ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 12, Issue 12, 2019

Online - 2455-3891
Print - 0974-2441

Research Article

SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM OF EFAVIRENZ: FORMULATION, *IN VITRO* EVALUATION AND CHARACTERIZATION

PAMU SANDHYA*

Department of Pharmaceutics, Shadan Women's College of Pharmacy, Hyderabad, Telangana, India. Email: sandhyapasikanti@gmail.com

Received: 04 August 2019, Revised and Accepted: 24 September 2019

ABSTRACT

Objective: The main objective of this study was to preparation and evaluation of efavirenz (EFV) to enhance its solubility and dissolution rate by self-emulsifying drug delivery system.

Methods: EFV self-emulsifying drug delivery systems (SNEDDS) were formulated using different oils, surfactant, and co-surfactant. Peceol, Tween 20, and Capmul MCM were used as oil, surfactant, and co-surfactant, respectively, followed by the evaluation by the performance of different tests such as visual observation, solubility studies, thermodynamic stability study, transmittance studies, drug content, and *in-vitro* release study.

Results: Fourier-transform infrared studies revealed negligible drug and polymer interaction. From the phase diagram, it was observed that self-emulsifying region was enhanced with increasing surfactant and co-surfactant concentrations with oil. F13 was selected as optimized formulation on the basis of physicochemical parameters, particle size, and *in-vitro* dissolution studies with the release of 98.39±5.10% drug in 1 hour. The optimized formulation size was found to be 156.7 nm as mean droplet size and Z-Average of 808.6 nm with -18.3 mV as zeta potential.

Conclusion: The study demonstrated that SNEDDS was a promising strategy to enhance the dissolution rate of EFV by improving solubility.

Keywords: Efavirenz, Antiretroviral, Self-emulsifying drug delivery systems, Peceol, Z-Average.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i12.35227

INTRODUCTION

Self-emulsifying drug delivery systems (SNEDDS) is a potential tool for bioavailability enhancement of poor aqueous soluble drugs [1]. SNEDDS is basically an isotropic mixture of drug, oil, surfactant, and co-surfactant. Such dosage forms exhibit a characteristic feature spontaneous emulsion formation on dilution with water with little or no energy input [2]. Depending on the excipients and formulation techniques, self-micro and self-nanoemulsifying drug delivery systems (self-microemulsifying drug delivery system [SMEDDS]/SNEDDS) may be developed [3]. SMEDDS has a droplet size range of 100–250 nm and form optically clear to translucent dispersions. Contrarily, SNEDDS has a droplet size of <100 nm [4].

Efavirenz (EFV) is an anti-HIV drug that acts by inhibition of non-nucleoside reverse transcriptase of HIV [5]. EFV majorly exhibits the non-competitive inhibitory activity of HIV-1 reverse transcriptase. Being a BCS class II drug, its aqueous solubility is low, whereas permeability is high that is responsible for low bioavailability [6].

In the present study, EFV would be formulated as SNEDDS, and the assessment of influence of varying ratios of oil: Smix (a mixture of surfactant and co-surfactant) in different concentrations on release of EFV would be studied. The influence of amounts of surfactant, co-surfactant, and oil on globule size, turbidly, and percentage drug release in 20 min was studied during the process of optimization. The formulation with all parameters optimized along with having enhanced *in-vitro* drug release is expected to increase oral absorption of the drug [7].

MATERIALS AND METHODS FOR EFV SNEDDS

Materials

EFV was obtained from Hetero drugs ltd, Hyderabad. Labrafac PG and Labrafil M 2125 Capmul MCM, Cremophor EL, Capyrol PGMC, Miglynol 812N and Transcutol P, Acrysol K-150, Kolliphor ELP, Kolliphor HS 15, and Brji-35 were procured from Gattefosse Ltd., Mumbai; PEG 200, PEG-600, polysorbate 20, Tween 20, Tween 80, and Oleic acid were obtained from SDFCL, Mumbai.

Methods

Solubility studies

An excess amount (10 mg) of EFV on addition to 2 ml of each excipient (Oils – Labrafac PG, Peceol, Acrysol k-150, Capryol PGMC, Oleic acid, and Miglynol 812N; Surfactants – Lauroglycol, Tween 20, Cremophor EL, Kolliphor ELP, and Kolliphor HS 15; Co-surfactants – PEG 200, Capryol PGE, Brji-35, Capryol 90, and Capmul MCM) were kept in mechanical shaker for 24 h and centrifuged at 10,000 rpm for 20 min using a centrifuge. Supernatant was filtered through membrane filter using 0.45 µm filter disk. The resultant solution was analyzed for ultraviolet (UV) absorbance at 248 nm after dilution with methanol and determination of amount of drug was done. Suitable surfactant, co-surfactant, and oil in which drug exhibited good solubility were selected by solubility studies [8].

Pseudo-ternary phase diagram

Pseudo-ternary phase diagrams have been constructed by the water titration method maintaining the temperature at 25°C. The first step was a proper mixing of different volume ratio (1:1, 2:1, and 3:1) of surfactant and co-surfactant (Smix) in each group followed by mixing of oil and surfactant/co-surfactant mixture (Smix) in variable volume ratios 1:9–9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) w/w for all the three Smix ratios 1:1, 2:1, and 3:1. Titration of certain ratios of oil, surfactant, and co-surfactant mixture by drop wise addition of deionized water was performed simultaneously agitating the mixture gently. Determination of proper ratio of one excipient to another in SNEDDS formulation was made, and Chemix software was employed for the construction of pseudo-ternary plots [9].

Visual observation

About 0.2 ml volume of the mixture was added to a glass beaker containing 300 ml of water under stirring using a magnetic stirrer

and maintaining the temperature at 37°C simultaneously observing emulsion forming tendency. Easy spreading of droplet in water implied good emulsion, whereas oil droplets presence, milky emulsion, or absence of emulsion implied bad emulsion [10].

Development of SNEDDS formulation

Solubility studies, pseudo-ternary phase diagram, and visual observation formed the basis of SNEDDS formulations of EFV. Peceol as oil phase and Tween20 and Capmul-MCM as surfactant and co-surfactant, respectively, were used (Table 1). EFV (10 mg) added to accurately weighed amount of oil in screw-capped glass vial was subjected to heating in a water bath at 40°C followed by the addition of the surfactant and co-surfactant oily mixture using positive displacement pipette with continuous stirring using a magnetic bar. The storage of formulation was done at room temperature after sonication for 15 min.

Freeze thawing (thermodynamic stability studies)

Formulations were subjected to thermodynamic stability tests in order for evaluating phase separation and temperature variations effect on SNEDDS formulations. Formulations were subjected to freeze cycle (−20°C for 2 days followed by 40°C for 2 days). Stable formulations were opted for further studies [11].

Centrifugation

Phase separation of formulations was observed after centrifuging them for 5 min at 3000 rpm. Formulations stable to phase separation were chosen for further studies [12].

% Transmittance measurement

Percentage transmittance of various SNEDDS formulation on reconstitution with distilled water was measured at 248 nm using UV spectrophotometer against water as a blank [13].

Determination of drug content

SNEDDS equivalent to 10 mg of EFV was dissolved in 100 ml of Phosphate buffer pH 6.8 after accurate weighing. The drug content was analyzed at λ_{max} 247 nm against blank by UV spectrometer after filtration and dilution [14] followed by calculation of actual drug content using the equation specified below:

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SNEDDS}}{\text{Theoretical amount of drug in SNEDDS}} \times 100$$

***In-vitro* dissolution studies**

Dissolution studies of SNEDDS of EFV (equivalent to 10 mg of EFV) filled in size "0" hard gelatin capsules were performed in US Pharmacopoeia Type II dissolution apparatus with Phosphate buffer pH 6.8, maintaining temperature at 37°C and speed at 50 rpm. 5 ml of sample withdrawal was performed at predefined intervals of 2, 5, 10, 15, 20, 25, 30, 45, and 60 min followed by filtration through 0.45 µm pore size membrane filters simultaneously replacing with an equivalent volume of fresh medium buffer at each replacement. The samples were then subjected to spectrophotometric assay at 247 nm.

Characterization of SNEDDS

Drug-excipient compatibility studies

Compatibility studies between drug and excipients were carried out by Fourier transform infrared (FTIR) spectroscopy method.

FTIR spectroscopy

The infrared spectra of drug in isotropic mixtures of excipients were obtained by FTIR-8400S Spectrophotometer (Shimadzu, Japan) endowed with attenuated total reflectance accessory, whereas pure drug, i.e., EFV and physical mixtures of the drug with the excipients analysis were done using diffuse reflectance spectroscopy-FTIR with KBr disc. Residual moisture effect was removed by vacuum drying the samples before obtaining any spectra [15]. Eight scans for each spectrum were obtained at a resolution of $4cm^{-1}$ from a frequency range of 400 to $4000cm^{-1}$.

Determination of droplet size

Photon correlation spectroscopy was used in the measurement of mean droplet size of EFV SNEDDS formulations by diluting selected formulations with deionized water followed by placement in an electrophoresis cell [16].

Determination of zeta potential

Zetasizer was used to determine zeta potential of the diluted SNEDDS formulation formed by diluting SNEDDS using distilled water in a ratio of 1:2500 (v/v) with mixing by magnetic stirrer [17].

Scanning electron microscopy (SEM)

SEM gives a picture of the surface morphology and shape of microspheres. Metal stubs were used for mounting of emulsion that resulted from SNEDDS followed by coating with conductive gold by a sputter coater affixed to the instrument (HITACHI, S-3700N) [18].

Percent entrapment efficiency

Free drug was separated from emulsion by ultra-filtration at 3500 Da followed by centrifugation at 3000 g for 5–10 min, then quantifying drug content by high-performance liquid chromatography [19]. The entrapment efficiency was calculated as follows:

$$\text{Entrapment efficiency} = \frac{\text{Total amount of drug in SNEDDS}}{\text{Total weight of ingredients in emulsion}} \times 100$$

Stability studies

Three-month stability tests were conducted at 40°C±2°C/75%±5% RH using stability chamber (Thermo Lab, Mumbai) as per the International Council for Harmonization guidelines. At predefined intervals, 0, 30,

Table 1: Formulation trials of liquid self-emulsifying drug delivery systems

Smix (Surfactant:Co-surfactant)	Oil:Smix	Formulation code	Drug (efavirenz) (mg)	Oil (Peceol mL)	S-mix (mL)	Water (mL)
1:1	1:9	F1	10	0.15	1.35	0.15
	2:8	F2	10	0.3	1.2	0.3
	3:7	F3	10	0.45	1.05	0.45
	4:6	F4	10	0.6	0.9	0.6
	5:5	F5	10	0.75	0.75	0.75
2:1	4:6	F6	10	0.6	0.9.	0.6
	5:5	F7	10	0.75	0.75	0.75
	6:4	F8	10	0.9	0.6	1.90
	7:3	F9	10	1.05	0.45	2.00
	8:2	F10	10	1.2	0.3	2.10
3:1	6:4	F11	10	0.9	0.6	3
	7:3	F12	10	1.05	0.45	3.2
	8:2	F13	10	1.2	0.3	4.01
	9:1	F14	10	1.35	0.15	5.2
	1:9	F15	10	0.15	1.35	2.25

60, and 90 days samples were withdrawn. Percent yield, entrapment efficiency, and *in-vitro* release studies were carried out thereafter [20].

RESULTS AND DISCUSSION

Solubility studies

Initially, preliminary solubility studies were conducted for the selection of appropriate excipient from various (Oils – Labrafac PG, Peceol, Acrysol k-150, Capryol PGMC, Oleic acid, and Miglynol 812N; Surfactants – Lauroglycol, Tween 20, Cremophor EL, Kolliphor ELP, and Kolliphor HS 15; and Co-surfactants – PEG 200, Capryol PGE, Brji-35, and Capmul MCM). The solubility of pure drug was 0.009 mg/mL. Peceol, Tween 20, and Capmul MCM were selected as oil, surfactant, and co-surfactant, respectively, on drug solubility basis. The solubility values of drug in these polymers were the highest in comparison to pure drug and other polymers. (Tables 2-4 and Figs. 1-3).

Pseudo-ternary phase diagram

Peceol, Tween 20, and Capmul MCM were selected as oil, surfactant, and co-surfactant, respectively, by the study of solubility studies. From the ternary phase diagram (Fig. 4), it was observed that self-emulsifying region was enhanced with increasing the concentrations of surfactant and co-surfactant with oil. The efficiency of self-emulsification was good when the surfactant concentration increased.

Table 2: Solubility studies of efavirenz in various oils

Oils	Solubility (mg/ml)
Labrafac PG	198.21±0.43
Peceol	288.12±0.31
Acrysol K-150	170.51±0.16
Capryol PGMC	93.27±0.17
Oleic acid	42.56±0.52
Miglynol 812N	120.27±0.48

Table 3: Solubility studies of efavirenz in various surfactants

Surfactants	Solubility (mg/ml)
Lauroglycol	137.2±0.72
Cremophor EL	190.3±0.43
Tween 20	267.2±0.62
Kolliphor ELP	150.42±1.11
Kolliphor HS 15	188.22±2.08

Table 4: Solubility studies of efavirenz in various co-surfactants

Co-surfactants	Solubility (mg/ml)
PEG 200	235.26±0.49
Capryol PGE	98.37±0.29
Brij 35	130.59±0.17
Capmul MCM	295.37±0.17
Capryol 90	220.17±0.27

Table 5: Visual observation test for Smix (surfactant: co-surfactant) ratio 1:1

Oil:Smix	Time of self-emulsification (min)	Grade
1:9	<1	I
2:8	<1	I
3:7	<1	I
4:6	<1	I
5:5	<1	I
6:4	<1	I/II
7:3	<1	I
8:2	<2	III
9:1	<2	III

Visual observation

Emulsion formation tendency was noted by the visual observation method. This test was performed on different formulations prepared by varying ratios of surfactant and co-surfactant ratio (Smix) as 1:1, 2:1, and 3:1. Based on micro-emulsion formation tendency, grades were given to the ratios. Ratios 1:9, 2:8, 3:7, 4:6, and 5:5 of Smix 1:1, 4:6, 5:5, 6:4, 7:3, and 8:2 of Smix 2:1, and 6:4, 7:3, 8:2, 9:1, and 1:9 of Smix 3:1 showed rapid formation of emulsion within a minute having a clear appearance. Therefore, these ratios were selected for the formulation of SNEDDS. The results are tabulated in Tables 5-7.

Preparation of EFV SNEDDS

SNEDDS of EFV was formulated using Peceol (Oil), Tween 20 (surfactant), and Capmul MCM (co-surfactant). In the present study, 15 formulations were prepared, and their complete composition is shown in Table 1. All the formulations prepared were found to be clear and transparent. Pictorial representations of formulations F1-F15 are shown in Fig. 5.

Thermodynamic stability studies

Insignificant phase separation was observed along with negligible varying temperature effects on prepared formulations. Visual

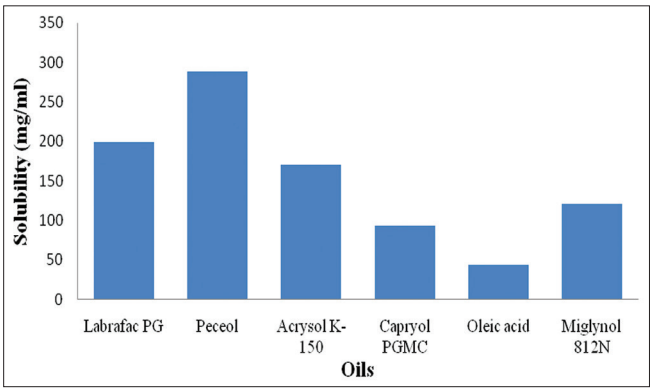

Fig. 1: Solubility studies of efavirenz in oils

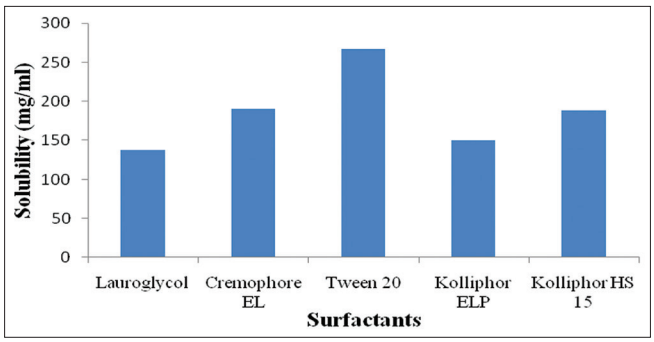

Fig. 2: Solubility studies of efavirenz in surfactant

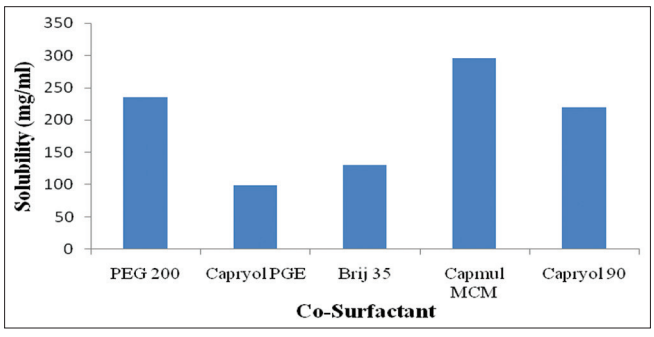

Fig. 3: Solubility studies of efavirenz in co-surfactants

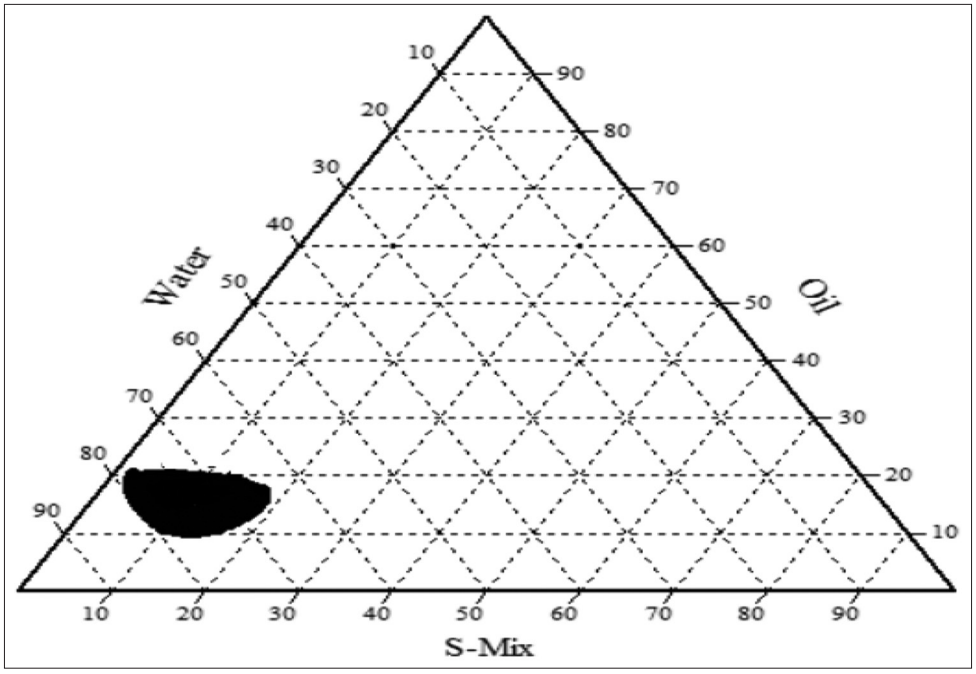

Fig. 4: Ternary phase diagram of peceol, tween 20+Capmul MCM, and water

Table 6: Visual observation test for Smix (surfactant: co-surfactant) ratio 2:1

Oil:Smix	Time of self-emulsification (min)	Grade
1:9	<1	I/II
2:8	<1	I/II
3:7	<2	III
4:6	<1	I
5:5	<1	I
6:4	<1	I
7:3	<1	I
8:2	<1	I
9:1	<2	III

Table 7: Visual observation test for Smix (surfactant: co-surfactant) ratio 3:1

Oil:Smix	Time of self-emulsification (min)	Grade
1:9	<1	I
2:8	<2	III
3:7	<2	III
4:6	<1	I/II
5:5	<1	I/II
6:4	<1	I
7:3	<1	I
8:2	<1	I
9:1	<1	I

inspection of samples after centrifugation freeze-thaw cycles indicated no significant changes. Thermodynamically stable formulations were chosen for other characterization (Table 8).

Percent transmittance measurement

The emulsions were checked for transparency, measured in terms of transmittance (%T). SNEDDS forms o/w emulsion since water is external phase Formulation F13 has percent transmittance value >99% which demonstrates high clarity of emulsion. In general, emulsions exhibiting less clarity have t<99% due to higher globule size that might be the reason for reduction in emulsion transparency and thereby values of %T (Table 9).

Fig. 5: Formulation No. 1 to No. 15

Drug content of SNEDDS

Actual drug content of in total 15 formulations is specified in Table 9. The drug content of formulated SNEDDS was in the range of 90.66–98.56%. A maximum drug release of 98.56% was noted for formulation F13.

***In-vitro* dissolution studies of SNEDDS**

Formulation of SNEDDS presents drug in a more solubilize form as droplets that on exposure to the dissolution medium result in rapid drug desolvation. F13 formulation exhibited faster and maximum amount of drug release when compared to other SNEDDS formulations and pure drug clearly illustrating effect of droplet size on drug dissolution rate. (Tables 10-12 and Figs. 6-8)

Interpretation of FTIR data

The IR spectra of pure drug rosuvastatin showed the presence of principal peaks responsible for different drug excipient interaction is mainly identified by FT-IR spectrums of the both. The wave number 3396.76 cm^{-1} due to stretching vibration of O-H; 2856.7 cm^{-1} due to C-H stretching vibrations; 1375.29 cm^{-1} due to C-F stretching vibrations, and 835.21 cm^{-1} due to C=C bending confirm the drug purity. Optimized formulations FTIR spectra had similar fundamental peaks and pattern.

Table 8: Thermodynamic stability studies of the formulations

Formulation code	Centrifugation	Freeze-thaw method	
		−20°C for 2 days	+40°C for 2 days
F1	No phase separation	No change	No change
F2	No phase separation	No change	No change
F3	No phase separation	No change	No change
F4	No phase separation	No change	No change
F5	No phase separation	No change	No change
F6	No phase separation	No change	No change
F7	No phase separation	No change	No change
F8	No phase separation	No change	No change
F9	No phase separation	No change	No change
F10	No phase separation	No change	No change
F11	No phase separation	No change	No change
F12	No phase separation	No change	No change
F13	No phase separation	No change	No change
F14	No phase separation	No change	No change
F15	No phase separation	No change	No change

Table 9: Percentage transmittance of different formulations

S. No.	Formulation code	Visual observation	% Transmittance	% Drug content
1.	F1	Transparent	84.30	92.78
2.	F2	Transparent	92.14	96.44
3.	F3	Transparent	90.67	95.77
4.	F4	Slightly clear	85.37	93.12
5.	F5	Turbid	65.77	97.39
6.	F6	Transparent	92.98	94.89
7.	F7	Slightly clear	75.49	92.74
8.	F8	Slightly clear	79.67	94.33
9.	F9	Transparent	94.30	91.27
10.	F10	Slightly clear	82.77	90.66
11.	F11	Slightly clear	85.67	93.48
12.	F12	Turbid	62.79	96.48
13.	F13	Transparent	98.96	98.56
14.	F14	Slightly clear	89.63	95.31
15.	F15	Slightly clear	90.68	93.12

Table 10: Dissolution profiles of efavirenz self-emulsifying drug delivery systems from F1 to F5

Time (min)	Dissolution media – phosphate buffer pH 6.8 (% drug release) formulation code F1-F5 (1:1)					
	Pure drug	F1	F2	F3	F4	F5
0	0	0	0	0	0	0
2	5.66±0.07	14.04±0.90	12.32±0.85	10.38±0.84	13.36±0.86	11.89±0.84
5	8.49±0.59	19.36±0.99	20.98±1.10	18.39±0.98	23.45±1.20	24.36±1.21
10	11.39±0.85	22.45±1.15	28.38±1.45	25.67±1.19	32.98±2.37	30.38±2.35
15	14.98±0.90	35.77±2.36	35.17±2.36	30.37±2.32	48.16±3.32	38.96±2.36
20	22.39±1.15	47.32±3.32	42.80±3.34	40.89±3.32	55.39±3.99	49.35±3.33
25	28.39±1.45	52.14±3.98	54.38±3.99	49.38±3.34	62.78±4.08	55.96±3.99
30	32.47±2.25	65.74±4.02	66.32±4.08	58.90±3.99	77.18±4.22	79.36±4.22
45	38.12±2.98	86.39±4.38	78.38±4.23	75.39±4.20	83.49±4.92	85.32±4.36
60	45.16±3.15	90.24±5.01	91.39±5.01	89.90±4.99	92.90±5.02	91.90±5.01

Table 11: Dissolution profiles of efavirenz self-emulsifying drug delivery systems from F6 to F10

Time (min)	Dissolution media – Phosphate buffer pH 6.8 (% drug release) formulation code F6-F10 (2:1)					
	Pure drug	F6	F7	F8	F9	F10
0	0	0	0	0	0	0
2	5.66±0.07	9.89±0.80	12.36±0.86	14.38±0.94	11.36±0.85	10.38±0.81
5	8.49±0.59	18.36±0.98	20.98±1.20	22.36±1.21	24.38±1.25	19.45±0.99
10	11.39±0.85	24.32±1.25	28.39±1.45	31.45±2.32	35.36±2.30	26.39±1.28
15	14.98±0.90	38.36±1.89	37.15±2.98	40.39±2.98	42.36±2.98	35.17±2.30
20	22.39±1.15	44.12±2.32	43.18±3.10	49.47±3.10	51.32±3.05	47.38±3.09
25	28.39±1.45	56.90±2.89	58.39±3.02	52.31±3.05	60.23±3.51	54.98±3.08
30	32.47±2.25	69.31±3.58	66.45±3.58	61.36±3.50	72.38±4.08	75.39±4.09
45	38.12±2.98	79.36±4.10	80.39±4.80	75.56±4.15	89.47±4.98	84.38±4.80
60	45.16±3.15	89.92±4.98	91.28±5.01	90.45±5.00	92.35±5.02	93.66±5.02

Table 12: Dissolution profiles of efavirenz self-emulsifying drug delivery systems from F11 to F15

Time (min)	Dissolution media – Phosphate buffer pH 6.8 (% drug release) formulation code F11-F15 (3:1)					
	Pure drug	F11	F12	F13	F14	F15
0	0	0	0	0	0	0
2	5.66±0.07	9.36±0.80	11.45±0.85	17.32±0.97	13.48±0.88	15.39±0.95
5	8.49±0.59	18.36±0.98	20.45±1.20	28.92±1.45	22.36±1.21	24.98±1.25
10	11.39±0.85	28.36±1.45	31.45±2.32	40.67±2.98	35.48±2.32	38.36±1.89
15	14.98±0.90	34.38±2.32	38.49±2.98	55.36±2.89	42.38±310	45.39±2.32
20	22.39±1.15	42.36±3.10	49.16±3.10	67.39±3.58	54.36±2.89	58.39±3.02
25	28.39±1.45	53.45±3.05	55.42±2.89	72.39±4.08	62.39±3.55	65.23±3.58
30	32.47±2.25	64.39±3.55	68.36±3.58	80.39±4.80	70.98±4.08	72.15±4.08
45	38.12±2.98	79.86±4.10	81.32±4.80	89.38±4.98	85.49±4.80	88.91±4.98
60	45.16±3.15	89.45±4.99	91.45±5.01	98.39±5.10	94.36±5.05	93.45±5.04

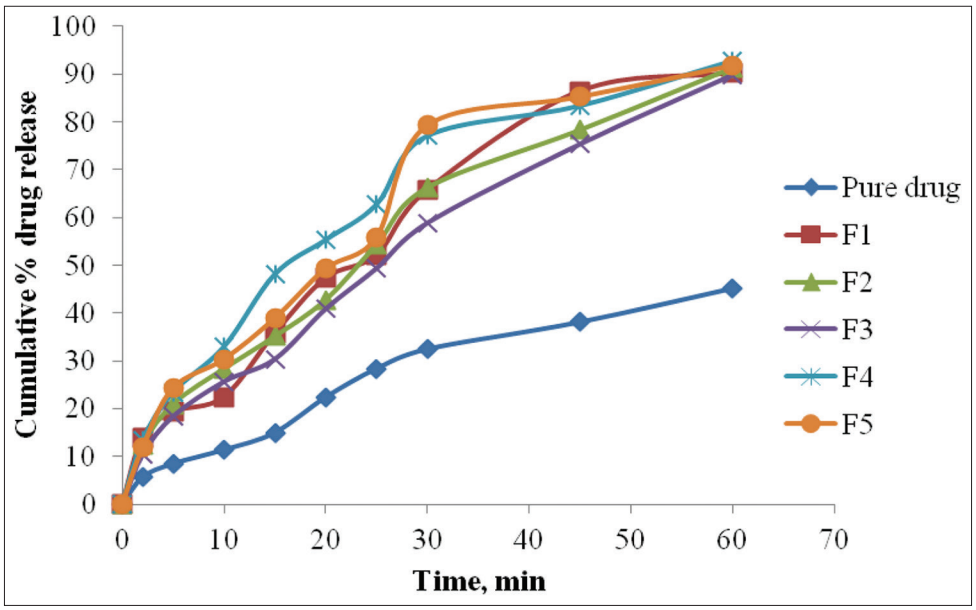

Fig. 6: Dissolution profiles of efavirenz pure drug and formulations (F1 to F5)

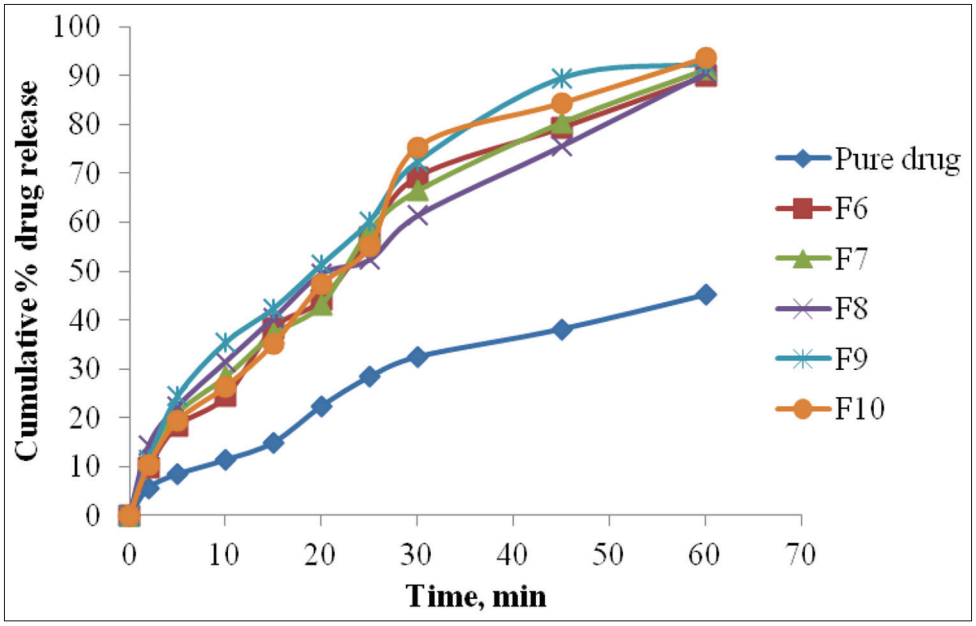

Fig. 7: Dissolution profiles of efavirenz pure drug and formulations (F6 to F10)

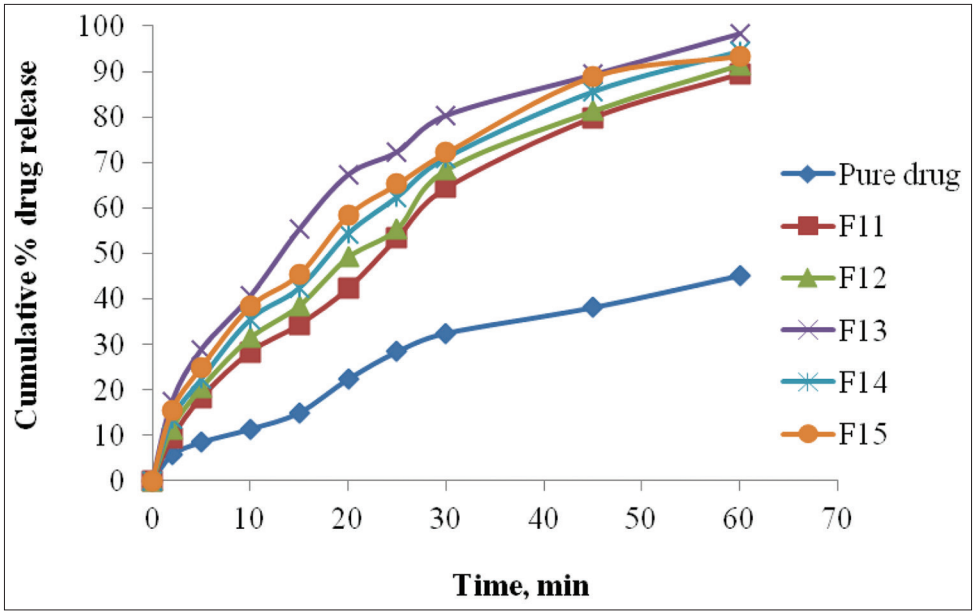

Fig. 8: Dissolution profiles of efavirenz pure drug and formulations (F11 to F15)

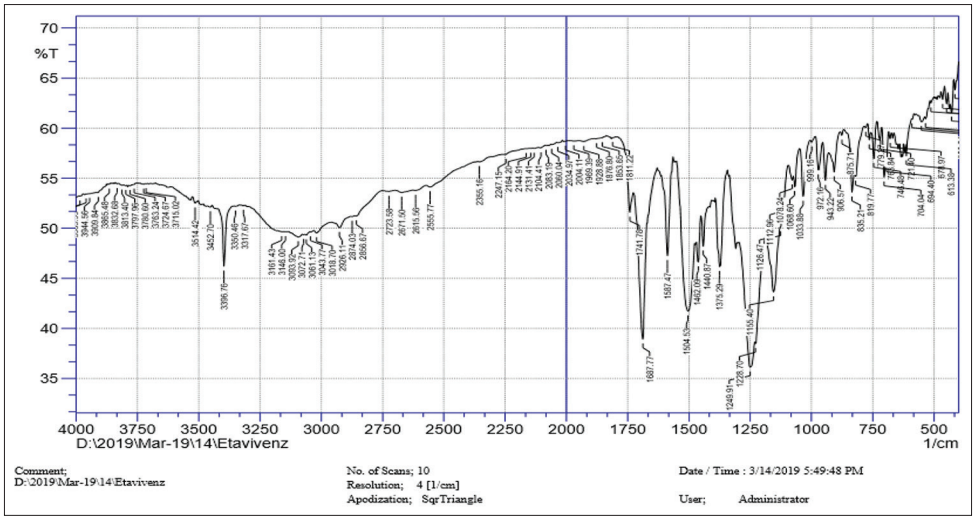

Fig. 9: Fourier transform infrared spectrum of pure drug

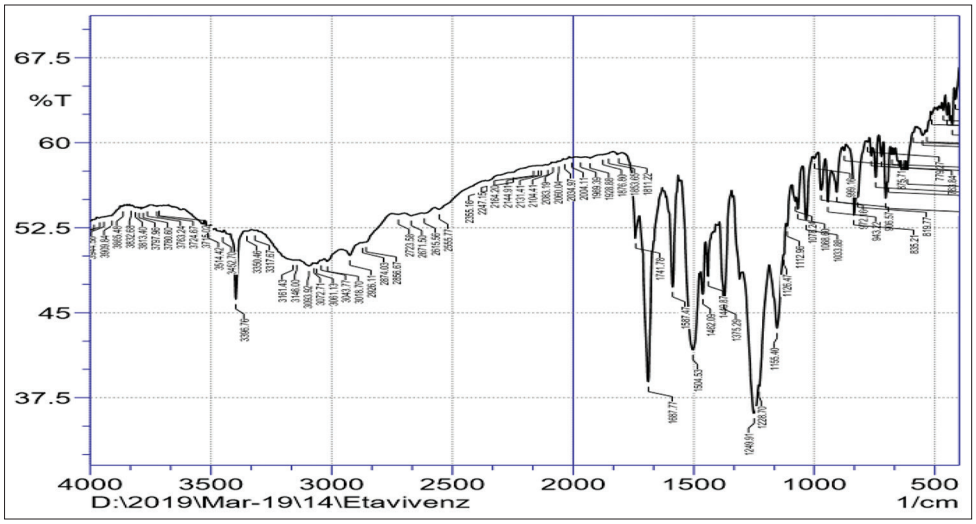

Fig. 10: Fourier transform infrared spectrum of optimized formulation (F13)

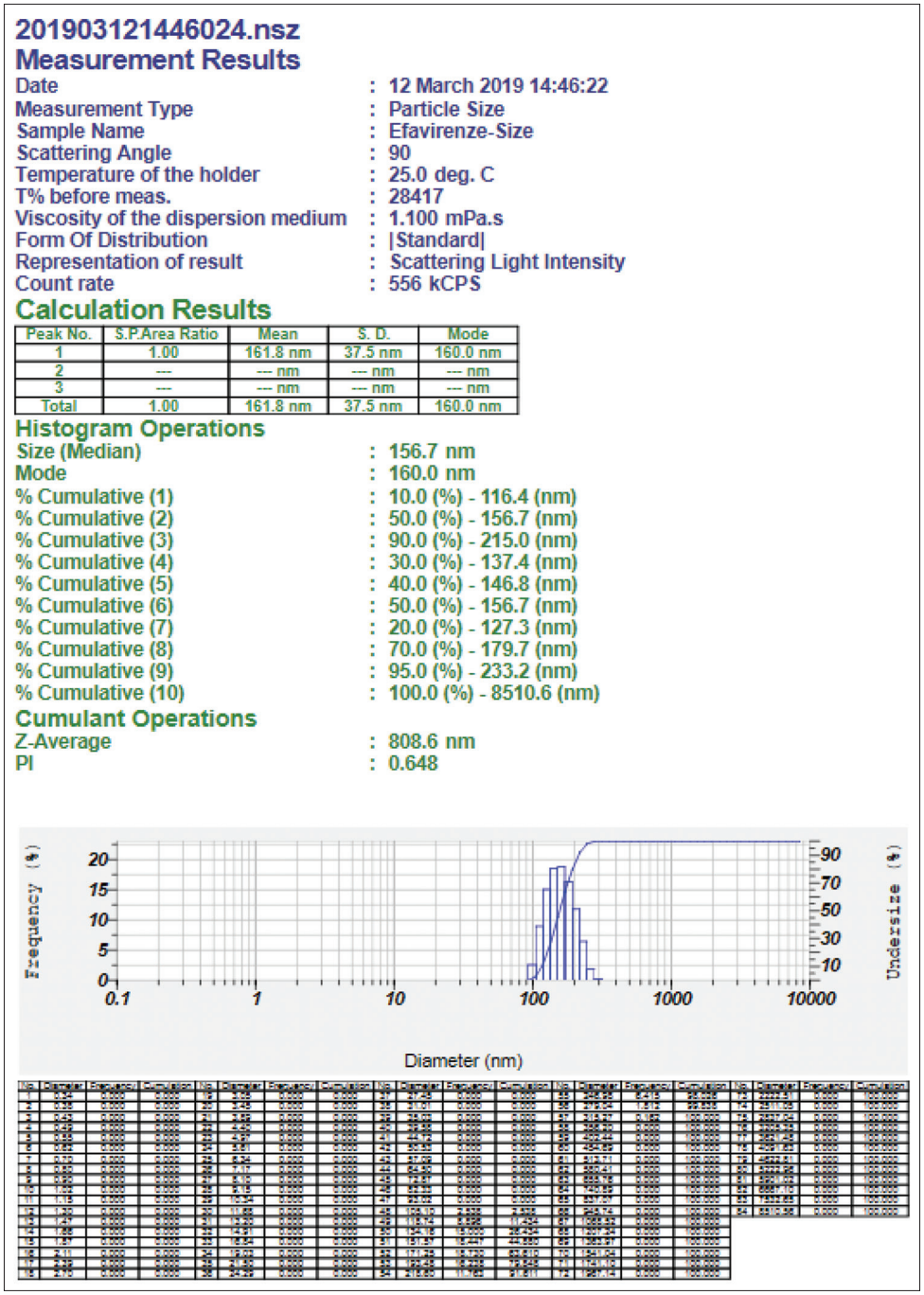

Fig. 11: Particle size analysis of optimized formulation (F13) of efavirenz self-emulsifying drug delivery systems

Thus, there are no significant interactions among the drug and excipients. (Figs. 9 and 10).

Particle size analysis of SNEDDS

Droplet size is a crucial factor that regulates the drug release rate and extent in addition to absorption profile of the drug. An enhanced bioavailability because of rapid absorption is achieved due to relative increase in interfacial surface area resulting from decreased particle size. An excellent bioavailability has been observed with SNEDDS exhibiting an average droplet size below 200 nm. Optimized SNEDDS formulation had an average droplet was found to be 156.7 nm and Z-Average of 808.6 nm with a clear indication of nanometer size ranged droplets (Fig. 11).

Zeta potential of SNEDDS

Zeta potential is responsible for the extent of repulsion between similar charged, adjacent dispersed droplets. A zeta potential value of ±30 mV is sufficient for the stability of a micro emulsion. Optimized formulation had zeta potential of −18.3 mV that was in accordance with the zeta potential required for stability (Fig. 12).

SEM for EFV SNEDDS

SEM studies of optimized formulation (F13) revealed oval-shaped globules. The size is within nanometers. There are clear liquid droplets without any pores (Fig. 13).

Stability studies

Six months stability study was performed on hard gelatin capsules, filled with EFV SNEDDS F13 formulation. Insignificant change in the release of drug and its contents was observed. There was no significant change in drug content and drug release. The compatibility of formulation with the hard gelatin capsule shells was also noted without any sign of capsule shell deformation.

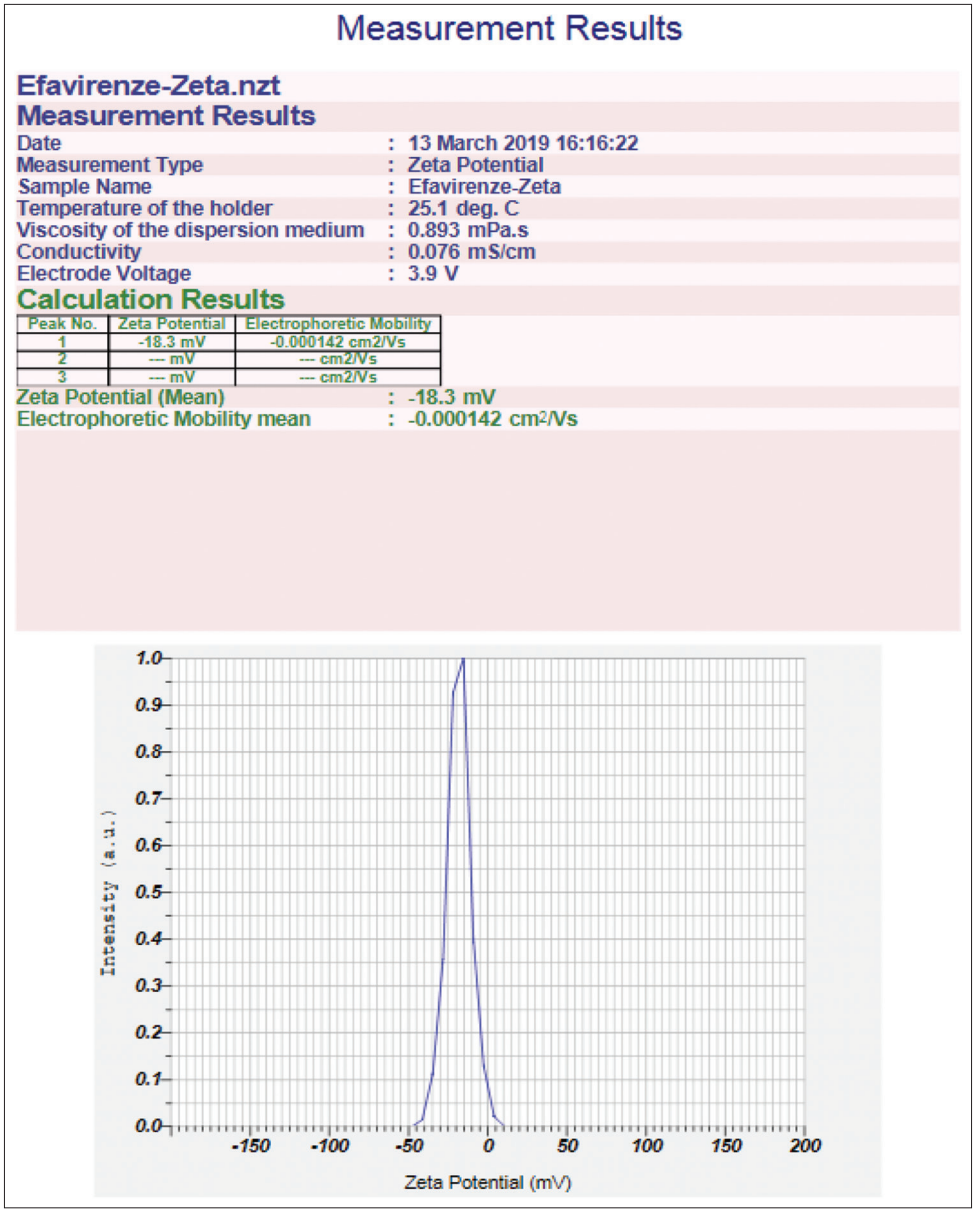

Fig. 12: Zeta potential of the optimized formulation (F13) of efavirenz self-emulsifying drug delivery systems

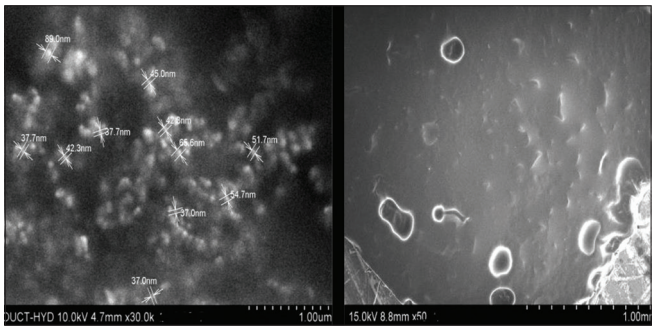

Fig. 13: Scanning electron microscopy of optimized self-emulsifying drug delivery systems formulation

There was negligible change in appearance or microemulsifying property.

SUMMARY AND CONCLUSION

Different formulations of EFV were formulated using different polymers. From solubility studies, it was observed that EFV showed good solubility in Peceol (Oil), Tween 20 (surfactant), and Capmul MCM which were then chosen as oil, surfactant, and co-surfactant, respectively. Study of pseudo-ternary phase diagram with Peceol, Tween 20, and Capmul MCM as oil, surfactant, and co-surfactant, it was observed that self-emulsifying region was enhanced with increasing concentrations of surfactant and co-surfactant with oil. The drug content of all the formulations was performed with maximum drug content of Formulation F13 that was then selected as optimized one based on other parameters tested. The average droplet size of F13 formulation was 156.7 nm and Z-Average of 808.6 nm with clear indication of nanometer ranges particles. The zeta potential of the optimized SNEDDS formulation was found to be −18.3 mV which was in accordance with the zeta potential required for stability. Thus, this emulsion may serve as a promising alternative approach for the oral delivery of EFV with increased bioavailability.

AUTHOR CONTRIBUTION

All authors contributed equally.

CONFLICT OF INTEREST

No conflict of interest by authors.

REFERENCES

1. Mistry RB, Sheth NS. A review: Self emulsifying drug delivery system. Int J Pharm Pharma Sci 2011;3:238.
2. Saurabh SS, Issarani R, Nagorib P. Formulation and evaluation of selfemulsifying drug delivery system of etoricoxib. Asian J Pharm Clin Res 2017;10:367-72.
3. Vijaykumar N, Sandeep K. Development of novel lipid based drug delivery system forraloxifine hydrochloride. Int Res J Pharm 2012;3:2230-8407.
4. PatroSisinthy S, Rao NK, Sarah CL. Design, optimization and *In vitro* characterization of self nano emulsifying drug delivery system of olmesartan medoxomil. Int J Pharm Sci 2011;3:238.
5. Koh PT, Chuah JN, Talekar M, Gorajana A, Garg S. Formulation development and dissolution rate enhancement of efavirenz by solid dispersion systems. Indian J Pharm Sci 2013;75:291-301.
6. Venkateswara Reddy B, Krishna Veni K. Formulation and evaluation of efavirenz microspheres. Der Pharm Lett 2015;7:1-9.
7. Basalious EB, Shawky N, Badr-Eldin SM. SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I: Development and optimization. Int J Pharm 2010;391:203-11.
8. Patel J, Kevin G, Patel A, Raval M, Sheth N. Design and development of a self-nanoemulsifying drug delivery system for telmisartan for oral drug delivery. Int J Pharm Investig 2011;1:112-8.
9. Sermkaew N, Ketjinda W, Boonme P, Phadoongsombut N, Wiwattanapatapee R. Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from a crude extract of *Andrographis paniculata*. Eur J Pharm Sci 2013;50:459-66.
10. Kaur G, Chandel P, Harikumar SL. Formulation development of self nanoemulsifying drug delivery system (snedds) of celecoxib for improvement of oral bioavailability. Pharmacophore 2013;4:120-33.
11. Gupta AK, Mishra DK, Mahajan SC. Preparation and in-vitro evaluation of self-emulsifying drug delivery system of antihypertensive drug Valsartan. Int J Pharm and Life Sci 2011;2:633-9.
12. Bhikshapathi DV, Madhukar P, Dilip KB, Aravind KG. Formulation and characterization of Pioglitazone HCl self-emulsifying drug delivery system. Sch Res Library 2013;5:292-305.
13. Chirag R. Enhanced oral bioavailability of olmesartan by using novel solid SNEDDS. Int J Adv Pharm 2012;2:82-92.
14. Kapil A, Aggarwal G, Harikumar S. Formulation and evaluation of nano suspension and nano emulsion of rosuvastatin and their comparative study. Asian J Biochem Pharm Res 2015;1:101-16.
15. Nasr V, Gardouh A, Ghorab A. Novel Solid Self-Nano emulsifying drug delivery System (S-SNEDDS) for oral delivery of olmesartan medoxomil: Design formulation, pharmacokinetic and bioavailability evaluation. Pharmaceutics 2016;8:1-29.
16. VanitaSagar S, Subhashini NJ. Self-nano emulsion drug delivery system of fenofibrate with improved bio-availability. Int J Pharm Bio Sci 2013;4:511-21.
17. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm 2007;329:166-72.
18. Ruan G, Feng SS. Preparation and characterization of poly(lactic acid)-poly(ethylene glycol)-poly(lactic acid) (PLA-PEG-PLA) microspheres for controlled release of paclitaxel. Biomaterials 2003;24:5037-44.
19. Ke Z, Hou X, Jia XB. Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine D. Drug Des Devel Ther 2016;10:2049-60.
20. Lalit KT, Mohan LK. Stability study and *In-vivo* evaluation of lornoxicam loaded ethyl cellulose microspheres. Int J Pharm Sci Drug Res 2014;6:26-30.