Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Design and Characterization of Ceritinib Self-nanoemulsifying Drug Delivery Systems

Sujitha Katuri, Bhikshapathi Darna*

Career Point University, Kota-325003, Rajasthan, India

ARTICLE INFO

Article history:

Received: 29 April, 2021

Revised: 13 May, 2021

Accepted: 17 May, 2021

Published: 30 May, 2021

Keywords:

Anaplastic lymphoma kinase (ALK),
Ceritinib,
SNEDDS,
Zeta potential.

DOI:

10.25004/IJPSDR.2021.130316

ABSTRACT

Objective: The main objective of the current study was to develop ceritinib SNEDDS for the improvement of solubility, permeability, and drug release.

Methods: Solubility of ceritinib was studied in various oils, surfactants, and co-surfactants, and based on its maximum solubility, an oil, surfactant, and co-surfactant were chosen (captex355, tergitol, and propylene glycol) and mixed in varying ratios, the ratios with no phase separation, maximum transmittance and clear in appearance were identified and used for plotting pseudo tertiary phase diagram. Fifteen self-nanoemulsifying drug delivery systems (SNEDDS) formulations were selected from miscible regions of the pseudo ternary phase diagram subjected to thermodynamic stability testing. Formulations that passed stability testing were evaluated for % transmission, drug content, and in vitro drug release analysis. The final optimized formulation was analyzed for particle size, Z average, and zeta potential, followed by fourier transform infrared spectroscopy (FTIR) and SEM analysis.

Results: Formulation F13 with maximum drug release of 98.9% in 60 minutes higher than 48 % of the pure drug is considered the optimized formulation. The particle size, Z average, and zeta potential of the ceritinib SNEDDS formulation F13 were 144 nm, 132 nm, and -7.2 mV, respectively. The FTIR and SEM studies do not indicate any drug excipient interaction and confirm uniform drug distribution. The formulation subjected to accelerated stability study is proved to be stable over six months.

Conclusion: The results indicate that ceritinib SNEDDS formulations can be designed to enhance the solubility of ceritinib and increase its absorption rate and drug release.

Introduction

Cancer is a disease caused by uncontrolled cell division or abnormal growth of cells which is hard to eradicate. Cancer is differentiated into benign and malignant tumors, where benign tumors are localized and not spread to other body parts, and whereas malignant tumors spread to other parts of the body and invade by a process known as metastasis. Metastatic tumors are challenging to treat as the cells break down from the tumor and spread to other body parts through the lymphatic system and bloodstream. In addition, alteration or mutation in genes causes cancer.

Anaplastic lymphoma kinase (ALK) gene, a tyrosine kinase receptor, is responsible for controlled cell proliferation and other functions related to cell division in the body. Alteration in this gene causes cancer as it disturbs many signal pathways which control cell division in the human body and result in malignant tumors like neuroblastoma, Anaplastic large cell lymphoma, inflammatory myofibroblastic tumors, and non-small cell lung cancer. Any alteration in ALK gene results in cancer, and the patients are said to be ALK-positive cancer patients. Drugs like ceritinib, crizotinib, and alectinib effectively treat ALK gene-positive patients, especially people with non-small cell lung cancer. ALK activates different signalling pathways, which affect cell growth and the anti-apoptotic process n the human body, this can be controlled by using drugs that inhibit this process.[1,2]

***Corresponding Author:** Bhikshapathi Darna

Address: Career Point University, Kota-325003, Rajasthan, India

Email ✉**:** dbpathi71@gmail.com

Tel.: +91-9848514228

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ceritinib is used to treat lung cancer, specifically non-small cell lung cancer caused by activation of ALK gene. Ceritinib belongs to class IV in BCS classification of drugs, so it has low permeability and low solubility characteristics. For increasing the solubility of the drug novel approaches in nanotechnology like self-nano emulsifying drug delivery systems SNEDDS have gained importance in recent times.[3-5]

SNEDDS are lipid-based formulation, one of the solubility enhancement techniques used in developing dosage forms of drugs with low solubility for BCS class I and BCS class IV drugs. SNEDDS formulation consists of an oil surfactant and co-surfactant chosen in which the drug is maximum soluble. In addition, this nano-sized formulation has more surface area and less interfacial tension when emulsion (with particle size less than 100 nm) is formed when in contact with GIT fluids, thus resulting in more absorption, thereby increasing drug release. The present study is aimed to develop captex 355 based ceritinib SNEDDS for increasing solubility and thereby release characteristics.[7,8]

Materials and Methods

Materials

Hetero Labs Limited, Hyderabad gifted Ceritinib. Triacetin, Oleic acid, isopropyl myristate, miglyol, arachis oil, capric acid captex355, lauric acid obtained from Sisco laboratory Pvt limited, palm kernel oil, caproic acid, Corn oil, labrafac CC, cotton seed oil, labrafil M 1944 CS procured from Yarrow Chemical Products, Mumbai. Brij 30, tween 20, span 80, Triton, tergitol, solutol HS15/Kolliphor HS 15, and transcutol HP were gifted from Gattefosse, Mumbai.

Solubility Studies

The solubility of ceritinib in different oils (triacetin, oleic acid, isopropyl myristate, miglyol, arachis oil, capric acid captex355, lauric acid, palm kernel oil, caproic acid, Corn oil, labrafac CC, cotton seed oil, labrafil M 1944 CS), surfactants (brij 30, tween 20, span 80. triton, tergitol, solutol HS15/Kolliphor HS 15, span2, transcutol HP), co-surfactants(PEG-400, PEG-600, propylene glycol, lauro glycol FCR) was studied by adding an excess amount of ceritinib (approximately 10 mg) with 2 mL vehicle each in vial and heated in a hot water bath at 40°C for solubilizing the drug. The samples were mixed using a vortex mixer and kept aside for 48 hours in orbital shaker at room temperature to attain equilibrium solubility. Later these vials were centrifuged at 3000 rpm for 10 minutess, the excess drug gets settled, and from the supernatant, the drug concentration is quantified by using UV spectrophotometry at 319 nm.[8-10]

Construction of Pseudo Ternary Phase Diagrams

Oil, surfactant, and co-surfactant chosen from solubility studies were mixed in different ratios of oil and Smix (surfactant: co-surfactant) ranging from 1:9 to 9:1 were prepared and filled in vials and thoroughly shaken. The phase diagram was constructed for the ratios that spontaneously formed nano-emulsion upon gentle agitation with water. The Ternary phase diagram was plotted for ratios that showed no phase separation, clear appearance, and transmittance values greater than 80% were considered the apex of the triangle representing each vehicle. As it is lipid-based formulation the level of oil ranges from 75 to 90% (v/v), and surfactant and co-surfactant 5 to 13% (v/v) and 5 to 12.5% (v/v) respectively. Excess surfactant concentration causes GI irritation and toxicity, so the levels of surfactant and co-surfactant have to be kept to a minimum. Pseudo ternary plots constructed using Chemix software.[9]

% Transmittance

Maximum transmittance values indicate the formation of small size particles in the nano range. The varying ratios of oil and S_{mix} were first diluted with water and visually observed for phase separation and turbidity. Solutions with a clear appearance and no phase separation were used for measuring transmittance values using UV spectrophotometer at 319 nm. Ratios showing a percentage transmittance value of more than 80 were considered for plotting the pseudo ternary phase diagram as these ratios indicate nano-emulsion formation.[10]

Development of Ceritinib SNEDDS Formulations

The emulsification region indicates the nano-emulsion region in pseudo-ternary phase diagram; fifteen ratios were chosen to formulate ceritinib SNEDDS. Based on solubility studies conducted for choosing vehicles for the formulation, Captex 355 as oil phase and tergitol and propylene glycol as surfactant and co-surfactant were screened for the formulation of Ceritinib SNEDDS. Ceritinib (150 mg) added to the oil into the glass vial and heated in a hot water bath at 40°C until drug solubilized. Then to this oily mixture were added surfactant and co-surfactant and sonicated for 15 minutes.[11]

Thermodynamic Stability Test and Drug Content

The stable samples were centrifuged for 5 minutes at 3000 rpm and examined for any phase separation. The stability of the formulation is checked by centrifugation study and freeze-thawing test. A UV spectrometer estimates the extent of the drug present in 0.2 mL of the formulation. The solution was filtered, diluted with 0.01N HCl with 2% polysorbate 80 as dissolution media, and analyzed at λ_{max} 319 nm against blank.

In vitro Dissolution Studies of Ceritinib SNEDDS Formulations

The liquid SNEDDS, whose weight equivalent to 150 mg of ceritinib was filled into hard gelatin capsules with

0.01N HCl as dissolution media, stirred at 37°C at 50 rpm. 5 mL of sample withdrawn at pre-set time intervals, filtered through 0.45-µm membrane filter, and analyzed spectroscopically at 319 nm.[12]

Characterization of SNEDDS[13]

Drug-Excipient Compatibility Studies

The drug excipient compatibility studies were carried out by Fourier Transform infrared spectroscopy (FTIR) method.

FTIR studies

An FTIR-8400S Spectrophotometer (Shimadzu, Japan) equipped with attenuated total reflectance (ATR) accessory was used to obtain the infrared spectra of the drug in the isotropic mixtures of excipients. Analysis of pure drug, i.e., ceritinib and physical mixtures of the drug with the excipients, were carried out using diffuse reflectance spectroscopy (DRS)-FTIR with KBr disc. All the samples were dried under vacuum before obtaining any spectra to remove the influence of residual moisture. For each spectrum, 8 scans were obtained at a resolution of 4 cm^{-1} from a frequency range of 400–4000 cm^{-1}.

Determination of Droplet Size

The average droplet size of Ceritinib SNEDDS formulations was determined by Photon correlation spectroscopy (Malvern Instrument UK), measuring sizes between 10 and 5000 nm. The selected formulations were diluted with deionized water and placed in an electrophoretic cell for measurement.

Determination of Zeta Potential

The emulsion stability is directly related to the magnitude of the surface charge. In conventional SNEDDS, the charge on an oil droplet is harmful because of free fatty acids. The zeta potential of the diluted SNEDDS formulation was measured using a zeta meter system. The SNEDDS were diluted with a ratio of 1:2500 (v/v) with distilled water and mixed with a magnetic stirrer. The Zeta-potential of the resulting micro-emulsion was determined using a Zetasizer.[14]

Scanning Electron Microscopy

The shape and surface morphology of microspheres was studied using scanning electron microscopy (SEM). The SNEDDS, after converting to the emulsion, were mounted on metal stubs, and the stub was then coated with conductive gold with sputter coater attached to the instrument HITACHI, S-3700N.

Stability Studies

Stability testing was conducted at 40°C ± 2°C/75% RH ± 5% RH for 3 months using a stability chamber (Thermo Lab, Mumbai). According to ICH guidelines, samples were withdrawn at predetermined intervals 0, 30, 60, 90 and 180 days period. In addition, various *in vitro* parameters were evaluated.

Results

Solubility Studies

From the solubility studies, it was evident that medium-chain triglycerides were highly influencing the solubility of the drug. These are obtained from a vegetable source and are resistant to oxidation. Captex 355, a medium-chain triglyceride with high solvent capacity, showed a high degree of solubility for ceritinib. The water solubility of ceritinib is very low (0.0002mg/mL).[9] Surfactants and Co-Surfactants with high HLB values were useful in solubilizing Ceritinib, and these are most commonly used as they are more stable and non-toxic in the formulation. From the solubility study, tergitol and propylene glycol were showing high solubilizing efficiency for ceritinib. (Table 1,2,3 and Fig.1,2,3)

Construction of Ternary Phase Diagram

The ratios exhibiting transmittance of more than 80% were considered for constructing a pseudo ternary

Table 1: Solubility studies of ceritinib in various oils

OILS	*SOLUBILITY(mg/mL)*
Water	0.00222
Triacetin	115.17±0.20
Arachis oil	118.33±0.15
Isopropyl myristate	131.11±0.35
Oleic acid	135.36±0.25
Miglyol	119.23±0.20
Capric acid	129.17±0.25
Captex355	158.33±0.15
Lauric acid	132.11±0.30
Palm kernal oil	130.36±0.25
Caproic acid	118.23±0.20
Corn oil	111.17±0.20
Labrafac CC	128.13±0.15
Cotton seed oil	122.11±0.35
Labrafil M1944 CS	125.36±0.25

Table 2: Solubility studies of ceritinib in various surfactants

SURFACTANT	*SOLUBILITY(mg/mL)*
Water	0.00222
Brij 30	7.17±0.20
Tween 20	6.33±0.15
Span 80	3.11±0.35
Triton	15.36±0.25
Tergitol	21.23±0.20
Solutol HS 15	11.17±0.20
Transcutol HP	13.33±0.15

phase diagram from the miscibility study of varying oil, surfactant, and co-surfactant ratios. The shaded region in the Pseudo ternary phase diagram represents the miscibility region where the oil, surfactant, and co-surfactant are entirely miscible and spontaneously form Nano-emulsion on simple agitation GI fluids. (Table 4, Fig.4).

Ceritinib SNEDDS Formulation Ratios

From the shaded region of the pseudo ternary phase diagram, 15 ratios were selected and formulated into SNEDDS. The calculated amount of Ceritinib was loaded into oil and mixed with surfactant and co-surfactant until a clear solution is formed (Table 5).

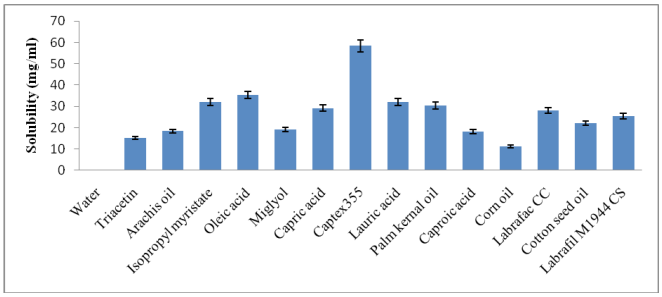

Fig.1: Solubility studies of ceritinib in various oils

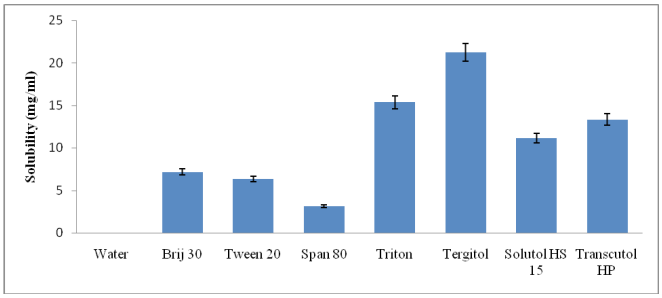

Fig.2: Solubility studies of ceritinib in surfactants

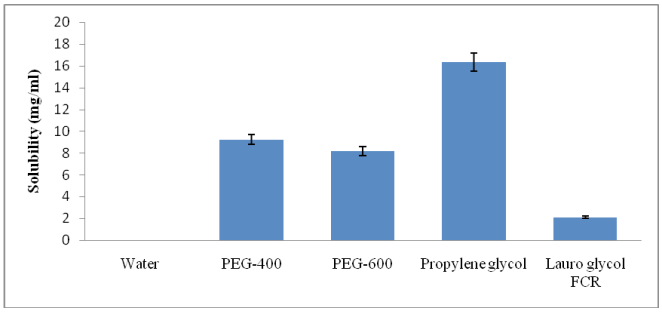

Fig.3: Solubility studies of ceritinib in co-surfactants

Table 3: Solubility studies of ceritinib in various co-surfactants

Co-surfactant	*Solubility(mg/mL)*
Water	0.00222
PEG-400	9.23±0.20
PEG-600	8.17±0.20
Propylene glycol	16.33±0.15
Lauro glycol FCR	2.11±0.35

In-vitro Dissolution Studies of Ceritinib SNEDDS Formulation

The proposed dissolution media for ceritinib dissolution in 0.1 N HCl, pH 1 at 37°C USP II apparatus at 60rpm, the volume of dissolution media 900 mL.[9] Fifteen formulations from the miscibility region were formulated, and in-vitro dissolution studies were conducted; all the fifteen formulations showed good drug release than the pure drug, which indicates the formation of small size

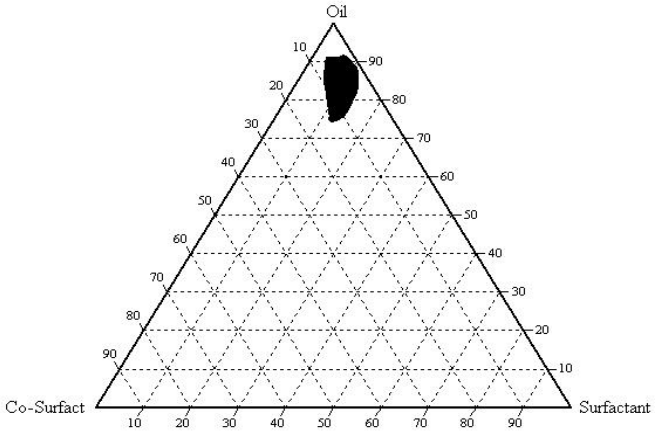

Fig.4: Phase diagram with emulsification region.

Table 4: Construction of phase diagram

S.NO	*Oil:S_{mix}*	*S_{mix} (surf: co-surf)*	*%Oil*	*%Sur-factant*	*%Cosur-factant*	*%T*
1	09:01	01:01	90	5	5	91.89
2	08:01		88.88	5.55	5.55	91.78
3	07:01		87.5	6.25	6.25	90.33
4	06:01		85.71	7.14	7.14	86.47
5	05:01		83.33	8	8	84.85
6	04:01		80	10	10	82.75
7	03:01		75	12.5	12.5	80.18
8	09:01	02:01	90	6.6	3.3	93.92
9	08:01		88.88	7.4	3.7	95.69
10	07:01		87.5	8.3	4.1	90.04
11	06:01		85.71	9.52	4.76	91.11
12	05:01		83.33	10.66	5.3	88.44
13	04:01		80	13.33	6.6	84.11
14	09:01	03:01	90	7.5	2.5	91.53
15	08:01		88.88	8.33	2.77	89.78
16	07:01		87.5	9.375	3.125	88.5
17	06:01		85.71	10.71	3.57	83.9
18	05:01		83.33	12	4	84.84
19	09:01	04:01	90	8	2	89.22
20	08:01		88.88	8.88	2.22	86.49
21	07:01		87.5	10	2.5	82.74
22	05:01		83.33	12.8	3.2	80.22

particles forming Nano-emulsion. When contact with the dissolution media, the formulation forms an emulsion whose interfacial tension is reduced by surfactants and co-surfactants. Hence the ratio with more surfactant and co-surfactant showed a high degree of drug release, and also in general, as the particle size is small with more surface area, more is the absorption and hence more is the drug release, and out of all formulation, F13 was showing maximum drug release of 98.9% at the end of 60 minutes with more Smix in the ratio compared to other formulations (Figs. 5-7, Tables 6-8).

Table 5: Ratios of ceritinib SNEDDS with formulation code

S.NO	*Formulation code*	*Oil : Surfactant : Co-surfactant*
1	F1	81:14:05
2	F2	83:10:07
3	F3	75:15:10
4	F4	85:09:06
5	F5	78:14:08
6	F6	81:12:07
7	F7	79:13:08
8	F8	82:12:06
9	F9	83:11:06
10	F10	78:13:09
11	F11	77:14:09
12	F12	79:14:07
13	F13	76:15:09
14	F14	75:16:09
15	F15	82:15:07

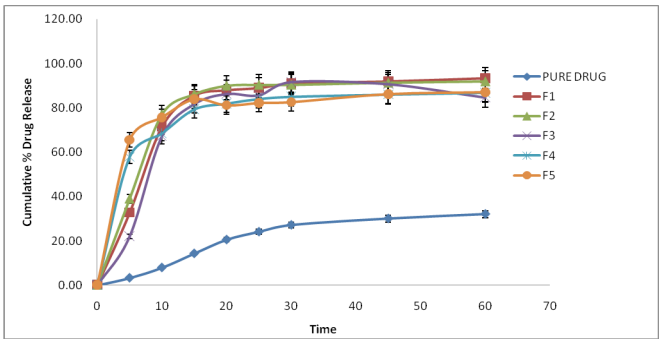

Fig.5: Dissolution profile of ceritinib pure drug and ceritinib formulations F1to F5

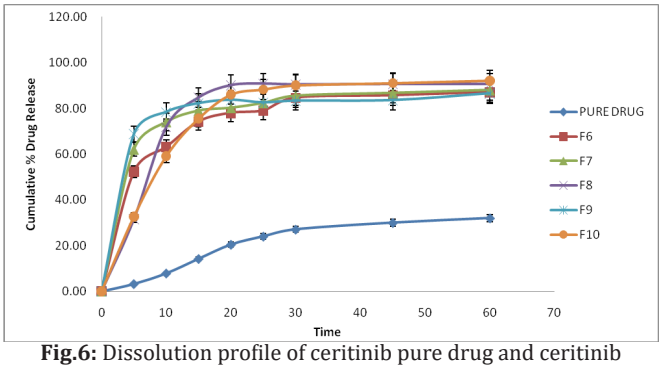

Fig.6: Dissolution profile of ceritinib pure drug and ceritinib formulations F6 to F10

Table 6: Dissolution profiles of various formulations of ceritinib SNEDDS (Pure drug and F1 to F5)

Time	*Pure drug*	*F1*	*F2*	*F3*	*F4*	*F5*
0	0.00	0.00	0.00	0.00	0.00	0.00
5	3.23 ± 0.17	32.68 ± 0.95	38.99 ± 1.10	22.00 ± 1.20	57.86 ± 0.99	65.44 ± 0.96
10	7.88 ± 0.98	71.51 ± 1.2	77.09 ± 1.15	67.14 ± 1.15	68.54 ± 1.17	75.68 ± 1.33
15	14.23 ± 1.12	85.54 ± 2.8	86.19 ± 2.43	81.58 ± 2.91	79.36 ± 2.89	83.86 ± 2.75
20	20.45 ± 2.22	88.00 ± 3.4	90.02 ± 3.15	86.13 ± 3.63	81.94 ± 3.33	81.13 ± 3.15
25	24.02 ± 3.12	89.00 ± 3.9	90.40 ± 3.9	85.50 ± 3.89	84.05 ± 3.76	82.19 ± 3.93
30	27.09 ± 3.9	91.00 ± 4.2	90.45 ± 4.15	91.52 ± 4.21	85.01 ± 4.18	82.58 ± 4.15
45	29.99 ± 4.0	92.00 ± 4.66	91.42 ± 4.35	90.54 ± 4.32	86.02 ± 4.56	86.18 ± 4.32
60	32.00 ± 4.11	93.4 ± 4.99	92.00 ± 4.98	84.52 ± 4.72	86.85 ± 4.89	87.07 ± 5.01

Table 7: Dissolution profiles of various formulations of ceritinib SNEDDS (Pure drug and F6 to F10)

TIME	*PURE DRUG*	*F6*	*F7*	*F8*	*F9*	*F10*
0	0.00	0.00	0.00	0.00	0.00	0.00
5	3.23 ± 0.17	52.32 ± 0.93	62.06 ± 1.13	31.59 ± 1.23	68.78 ± 0.98	32.68 ± 0.19
10	7.88 ± 0.98	63.09 ± 1.13	74.02 ± 1.16	71.81 ± 1.16	78.43 ± 1.18	59.09 ± 0.12
15	14.23 ± 1.12	74.22 ± 2.6	78.99 ± 2.33	84.71 ± 2.92	82.22 ± 2.86	75.55 ± 2.23
20	20.45 ± 2.22	77.99 ± 3.12	80.23 ± 3.42	90.09 ± 3.46	83.68 ± 3.45	85.99 ± 3.13
25	24.02 ± 3.12	79.04 ± 3.9	82.34 ± 3.87	90.74 ± 4.15	82.53 ± 3.80	88.23 ± 3.92
30	27.09 ± 3.9	84.64 ± 4.17	85.48 ± 4.17	90.41 ± 4.39	83.29 ± 4.20	90.00 ± 4.02
45	29.99 ± 4.0	85.66 ± 4.46	86.70 ± 4.44	90.56 ± 4.65	83.55 ± 4.66	91.00 ± 4.23
60	32.00 ± 4.11	87.09 ± 4.98	87.99 ± 4.89	90.59 ± 4.99	86.54 ± 4.98	92.09 ± 4.99

Table 8: Dissolution profiles of various formulations of ceritinib SNEDDS (Pure Drug and F11 to F15)

Time	*Pure drug*	*F11*	*F12*	*F13*	*F14*	*F15*
0	0.00	0.00	0.00	0.00	0.00	0.00
5	3.23 ± 0.17	34.7 ± 0.93	22.19 ± 0.95	48.99 ± 1.14	41.99 ± 1.13	22 ± 0.21
10	7.88 ± 0.98	49 ± 0.98	43.42 ± 1.01	65.34 ± 1.16	56.87 ± 2.50	35.43 ± 0.66
15	14.23 ± 1.12	59.02 ± 1.09	56.1 ± 2.43	75.64 ± 2.46	68.92 ± 3.33	56.76 ± 1.94
20	20.45 ± 2.22	68.23 ± 2.43	72.8 ± 3.12	83.44 ± 3.13	77.84 ± 3.8	65.73 ± 2.05
25	24.02 ± 3.12	77.8 ± 3.12	82.11 ± 3.92	87.67 ± 3.90	85.43 ± 4.24	75.78 ± 3.10
30	27.09 ± 3.9	87.11 ± 3.90	86.02 ± 4.14	90.67 ± 4.17	89.1 ± 4.40	80.65 ± 3.81
45	29.99 ± 4.0	92.2 ± 4.12	90.22 ± 4.35	94.82 ± 4.35	91.99 ± 4.7	84.65 ± 4.33
60	32.00 ± 4.11	95.5 ± 4.36	94.55 ± 4.99	98.9 ± 4.99	96.02 ± 4.96	90.99 ± 4.98

Table 9: Thermodynamic stability studies of ceritinib SNEDDS formulation

		Freeze thaw method	
Formulation	*Centrifugation*	*-20°C for 2 days*	*+40°C for 2 days*
F1	No separation of phases observed	Passed	Passed
F2	No separation of phases observed	Passed	Passed
F3	No separation of phases observed	Passed	Passed
F4	No separation of phases observed	Passed	Passed
F5	No separation of phases observed	Passed	Passed
F6	No separation of phases observed	Passed	Passed
F7	No separation of phases observed	Passed	Passed
F8	No separation of phases observed	Passed	Passed
F9	No separation of phases observed	Passed	Passed
F10	No separation of phases observed	Passed	Passed
F11	No separation of phases observed	Passed	Passed
F12	No separation of phases observed	Passed	Passed
F13	No separation of phases observed	Passed	Passed
F14	No separation of phases observed	Passed	Passed
F15	No separation of phases observed	Passed	Passed

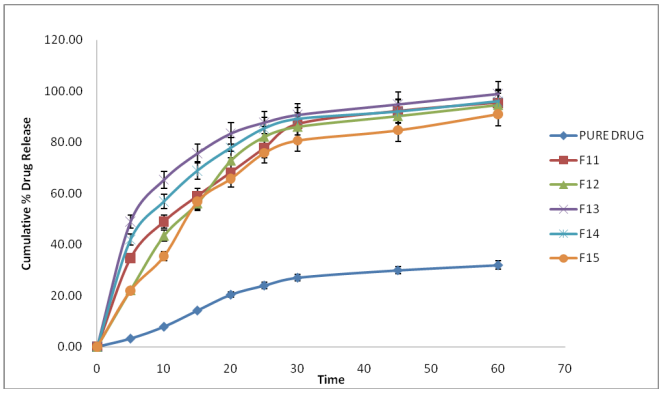

Fig.7: Dissolution profile of ceritinib pure drug and ceritinib formulations F11to F15

Thermodynamic Stability Studies

Fifteen formulations of Ceritinib SNEDDS were subjected to thermodynamic stability studies. The formulation

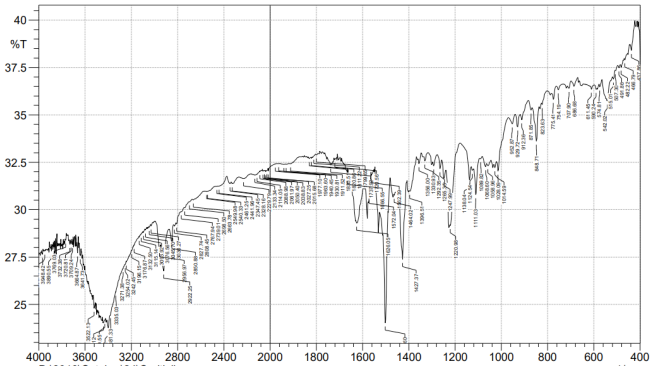

Fig. 8: FTIR spectroscopy of Ceritinib pure drug

was centrifuged at 3000 rpm for 5 minutes and checked for any phase separation, all fifteen formulations passed the centrifugation test by showing no phase separation of phases. Those formulations were freeze-thawed for 2 days at -20°C and +40°C, and as a result, all were stable and passed the stability test (Table 9).

Drug Excipient Compatibility Studies by FTIR Spectroscopy

FTIR spectrums are mainly used to identify any interactions between the pure drug (Fig. 8) and any excipients used. The presence of all these peaks confirms the purity of the drug. The FTIR spectra of the optimized formulation (Fig. 9) were having similar fundamental peaks and patterns. Thus there are no significant interactions between the drug and excipients.

Particle Size Analysis of SNEDDS

Droplet size determines the rate and extent of drug release as well as drug absorption. Smaller particle size, larger the interfacial surface area, may lead to more rapid absorption and improved bioavailability. SNEDDS with a mean droplet size below 200 nm exhibit excellent bioavailability. The emulsion particle size is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release and absorption. The particle size of the optimized SNEDDS formulation (F13) was found to be 144.4 nm & Z-Average of 132.4 nm,

indicating all the particles were in the nanometer range (Fig. 10).

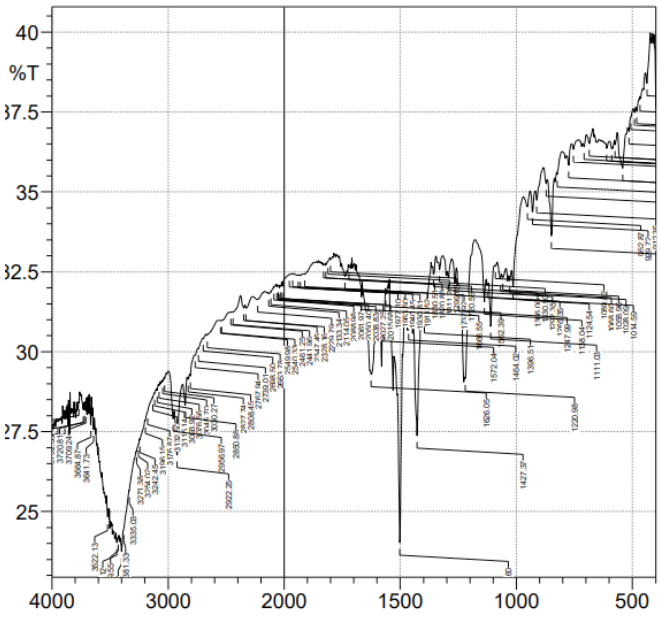

Fig.9: FTIR Spectroscopy of ceritinib optimized formulation

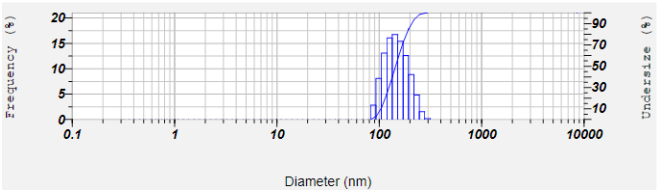

Fig.10: Particle size analysis of optimized formulation F13

Table 10: Different formulations of ceritinib SNEDDS with %T and % drug content after stability studies.

S.NO	*Formulation code*	*Oil : Surfactant : Co-surfactant*	*%Trans-mittance*	*%Drug content*
1	F1	81:14:05	82.34	85
2	F2	83:10:07	89.74	92
3	F3	75:15:10	77.46	80
4	F4	85:09:06	90.36	95
5	F5	78:14:08	80	83
6	F6	81:12:07	81.32	84
7	F7	79:13:08	79.24	83
8	F8	82:12:06	83.3	88
9	F9	83:11:06	89.65	94
10	F10	78:13:09	80.99	93
11	F11	77:14:09	79.9	82
12	F12	79:14:07	82	86
13	F13	74:18:08	97.76	98
14	F14	75:16:09	78.67	97
15	F15	82:15:07	88.54	95

NOTE: % Transmittance and Drug content of ceritinib SNEDDS measured after stability studies is shown in table 2.

Zeta Potential of SNEDDS

Zeta potential is responsible for the degree of repulsion between adjacent, similarly charged, dispersed droplets. A zeta potential value of ±30 mV is sufficient for the stability of a micro-emulsion. The zeta potential of the optimized SNEDDS formulation (F13) was found to be -7.2.0 mV, which complies with the requirement of the zeta potential for stability (Fig. 11).

SEM Studies of Ceritinib SNEDDS

Scanning electron microscope studies of optimized formulation of Ceritinib (F13) revealed oval-shaped globules. The size is within nanometers. In addition, there are clear liquid droplets without any pores (Figs.12A, B).

Stability Studies

According to ICH guidelines, the stability testing carried out for 3 months indicates no significant variation in % transmittance and drug content, indicating the stability of formulations. (Table 10)

Discussion

The current study involves the development of ceritinib SNEDDS for improved solubility and drug release. The solubility of ceritinib was found maximum in captex355 (oil), tergitol (surfactant), and propylene

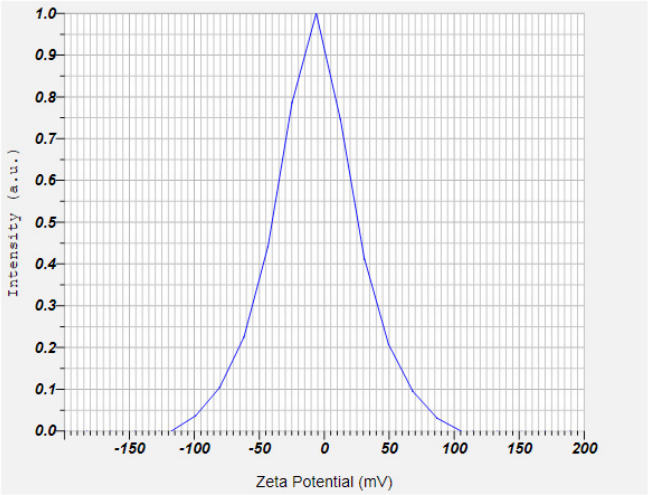

Fig.11: Zeta potential of the optimized formulation F13

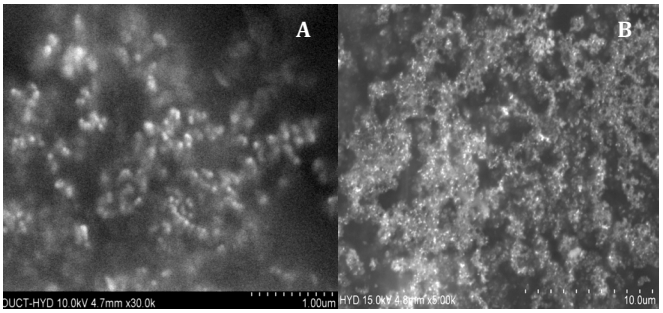

Fig.12: Scanning electron microscopy of ceritinib optimized formulation (F13)

glycol (cosurfactant). In addition, the excipients ratio was optimized from the pseudo tertiary phase diagram. F13 was found with a maximum drug release of 98.9% in 60 minutes, minimum particle size is 144 nm, and zeta potential of -7.2 mV, respectively. The formulations found stable towards freeze-thawing for 2days at -20°C and +40°C for 2 days. The FTIR and SEM studies do not indicate any drug excipient interaction and confirm uniform drug distribution. The formulation subjected to accelerated stability study is proved to be stable over six months.

References

1. Reck M, Popat S, Reinmuth N. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(3):27-39.
2. Khozin S, Blumenthal GM, Zhang L. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res. 2015;21(11):2436-2439.
3. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ. 1995;311:899-909.
4. Melosky B, Agulnik J, Albadine R. Canadian consensus: inhibition of ALK-positive tumours in advanced non-small-cell lung cancer. Curr Oncol. 2016;23(3):196-200.
5. Chow LQM, Barlesi F, Bertino EM. Ceritinib in ALK+ NSCLC metastatic to brain and/or leptomeninges: the ASCEND-7 study. In the proceedings of 16th World Conference on Lung Cancer, 2015.
6. Li B, Harich K, Wegiel L, Taylor LS, Edgar KJ. Stability and solubility en- hancement of ellagic acid in cellulose ester solid dispersions. Carbohydr Polym. 2013;92:1443-1450.
7. Wanga L, Donga D, Chena J, Eastoeb J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system. J. Colloid Interface Sci. 2009;330 (2) : 443-448.
8. Hosseini MH, Alizadeh N, Khanchi AR. Effect of menthol as solid cosolvent on the solubility enhancement of clozapine and lamorigine in supercritical CO2. J. Supercrit. Fluids. 2010;55:14-22.
9. Ramanaiah CF, Ravi T.In Situ Metastable Form: A Route for the Generation of Hydrate and Anhydrous Forms of Ceritinib. Cryst. Growth Des. 2017; 17:6341-6352.
10. Gaddam Suvarsha. Development and optimization of solid lipid nanoparticle formulation for enhanced solubility of ceritinib using box–behnken design.AJP;2020:14(1).
11. Ghai D, Sinha VR. Nano-emulsions as self-emulsified drug delivery carriers for enhanced permeability of the poorly water-soluble selective β1-adrenorecep- tor blocker Talinolol, Nanomedicine. Nanotechnol Biol Med. 2011;5:618-626.
12. Abdalla A, Klein S, Mader K. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets,. Eur J Pharm Sci. 2008;35:457-464.
13. XiongweiHua, Chen Linc, DingxiongChenc, Jing Zhanga, ZhihongLiua, Wei Wub, HongtaoSonga, Sirolimus. solid self-microemulsifying pellets: Formulation development, characterization and bioavailability evaluation. International Journal of pharmaceutics. 2012;438:123-133.
14. Shantanu Bandyopadhyay, Katare, Bhupinder Singh. Optimized self nano-emulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides,colloids and surfaces. B: Biointerfaces 2012;100:50-61.

HOW TO CITE THIS ARTICLE: Katuri S, Darna B. Design and Characterization of Ceritinib Self- Nanoemulsifying Drug Delivery Systems (SNEDDS). Int. J. Pharm. Sci. Drug Res. 2021;13(3):353-360. **DOI:** 10.25004/IJPSDR.2021.130316