.5	0	314.43	0.414	17.74
7	0.16666	0.666667	0.166667	233.12	0.312	19.12
8	0	0	1	172.66	0.27	20.62
9	0	1	0	201.64	0.329	18.88
10	1	0	0	438.46	0.514	15.86
11	0.16666	0.166667	0.666667	222.12	0.296	21.26
12	1	0	0	438.34	0.512	16.46
13	0	1	0	192.48	0.292	19.12
14	0.33333	0.333333	0.333333	265.22	0.368	21.22

Selection of a precipitation inhibitor

In-vitro precipitation experiments were carried out to estimate the concentration–time profile and supersaturated state of the drug [22]. Various polymers like PVP K30, Eudragit L100, Poloxamer 407 and HPMC K4M were used to maintain the stable supersaturation state. 100 mg of optimized formulation with selected polymer was added to simulated gastric fluid (100 ml) and homogenized with continuous stirring. 1 ml of each sample was withdrawn from the saturated solutions without volume replacement at specified time intervals. The samples were centrifuged at 12,000 × g for 10 min. The supernatant solution was collected and suitably diluted with methanol. Pemigatinib concentration of the diluted samples was determined using UV-spectrophotometer (Labindia UV-3000 +) at a wavelength of 262 nm.

Preparation of supersaturable SNEDDS of Pemigatinib

Supersaturable SNEDDS of Pemigatinib was obtained by a simple admixture method as reported elsewhere [23]. 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.

Characterization of SNEDDS and sSNEDDS formulations

Size distribution and zeta potential

Malvern particle size analyser (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.

Surface morphology

The formulation was suitably diluted using distilled water. One drop of diluted and homogenized sample was placed on a film coated copper grid. 2% 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.

Self-emulsification time

All the formulations were evaluated for emulsification time as reported elsewhere [24]. One millilitre of formulation was mixed with 200 ml of distilled water under agitation using magnetic stirrer. The time required for emulsification was recorded.

Transmittance percentage

The percent transmittance of diluted samples was determined using UV spectrophotometer at 630 nm against reference blank solution [25].

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 w/o type emulsion and vice-versa [26].

FTIR spectroscopy

FTIR spectra of individual components, physical mixture and optimized formulation was recorded using potassium bromide disk method. Two milligram 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.

DSC thermogram

Thermal analysis of pure Pemigatinib, SNEDDS formulation and sSNEDDS formulation was performed to using a differential scanning calorimeter (DSC 2500, TA instruments). Five milligrams of samples were 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.

Drug release study

The drug dissolution pattern of Pemigatinib formulations was studied using a USP II paddle apparatus under sink conditions [27]. Formulations (≈ 10 mg of drug) were added to 900 ml of phosphate buffer (pH 6.8). At specified time intervals 2 ml of samples were withdrawn and passed through a 0.22-µm syringe filter. The sample was then collected and diluted suitably with methanol. The concentration of Pemigatinib 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.

Dilution and pH stability

Both the formulations were evaluated for dilution and pH stability 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 [28].

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 two days [28].

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 [28].

Results

The results of solubility study of Pemigatinib are displayed in Fig. 1. In this study, Captex® 300 was selected as oil of choice on the basis of maximum Solubilization of drug of interest. 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. The number of inversions and percent transparency of different co-surfactants is as shown in Fig. 4. The phase diagrams were built for the three components namely Oil, S_{mix} and water. Phase diagrams were constructed for different mass ratios of S_{mix} as shown in Fig. 5.

Based on simplex-lattice design, fourteen trial experiments which consists of six simplex points were arbitrarily arranged. The experiments were performed as per the design and the obtained results were 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), Contour plots and 3D-Response surface plots.

The droplet side (Y_1) of all the batches were found to be in the range of 165.56–438.46 nm. Similarly, the polydispersity index (Y_2) values were in the range of 0.242–0.514 and the percent drug release at 15 min (Y_3) was found to be in the range of 15.86–23.38%. Mathematical equations were generated for each response and are presented in Table 2. 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.

The influence of individual variables on Y_1 was further elucidated using respective contour and 3-D response surface plots (Fig. 7a and b). Similarly, the influence of individual variables on Y_2 was further elucidated using respective contour and 3-D response surface plots (Fig. 7c and d). The influence of individual variables on Y_3 was further elucidated using respective contour and 3-D response surface plots (Fig. 7e and f).

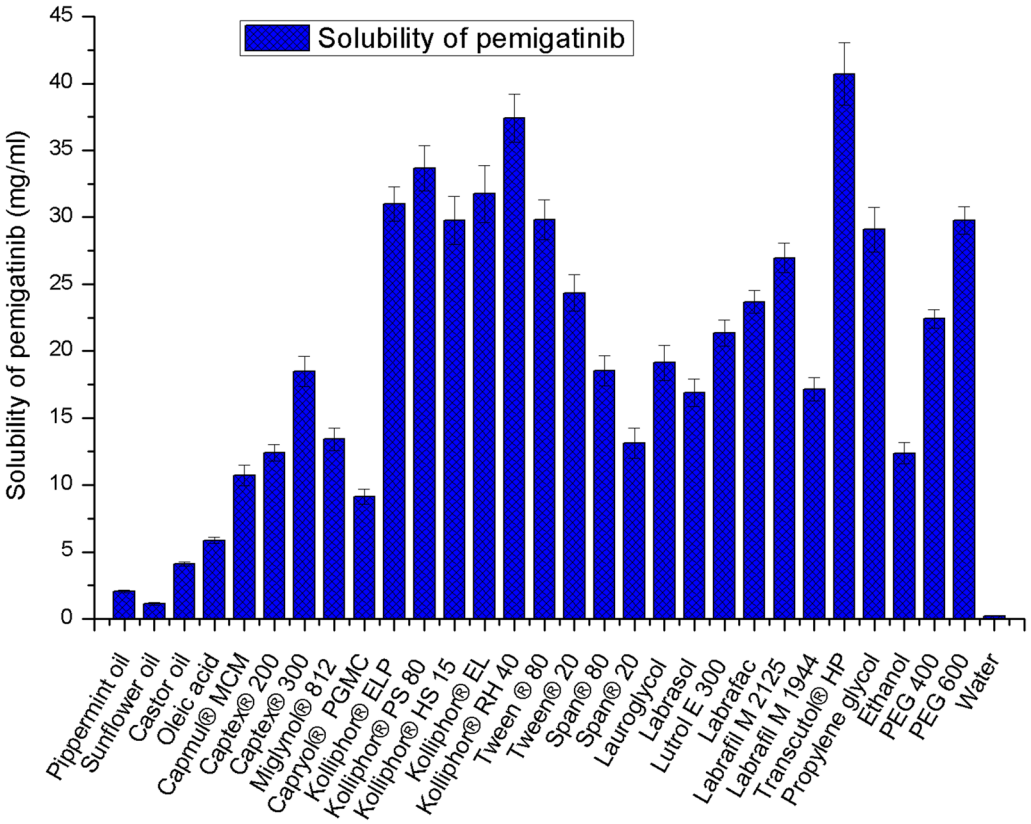

Fig. 1 Solubility of Pemigatinib in different vehicles

Derringer's desirability approach 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 inti the desirability scale. The criteria selected for the approach was based on minimization of droplet size and PDI, while maximizing the percent drug release at 15 min. The maximum desirability function was obtained with the response values at A: 0.078 (16.02496), B:0.000 (26%) and C:0.922 (57.97%) with the resultant D value of 0.853. 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.

Four different polymers namely PVP K30, HPMC K4M, Poloxamer 407 and Eudragit L100 were tested as precipitation inhibitors to determine the degree of supersaturation under non-sink conditions. The drug concentration–time profiles with different polymers are as shown in Fig. 8.

The droplet size and PDI for plain SNEDDS (S1-S3) was found to be in the range of 191.68 ± 1.34 to 194.74 ± 2.46 nm and 0.283 to 0.302, respectively. Whereas, the droplet size of sSNEDDS (F1-F4) ranges from 166.78 ± 3.14 to 178.86 ± 1.24 nm with PDI values ranges from 0.212 to 0.256. 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 were presented in Table 5.

TEM images (Fig. 9) revealed the spherical shape of the nanodroplets of both the formulations (SNEDDS and sSNEDDS) and the particle size observed was similar to the results obtained by dynamic light scattering method. The final optimized formulation formed spontaneous nanoemulsion within 15 secs when added to physiological fluid. The percent transmittance of the diluted sSNEDDS formulation was found to be 99.12 ± 0.46. The viscosity of the final sSNEDDS formulation was noted to be 574 ± 26 centipoises at 25 °C, indicating the free flowing property of the final formulation.

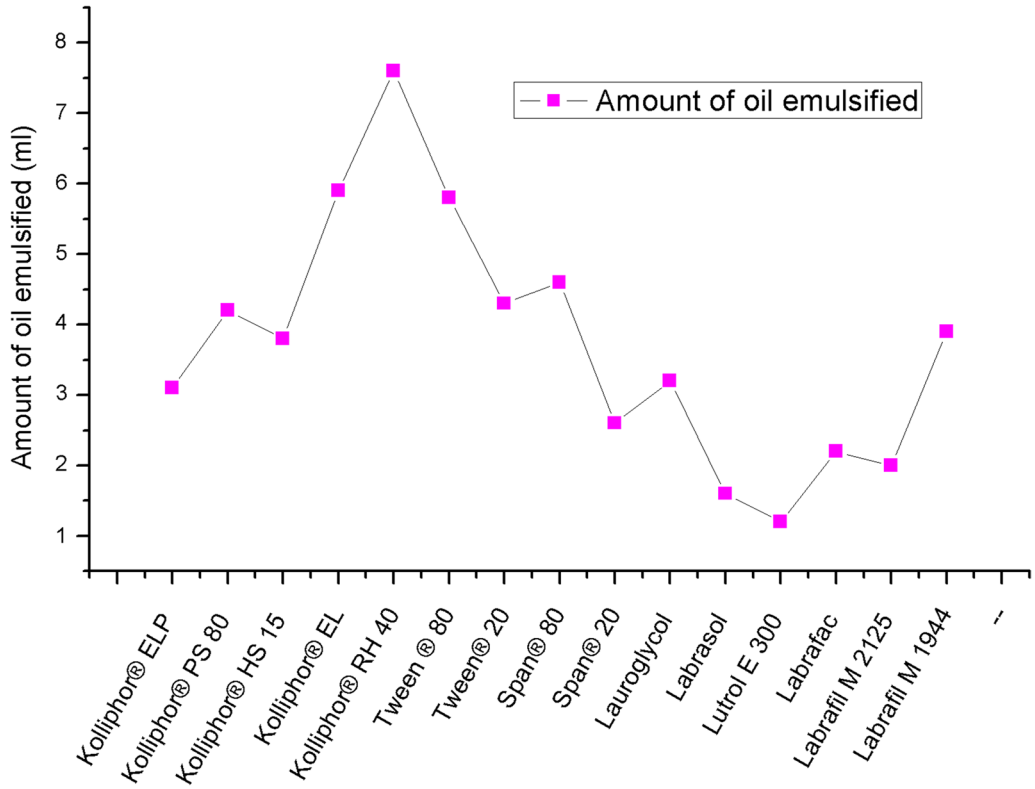

Fig. 2 Amount of oil emulsified by different surfactants

FTIR spectra of Pemigatinib, Captex®300, Kolliphor®RH 40, Transcutol®HP, 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 Pemigatinib corresponding to the structural groups in the FTIR spectrum at 3400, 3171, 2835, 1428 and 1060 cm^{-1} revealing the identity of the drug. The characteristic peaks of 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 thermogram of Pemigatinib, Captex®300, Kolliphor®RH 40, Transcutol®HP, Physical mixture, SNEDDS and sSNEDDS are as shown in Fig. 11. Pemigatinib have shown a distinct endothermic peak at 96.97 °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 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. 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. 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 sSNEDDS formulation was diluted 100, 500 and 1000 folds with distilled water, pH 6.8 Phosphate buffer and 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

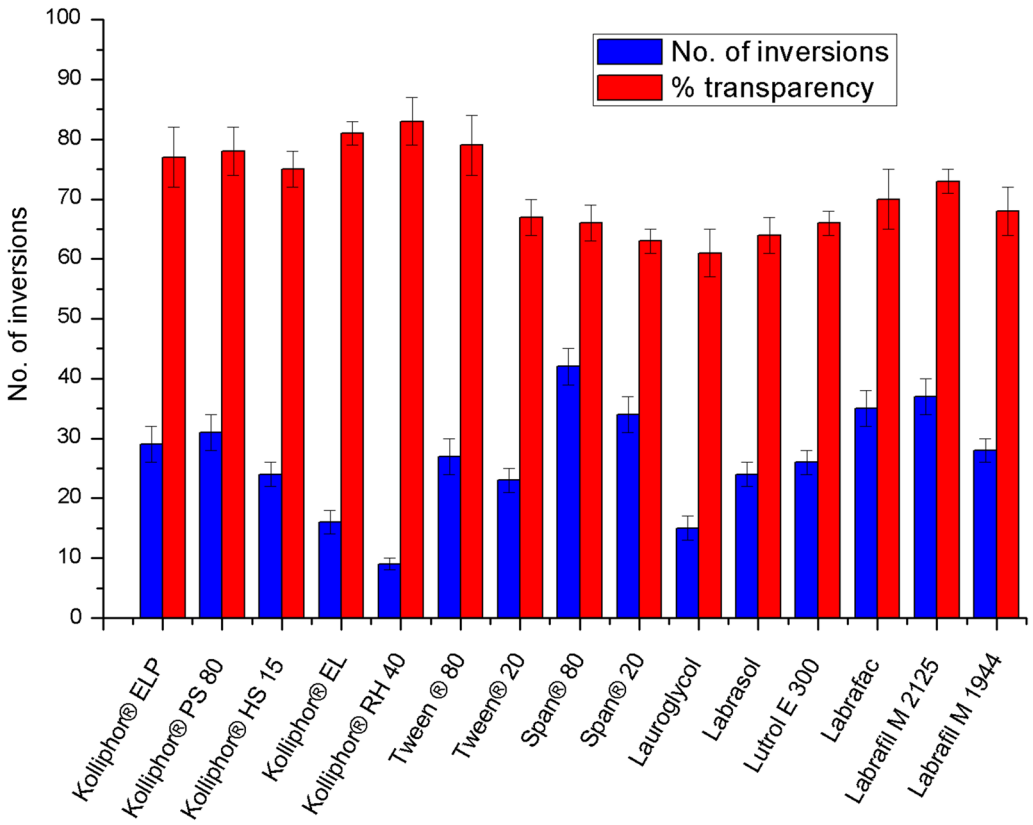

Fig. 3 Number of inversions and percent transmittance with different surfactants

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 6.

Discussion

SNEDDS form 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 [29]. In order to prepare an efficient SNEDDS formulation of Pemigatinib, selection of suitable oil phase, surfactant mixture, 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.

Drug loading capacity is an important parameter to be considered while selecting the Oil, Surfactant and Co-surfactant. The solubilization potential and extensive emulsification region in the phase diagram are the major factors in selecting the components. Among different oils studied, Captex® 300 have shown maximum solubilization potential. Captex® 300 is a semisynthetic medium chain triglyceride, obtained by the esterification of glycerine and fatty acids. The higher solubility of Pemigatinib in Captex® 300 is due to lipophilic nature of esterified medium chain glycerides [30]. 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 toward oil phase will have a great influence on droplet size emulsification characteristics. The selected surfactant should have suitable lipophilic character to offer the accurate curvature at the interfacial region. The surfactant should be able to lower 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

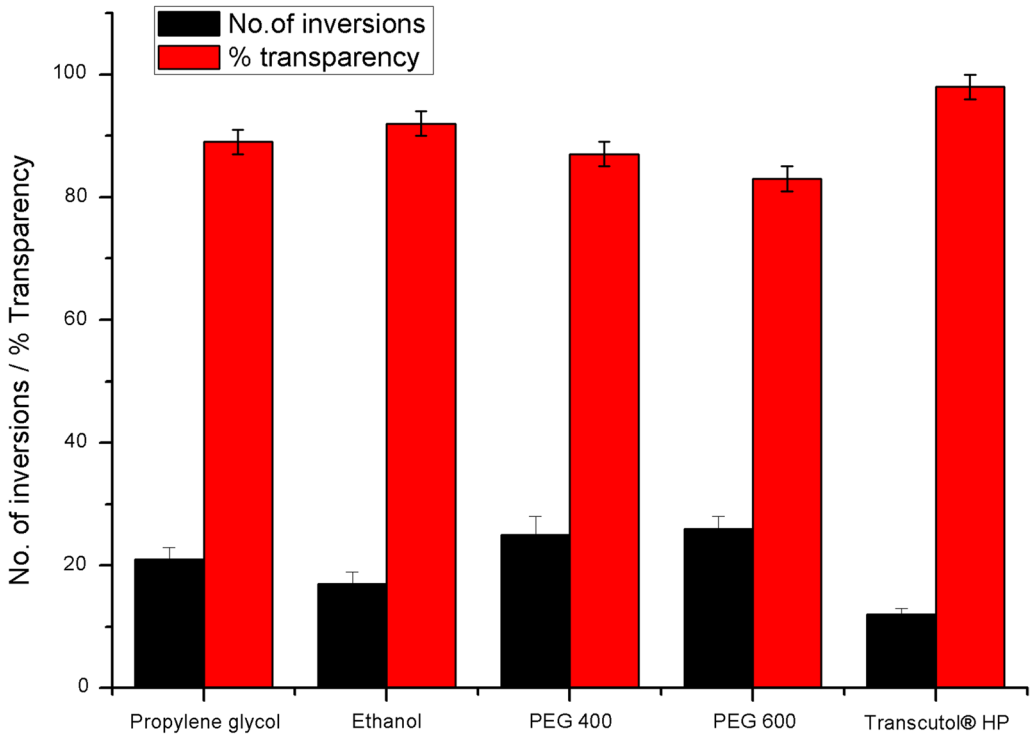

Fig. 4 Number of inversions and percent transmittance with different co-surfactants

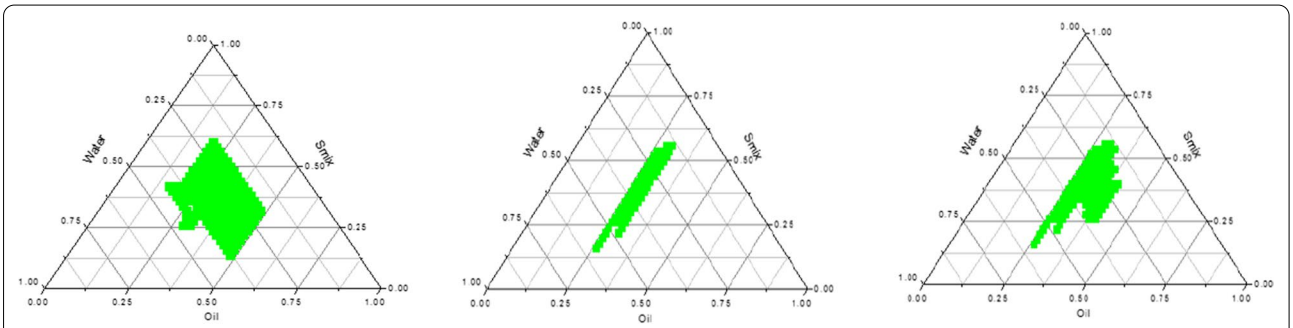

Fig. 5 Phase diagrams to depict the emulsification region for different ratio of S_{mix}

Table 2 Polynomial equations for the responses

Response	Polynomial equation
Y_1—Droplet size	438.1858A + 196.9078B + 168.4272C
Y_2—Polydispersity index	0.5068A + 0.307B + 0.253C
Y_3—Percent drug release at 15 min	16.13A + 18.859B + 20.566C + 19.871AC

features needs to be considered. Non-ionic surfactants are widely used in SNEDDS formulations because of their ability to stabilize the emulsion over a wide range of pH and ionic strength. Moreover, non-ionic surfactants are less toxic compared to other class of surfactants. The non-ionic surfactants with HLB values greater than 12 are highly endorsed because of their ability to form

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	112,124.2	2	56,062.11	4100.14	< 0.0001	Significant
Linear Mixture	112,124.2	2	56,062.11	4100.14	< 0.0001	
Residual	150.4054	11	13.67322			
Lack of Fit	58.60021	7	8.371458	0.364749	0.8842	Not significant
Pure Error	91.8052	4	22.9513			
Cot Total	112,274.6	13				
Y_2—Polydispersity index						
Model	0.091389	2	0.045694	197.0463	< 0.0001	Significant
Linear Mixture	0.091389	2	0.045694	197.0463	< 0.0001	
Residual	0.002551	11	0.000232			
Lack of Fit	0.001454	7	0.000208	0.757922	0.6495	Not significant
Pure Error	0.001097	4	0.000274			
Cot Total	0.093939	13				
Y_3—Drug release at 15 min						
Model	54.53438	3	18.17813	149.0781	< 0.0001	Significant
Linear Mixture	28.74925	2	14.37462	117.8857	< 0.0001	
AC	25.78513	1	25.78513	211.4629	< 0.0001	
Residual	1.219369	10	0.121937			
Lack of Fit	0.784569	6	0.130762	1.202958	0.4487	Not significant
Pure Error	0.4348	4	0.1087			
Cot Total	55.75375	13				

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.

Emulsification study revealed that Kolliphor® RH 40 has good potential for emulsification. Among various surfactants screened, maximum solubility was observed in Kolliphor® RH 40 with 37.423 mg/ml. High solubility in Kolliphor® RH 40 can be attributed to characteristic amphiphilic nature and high HLB value [31]. Hence, in the present study Kolliphor® RH 40 was the surfactant of choice for the preparation of Pemigatinib 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 dispersibility and solubility of the Surfactant in 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. The combination of Surfactant and Co-surfactant have shown better emulsification potential compared to surfactant alone. It is evident from the data that Transcutol® HP have shown highest emulsification of oil. In addition, the combination resulted in higher values of % Transparency and ease of emulsification compared to the surfactant alone. This indicated the importance of Co-surfactant for the preparation of SNEDDS. Among co-surfactants Transcutol® HP and PEG 600 exhibited maximum solubility with 40.723 ± 0.238 mg/ ml and 29.764 ± 0.432 mg/ml respectively. Based on 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 the 100% of respective component. The shaded area determines the composition of a three component system. 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. Based on ternary phase diagrams, the range of components was selected as follows: $16\% \leq$ Captex® $300 \leq 48\%$, $26\% \leq$ Kolliphor® RH $40 \leq 44\%$, $24\% \leq$ Transcutol®

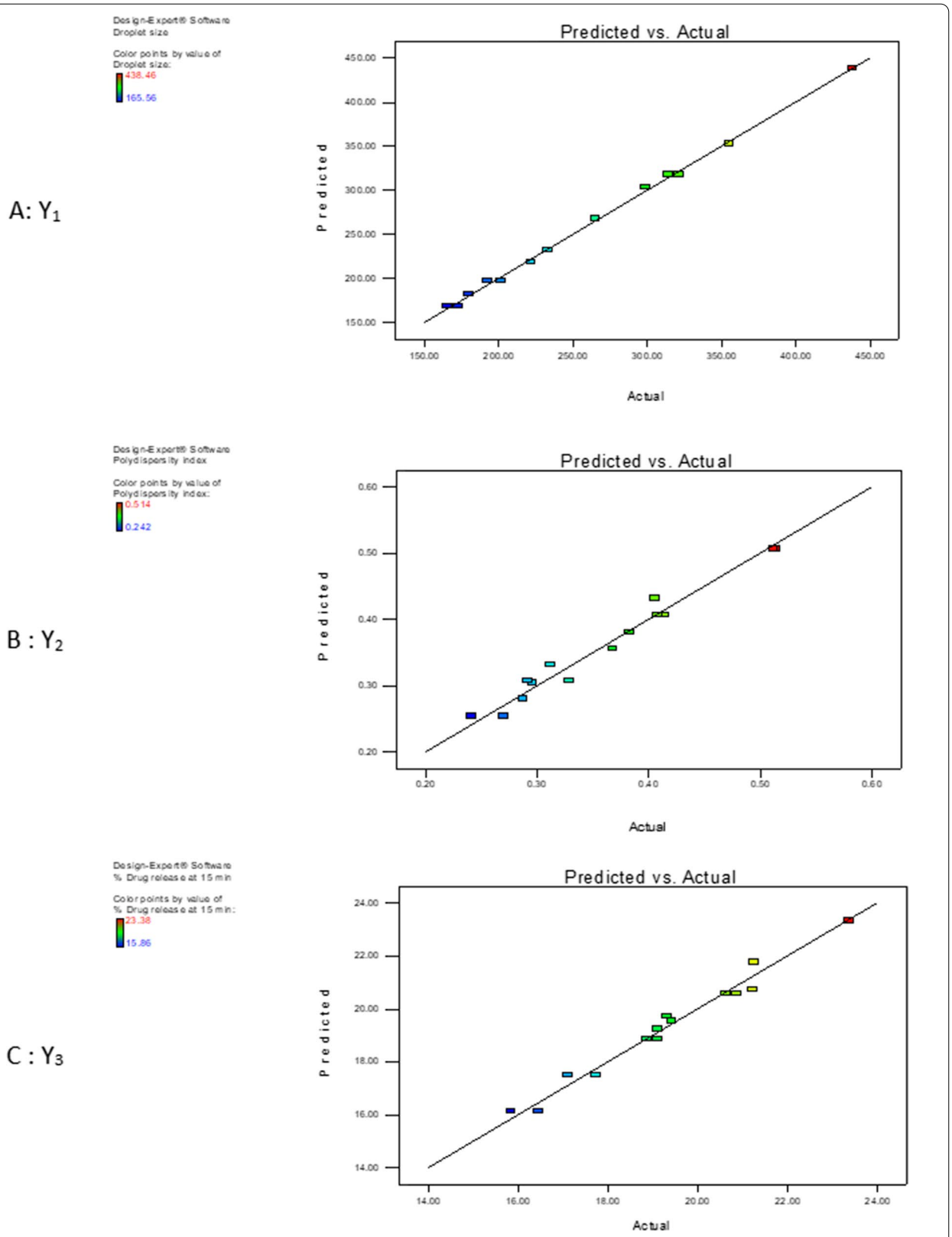

Fig. 6 2D plots illustrating the obtained versus predicted values for the responses **A** droplet size **B** polydispersity index **C** percent drug release at 15 min

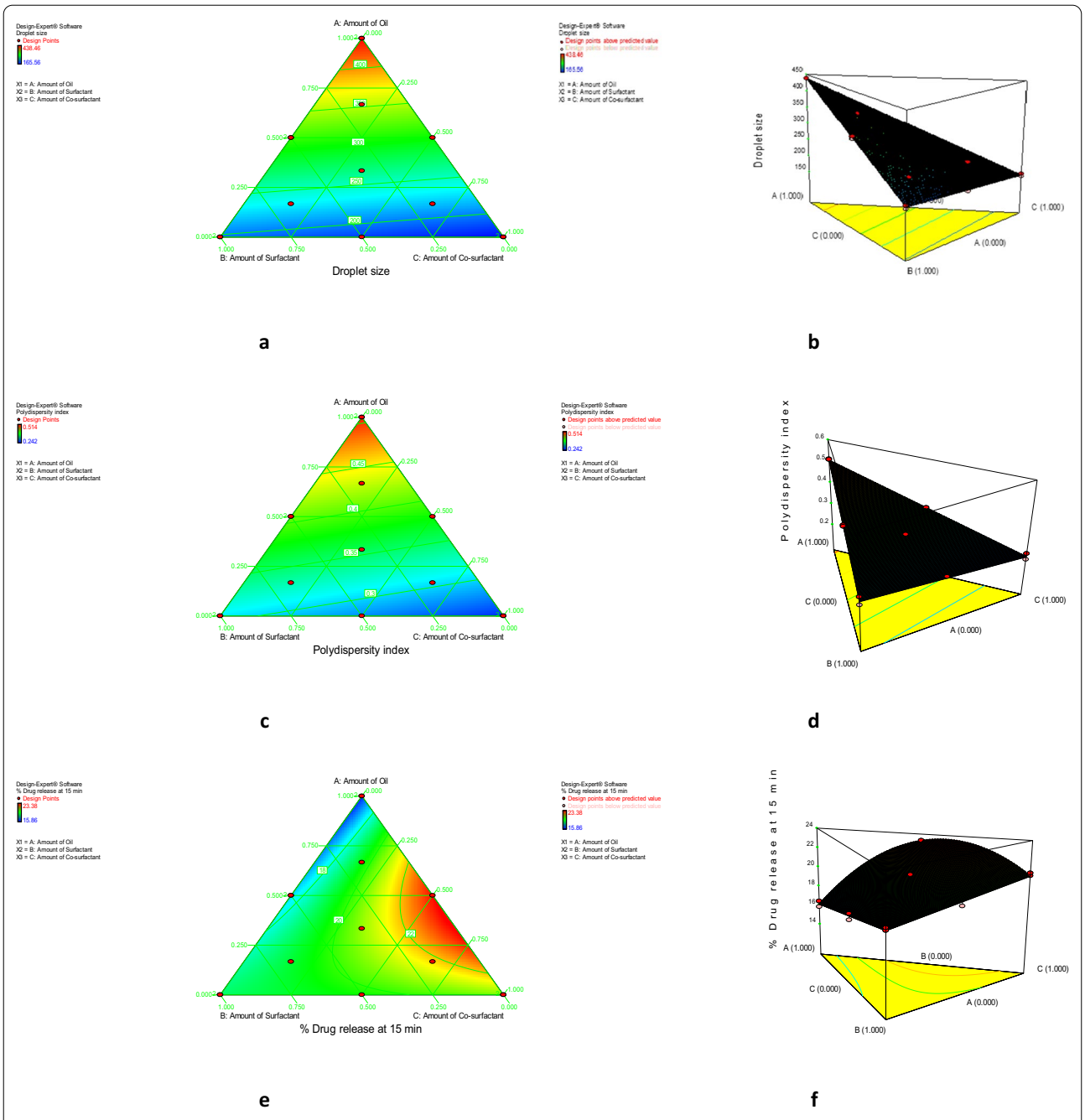

Fig. 7 Contour and 3-D response surface plots

HP ≤ 60%. 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 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. 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

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	0.078	189.46	0.27	21.64	S1	192.43	0.30	20.96
B—Amount of Surfactant	0.000				S2	194.74	0.29	19.88
C—Amount of Co-surfactant	0.922				S3	191.68	0.28	21.24

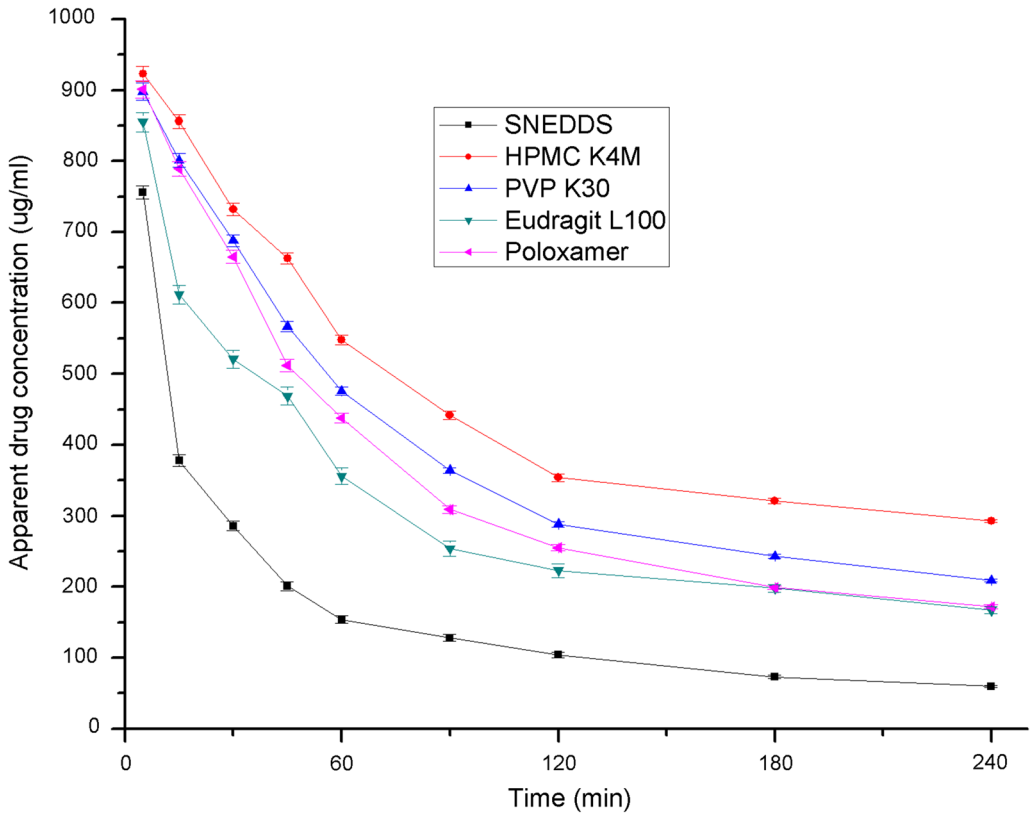

Fig. 8 The drug concentration–time profiles with various polymers

be selected as the independent variables. The proportion of components must sum to 100% complicates the regular designs and analysis of such experiments. 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 well spread over the factor space and identifies the optimal experimental composition in the factor space [16].

The obtained results were analyzed using multiple linear regression analysis and mathematical equations were generated to correlate each dependent variable.

Table 5 Results of droplet size, PDI and zeta potential

Formulation	Average droplet size (nm)	PDI	Zeta potential (mV)
SNEDDS			
S1	192.43 ± 3.32	0.30 ± 0.005	−22.4 ± 2.21
S2	194.74 ± 4.12	0.29 ± 0.005	−23.24 ± 1.89
S3	191.68 ± 3.54	0.28 ± 0.005	−24.56 ± 3.42
sSNEDDS			
F1	172.56 ± 2.86	0.212 ± 0.005	−25.34 ± 3.4
F2	169.82 ± 1.66	0.234 ± 0.005	−24.96 ± 2.8
F3	178.86 ± 1.24	0.242 ± 0.005	−26.34 ± 1.4
F4	166.78 ± 3.14	0.256 ± 0.005	−25.65 ± 2.1

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

The results were evaluated with Analysis of Variance (ANOVA), Regression coefficients (R^2), Contour plots and 3D-Response surface plots. 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 supercubic model. These equations represent the quantitative effect of amount of Captex® 300, Kolliphor® RH 40 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 effect of the individual variables on response parameters. The coefficients with more than one factor term indicates the interactive effect.

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. Polydispersity (PDI) is an important parameter used to describe the size distribution of nanocarriers systems. Usually the PDI values falls between 0 to 1. PDI values less than 0.05 indicates a highly monodisperse system. PDI values grated 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 behavior in vivo.

The quadratic model obtained for Y_1 was found to be significant with model F-value of 4100.14. This model revealed that the amount of Captex® 300, Kolliphor® RH 40 and Transcutol® HP have 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 have shown good correlation coefficient (0.9987).

The polydispersity index of the prepared SNEDDS was found to be in the range of 0.242–0.514. The supercubic model developed for polydispersity index (Y_2) was found to be significant with model F-value of 197.05. This model revealed that the amount of Captex® 300, Kolliphor® RH 40 and Transcutol® HP have 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

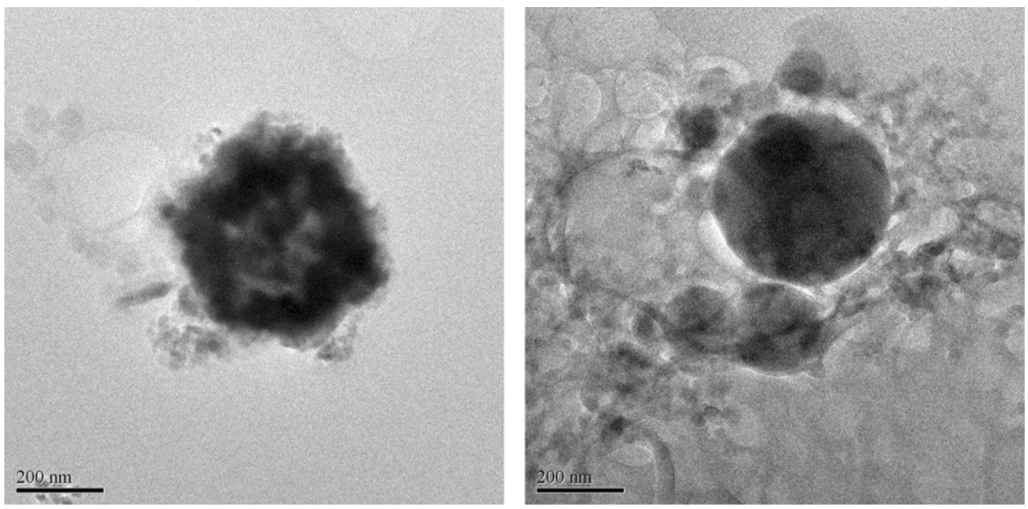

Fig.9 TEM images of Pemigatinib loaded SNEDDS AND sSNEDDS formulation

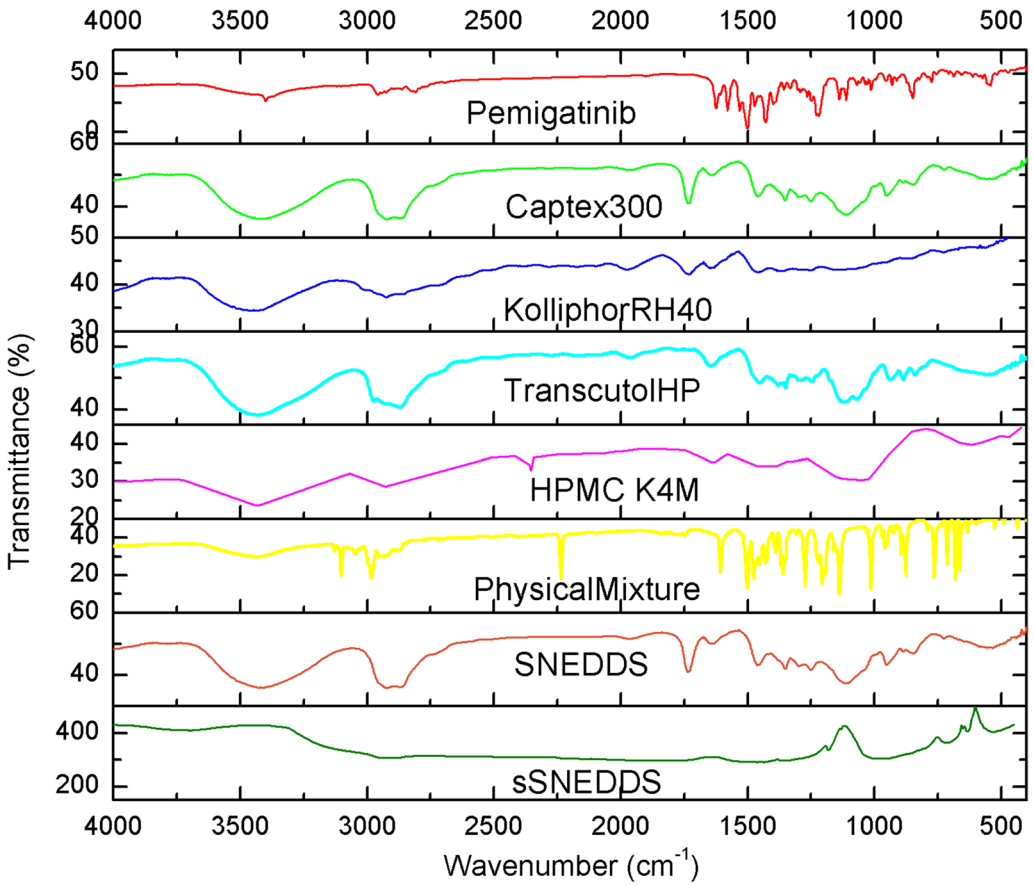

Fig. 10 FTIR spectra of Pemigatinib, Captex®300, Kolliphor®RH 40, Transcutol®HP, Physical mixture, SNEDDS and sSNEDDS

on Y_2. The resultant model for Y2 have shown good correlation coefficient (0.9728).

The percent drug release at 15 min (Y_3) from the developed formulations ranged between 15.86 to 23.38. The quadratic model obtained for Y_3 was found to be significant with model F-value of 149.08. This model revealed that the amount of Captex® 300, Kolliphor® RH 40 and Transcutol® HP have significant positive effect on Y_3. It is evident from the equation that the effect of variable C is more significant than B and A on Y_3. The resultant model for Y_3 have shown good correlation coefficient (0.9781).

Supersaturable self-nanoemulsifying drug delivery systems (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 supersaturation 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 results in kinetic stabilization of the supersaturated state by restricting the movement of drug particles. Inhibitory effects of these polymers remains 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 supersaturation 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 changes from one form to another. Significant higher concentration of drug with the addition of polymers indicating the inhibition of precipitation. The concentration of Pemigatinib in the test medium was calculated to be 1000 µg/ml (10 mg Pemigatinib

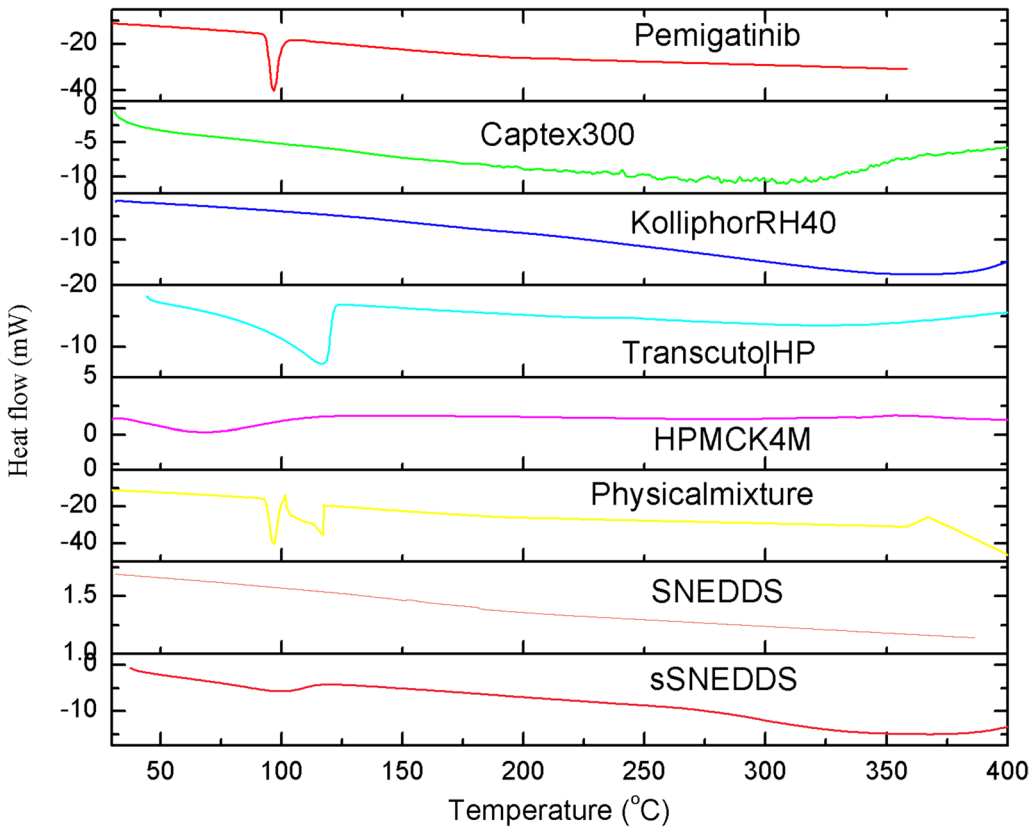

Fig. 11 DSC thermograms of Pemigatinib, Captex®300, Kolliphor®RH 40, Transcutol®HP, Physical mixture, SNEDDS and sSNEDDS

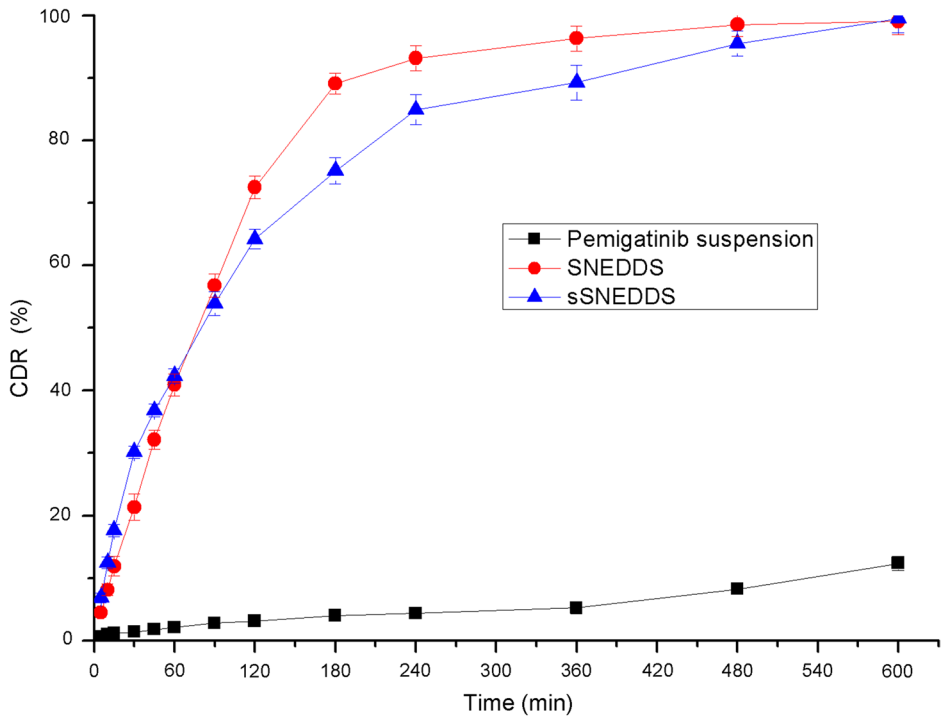

Fig. 12 Dissolution profile of Pemigatinib from sSNEDDS formulation

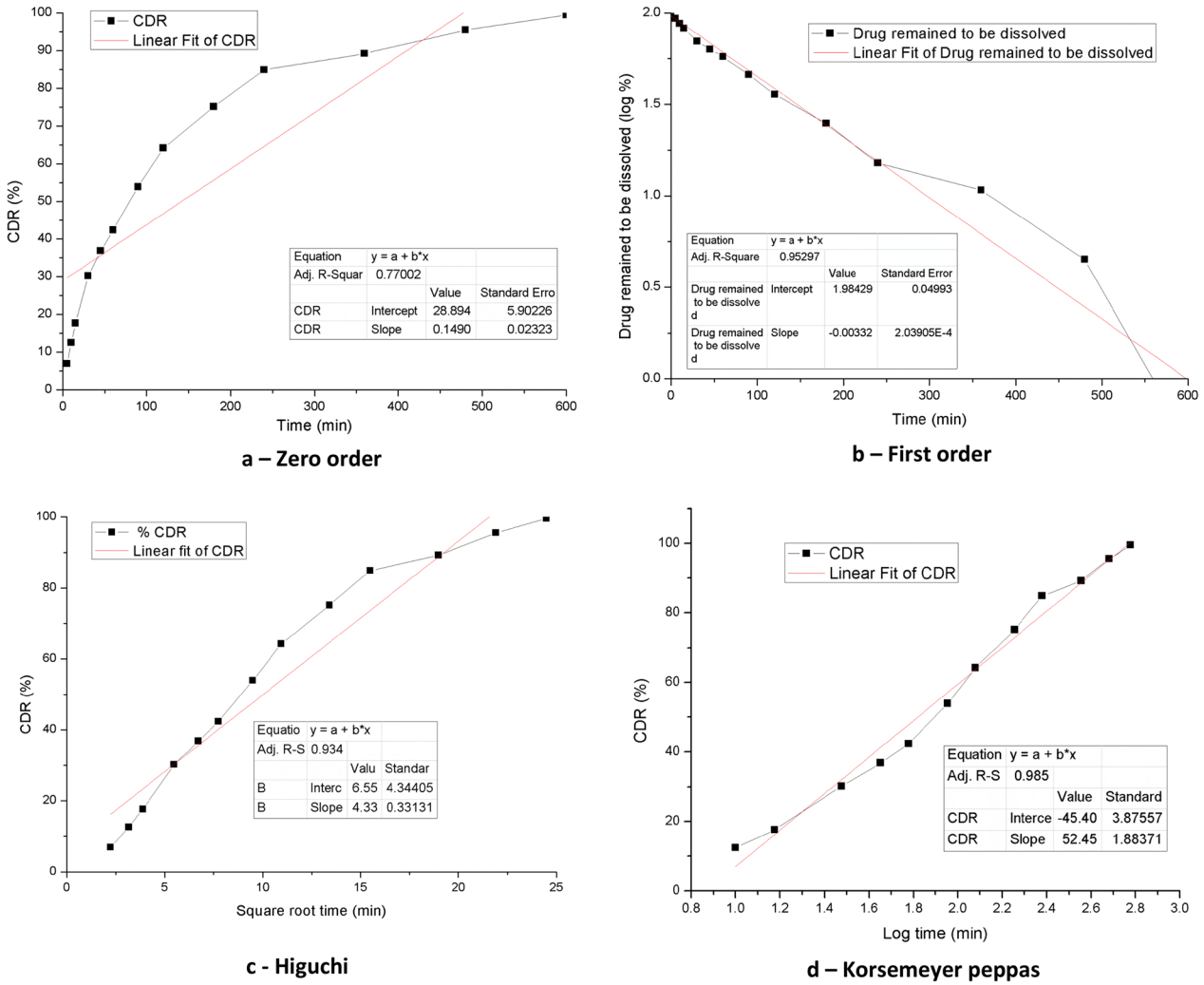

Fig. 13 Drug release kinetics curves

Table 6 Drug release kinetics data of Pemigatinib SSNEDDS

Model	R^2	*n*
Zero-order	0.7700	0.149
First-order	0.95297	−0.00332
Higuchi	0.98492	4.3742
Korsmeyer–Peppas	0.90799	46.583

in 100 ml medium). In case of plain SNEDDS formulation, the concentration of Pemigatinib rapidly declined to about 378 µg/ml and 286 µg/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, 5% HPMC K4M as precipitation inhibitor was used for the further studies.

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

Table 7 Stability data of Pemigatinib sSNEDDS

Parameter	Temperature (°C)	0 days	90 days	180 days
Average droplet size (nm)	4 ± 1 °C	166.78 ± 3.14	172.46 ± 4.26	173.56 ± 3.86
	25 ± 2 °C	166.78 ± 3.14	167.56 ± 2.28	172.48 ± 4.53
	40 ± 2 °C	166.78 ± 3.14	170.92 ± 5.12	169.89 ± 3.86
Zeta potential (mV)	4 ± 1 °C	−25.65 ± 2.1	−23.36 ± 2.2	−24.22 ± 3.1
	25 ± 2 °C	−25.65 ± 2.1	−24.58 ± 3.2	−25.12 ± 1.9
	40 ± 2 °C	−25.65 ± 2.1	−23.88 ± 4.1	−24.86 ± 2.7
Polydispersity index	4 ± 1 °C	0.256 ± 0.005	0.273 ± 0.005	0.276 ± 0.005
	25 ± 2 °C	0.256 ± 0.005	0.294 ± 0.005	0.282 ± 0.005
	40 ± 2 °C	0.256 ± 0.005	0.297 ± 0.005	0.278 ± 0.005

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

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 regression coefficient and slope of the curves are as shown in Table 7. 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 Korsemeyer-Peppas and Higuchi models. The regression coefficient value is closer to unity in case of Higuchi model (0.98492), which indicates the Fickian diffusion process.

Conclusions

A supersaturable self-nanoemulsifying drug delivery system of pemigatinib was prepared by using a supersaturation 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 temperatures 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 Pemigatinib by using HPMC K4M as precipitation inhibitor.

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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Author contributions

We both the authors contributed equally. All authors read and approved the final manuscript.

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Availability of data and materials

Will be made available on request.

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.

Competing interests

The authors declare that they have no competing interests.

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