Indian Journal of Pharmaceutical Education and Research | Association of Pharmaceutical Teachers of India

Preparation and Evaluation of Self-nanoemulsifying Formulation of Efavirenz

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ABSTRACT

Submitted: 20/03/2012 Revised: 23/08/2012 Accepted: 14/12/2012

Efavirenz is an antiretroviral drug which exhibits lower absorption in gastric fluid due to poor water solubility characteristics. Self-nanoemulsifying drug delivery systems (SNEDDS) were designed with the objective of improving the solubility and dissolution rate of the drug. Solubility of efavirenz was determined in various vehicles, which includes oils (/modified oils), surfactants and co-surfactants. Pseudo-ternary phase diagrams were constructed to identify the most efficient self-emulsification region. Based on the solubility labrafac PG(oil), tween 80 (surfactant), PEG 200 (Cosurfactant) were selected for preparation of SNEDDS. FTIR spectroscopy was performed in order to investigate the interaction between any of the ingredients used in the formulation. The prepared formulations were evaluated for thermodynamic stability (centrifugation, heating cooling cycle (H/C cycle), freeze thaw cycle), dispersibility, robustness to dilution, particle size measurements, zeta potential, refractive index, percent transmittance, viscosity, drug content and *In vitro* drug release. The FTIR data confirms that there is no interaction between the drug and the excipients. The optimized efavirenz SNEDDS contains labrafac PG(15%), Tween 80(19%) and PEG 200(38%) which shows mean globule size of 142.8 nm. *In vitro* drug release of the formulation was found to be 97.4 % in 20min whereas pure drug shows only 22.4% at the end of 30 min. The stability study of prepared SNEDDS shows same physicochemical properties as compare to initial SNEDDS after 3 month storing in stability chamber at 40°C and 75%RH.

Keywords: Efavirenz, antiretroviral, SNEDDS, Pseudo-ternary phase diagrams, thermodynamic stability

INTRODUCTION

The oral delivery of poorly water soluble drugs is frequently associated with implications of low bioavailability and high intra- and intersubject variability[1]. To overcome such problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, solid dispersions, micronization, permeation enhancers and lipids[2]. The use of lipid and surfactant based formulations is one of several approaches that has been applied in order to improve the oral bioavailability of poorly aqueous soluble compounds intended for oral administration[3]. Self emulsifying formulations can enhance the bioavailability of poorly water-soluble drugs due to the relatively small size of the dispersed oil droplets and the very high surface area to volume ratio, which may result in faster drug release from the emulsion in a reproducible manner and make the release characteristics independent of the gastro-intestinal physiology and the fed/fasted state of the patient[4]. Dosing drug substances that exhibit poor water solubility but sufficient lipophillic properties, in a predissolved state, for example in lipid-based formulations, are beneficial since the energy input associated with a solid–liquid phase transition is avoided, thus overcoming the slow dissolution process after oral intake[5].

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The human immunodeficiency virus (HIV) infects cells of the immune system, destroying these cells as well as the immune system's ability to fight off the invaders6. EFV is a first-choice non-nucleoside reverse transcriptase inhibitor used in the High Activity Antiretroviral Therapy (HAART) of the infection by the Human Immunodeficiency Virus (HIV) in both adults and children. Due to its high lipophilicity (log P = 5.4) and consequently poor aqueous solubility, the drug shows relatively low oral absorption and bioavailability (40–45%) and high inter-subject variability[7].There were few studies attempted to enhance the aqueous solubility of efavirenz. The results of some research work shows that solubility of efavirenz was significantly increased by solid dispersions techniques using PEG 6000[8,9]. In another research study, Poloxamines diblocks connected to a central ethylenediamine group were N-methylated and N-allylated with the objective of increasing their versatility as drug nanocarriers. Pristine and N-alkylated poloxamines emerged as highly efficient EFV solubilizers enhancing the aqueous solubility of the drug[6]. Chiappetta DA et al., developed a concentrated formulation of efavirenz by means of encapsulation within polymeric micelles. The aqueous solubility of the drug was improved significantly and preliminary preclinical data suggested the significantly greater oral bioavailability with respect to an extemporaneous suspension and an oleous solution[7]. In this research study, it is aimed to develop Efavirenz SNEDDS so that the solubility of the drug is improved which leads to better drug bioavailibility.

MATERIALS AND METHODS

Materials

Efavirenz was provided as a gift sample from Shasun labs(Pondicherry, India). Labrafac PG, Labrafil were generous gift from Gattefosse, France (through Bombay College of Pharmacy, Mumbai). Capmul MCM, Captex 200 was a gift sample provided from Abitec Group, (USA). Span 80, Triethanolamine, PEG 800, PEG 200, Oleic acid, Castor oil were purchased from Merck (Mumbai). Tween 80, Tween 20, Ethyl oleate were purchased from Loba chemie pvt ltd, Mumbai. All other chemicals and buffers used were of analytical grade.

Solubility studies

Screening of excipients can be done by determining the equilibrium solubility of efavirenz in different oils and surfactants. Two ml of each of selected oil, surfactant sample was added in glass vial containing excess amount of efavirenz, the drug was mixed in oil manually with glass rod for ½ h, after that the vials were kept in sonicator for 2 h. Mixture was kept in water bath for 48 h for reaching the equilibrium. After 48 h these vials were centrifuged at 3000 rpm for 20 m. After centrifugation the amount of dissolved drug was determined by diluting the supernatant in methanol by UV- spectrophotometer at 247 nm[10].

Compatibility Study

Chemical interaction between the drug, lipid and surfactants were studied by FTIR technique. For this blank KBr pellets were made and lipid, surfactant and cosurfactant were directly dropped onto the pellet individually and the two blank KBr pellets were pressed together like a sandwich using hydraulic press at 15 tons pressure. For pure drug it is mixed with KBr in 1:3 ratio and punched in a hydraulic press. It was scanned from 4000 to 400 cm^{-1} in a FT-IR spectrophotometer (FT-IR 8400 S, Shimadzu). The IR spectrum of the physical mixture was compared with those of pure drug, lipid and surfactants and peak matching was done to detect any appearance or disappearance of peaks.

Construction of pseudoternary phase diagram[11,12,13]

Pseudoternary phase diagrams of oil, surfactant/ cosurfactant (S/CoS), and water were developed using the water titration method. From these, the extent of nanoemulsion region can be identified and its relation to other phases can be established. The pseudo-ternary phase diagrams were constructed by drop wise addition of distilled water to homogenous liquid mixture of oil, surfactant, and co-surfactant, at ambient temperature. From the result of solubility studies labrafac PG, tween 80 and PEG 200 were selected as oily phase, surfactant and co-surfactant respectively.

The mixtures of oil and Smix(surfactant/cosurfactant) at certain weight ratios were diluted with water in a dropwise manner. For each phase diagram at a specific ratio of Smix (ie, 1:0, 1:1, 2:1, 3:1, and 4:1wt/wt), a transparent and homogenous mixture of oil and Smix was formed by vortexing for 5 m. Then each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements.

Through visual observation the following categories were assigned:

1. Transparent and easily flowable: oil/water nanoemulsions

2. Transparent gel: nanoemulsion gel

3. Milky or cloudy: emulsion

4. Milky gel: emulgel

Phase diagrams were then constructed using Chemix software (Arne Standnes, Ytre Laksevag, Norge)

Selection of formulations

From each phase diagram constructed different formulations were selected from NE region so that drug could be incorporated into it on the following basis.

1. 50mg of efavirenz was selected as the dose for incorporation into the oil phase.

2. From each phase diagram, different concentrations of oils were selected at a difference of 5% (10%, 15%, 20%, 25%, etc) from the NE region.

3. For each 5 % of oil selected, the formula that used the minimum concentration of Smix for its NE formulation was selected from the phase diagram.

EVALUATION

Thermodynamic stability tests: The problem of selecting metastable formulation can be overcome by performing thermodynamic stability studies. Formulations selected from ternary phase diagram were subjected to different thermodynamic stability tests.

Centrifugation: Selected formulations from phase diagrams were centrifuged at 3500 rpm for 30 m and observed for phase separation, creaming and cracking. Those formulations which were stable were taken for heating cooling cycle.

Heating cooling cycle (H/C cycle): Stability of SNEDDS on variation of temperature was studied by H/C cycle. Six cycles between refrigerator temperature 4°C and 45°C with storage at each temperature of not less than 48 h was studied. Those formulations, which were stable at these temperatures, were subjected to freeze thaw cycle.

Freeze thaw cycle: Three freeze thaw cycles between – 21°C and +25°C with storage at each temperature for not less than 48 h was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility tests for assessing the efficiency of selfemulsification.[14]

Dispersibility tests

The efficiency of dispersibility of formulation was assessed using a standard USP XXII dissolution apparatus 2. One ml of each formulation was added to 500 ml of water respectively at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50rpm provided gentle agitation .The *in vitro* performance of the formulations was visually assessed using the grading system as shown below.

Grade A: Rapidly forming (within 1 m) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 m.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 m).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.[15,16]

Those formulations that passed the thermodynamic stability and also dispersibility tests in Grade A and B were selected for further studies.

Robustness to dilution:

Robustness to dilution was studied by diluting it 50, 100 and 1000 times with various dissolution media viz. water and 0.1 N HCl. The diluted nanoemulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.[17]

Particle Size Measurements

The mean globule size and polydispersity index (P.I.) of the resulting nanoemulsions were determined by photon correlation spectroscopy, which analyses the fluctuations in light scattering due to Brownian motion of the particles using a Zetasizer 3000 (Malvern Instruments Worcestershire, UK) Light scattering was monitored at 25ºC at a 90ºangle.

Zeta potential determination[1]

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SNEDDS formulation was measured using a Malvern Zetasizer 3000. (Malvern Instruments Worcestershire, UK).

Viscosity[18]

Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc, Middleboro, MA, spindle # CPE40) was used to determine the viscosity of different formulations at 25 ± 1.0°C. The software used for the calculations was Rheocalc V2.6.

Refractive index and percent transmittance

The refractive index of the system was measured using Abbe refractometer by placing 1 drop of nanoemulsion on the slide. The percent transmittance of the system was measured using UV spectrophotometer (Shimadzu, Japan) keeping distilled water as blank.

Drug content estimation

Efavirenz was extracted from the SNEDDS by dissolving in methanol later it was analyzed spectrophotometrically at 247 nm, against solvent blank.

Drug release studies[19]

Drug release studies from SNEDDS were performed using dissolution apparatus II containing 900mL of 0.1N HCl as dissolution medium at 37±0.5°C. The speed of the paddle was adjusted to 50 rpm. 50 mg drug equivalent of the formulation (ie 1ml) was directly introduced into the medium and a suitable aliquot(ie 5 ml) of sample was collected at 0, 5, 10, 15, 20, 30, 40, 60, 80, 160 min and with further dilutions the samples were analyzed spectrophotometrically at 247nm. An equivalent volume of fresh dissolution medium was added to compensate for the loss due to sampling.

Stability study

Optimised efavirenz SNEEDS was sealed in ampoules and then placed in stability chamber which were maintained at 40°C /75%RH for 3 months. Duplicate samples were withdrawn at 0, 1, 2 and 3 months to evaluate their physical and chemical stabilities.

RESULTS AND DISCUSSION

Solubility studies

The solubility of drug in various oils, surfactants were reported in Table no 1. The solubility of the drug in the oil phase plays an important role in stability and bulkiness of the dosage form. Efavirenz showed highest solubility in Labrafac PG (Oil), tween 80 (Surfactant) and PEG 200 (Co surfactant) than other oils and surfactants. Hence these excipients were selected for the preparation of SNEDDS.

Compatibility Study

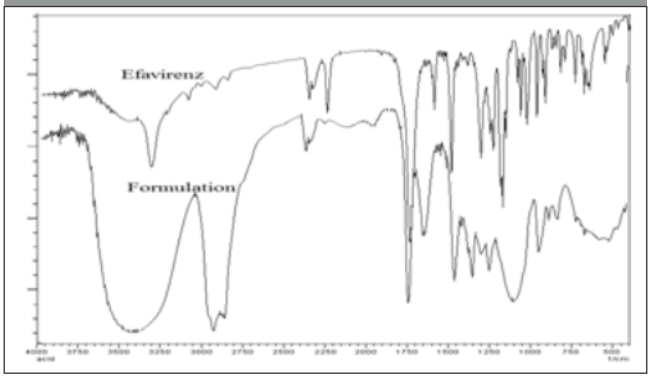
The characteristic peaks of efavirenz (3319cm^{-1}, 1060cm^{-1}, 750 cm^{-1}, 1039 cm^{-1}, 820 cm^{-1}) were not affected and prominently observed in IR spectra of efavirenz along with other excipients as shown in Fig no 1. This clearly shows there is no interaction between drug and excipients.

Table 1: Solubility of efavirenz in various vehicles.

Excipients	Solubility(mg/ml)
Ethyl oleate	173.2±2.1
Arachis oil	23.4±0.5
Castor oil	30.25±1.2
Oleic acid	36.72±0.9
Captex 200	255.4±1.6
Capmul MCM	291.7±2.1
Labrafac PG	330.2±1.3
Tween 20	256.6±1.9
Tween 80	314.89±2.1
PEG 200	793.5±1.7
PEG 800	780.1±1.9
Triethanolamine	216.7±0.8S
PAN 80	134.8±0.4
Water	<10µg/ml

Data are mean ± S.D. (n = 3).

Fig. 1: IR spectra of Pure drug and formulation



Construction of pseudoternary phase diagram

Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion regions and to optimize the concentration of the selected vehicles (Labrafac PG, Tween 80 and PEG 200). For development of a SNEDDS, optimum ratios of excipient concentrations established by means of phase diagram studies provided the area of the monophasic region. It is important to determine this area in order to ensure successful aqueous dilution without 'breaking' the nanoemulsions. Fig no 2 depicts the phase diagrams for different oil-Smix-water systems. These phase diagrams shows only nanoemulsions region, to avoid the overcrowding of phase diagram. Use of non-ionic surfactants generally leads to less toxicity along with lower critical miceller concentration (CMC) as compared to their ionic counterparts. Further, o/w nanoemulsions based on nonionic surfactants are likely to offer better in vivo stability. Transient negative interfacial tension and a fluid interfacial film are rarely achieved with the use of a single surfactant, usually necessitating the addition of a co-surfactant. The presence of co-surfactants decreases the bending stress of the interface and allows an interfacial film with sufficient flexibility to assume different curvatures required to form a nanoemulsion over a wide range of compositions.

Selection of formulations from phase diagrams

Hundreds of formulations can be prepared from the nanoemulsion region of the phase diagram. While going through pseudoternary phase diagrams, oil could be solubilized upto the extent of 42% w/w. Therefore, from each phase diagram different concentrations of oil that formed a

Fig. 2: Pseudoternary phase diagram of system with the following components: labrafac (oil), tween 80(surfactant), PEG 200(Cosurfactant). Surfactant:Cosurfactant ratio of A is 1:0, B is 1:1, C is 1:2, D is 1:3, E is 1:4, F is 2:1, G is 3:1, H is 4:1.

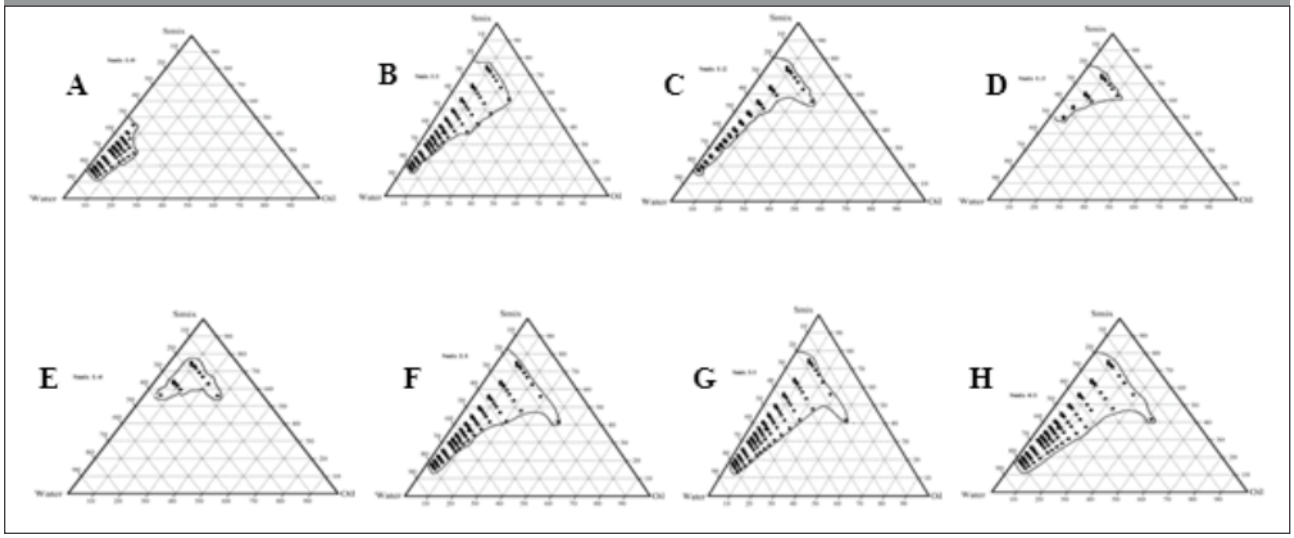


Table 2: Results of thermodynamic stability test and dispersion test

Smix	Oil	Smix	Aqueous	Centrifuge	H/C cycle	Freeze Thaw	Disperse Grade	Inference
1:0 (A)	10	15	75	Pass	Fail	Fail	D	Fail
	15	24	61	Pass	Fail	Fail	D	Fail
1:1 (B)	10	26	64	Pass	Fail	Fail	A	Fail
	15	34	51	Pass	Fail	Fail	A	Fail
	20	36	44	Pass	Fail	Fail	A	Fail
	25	48	27	Fail	Fail	Fail	A	Fail
1:2 ©	10	44	46	Pass	Fail	Fail	A	Fail
	15	57	28	Pass	Pass	Pass	A	Pass
	20	58	22	Pass	Pass	Pass	A	Pass
	25	55	20	Pass	Fail	Fail	A	Fail
1:3 (D)	10	54	36	Pass	Fail	Fail	A	Fail
	15	58	27	Pass	Fail	Fail	A	Fail
	20	60	20	Pass	Pass	Fail	A	Fail
1:4 (E)	10	54	36	Pass	Fail	Fail	A	Fail
	15	57	28	Pass	Fail	Fail	A	Fail
	20	60	20	Fail	Fail	Fail	A	Fail
	25	56	29	Pass	Fail	Fail	B	Fail
2:1 (F)	10	26	64	Pass	Fail	Fail	A	Fail
	15	37	48	Pass	Fail	Fail	A	Fail
	20	41	39	Fail	Fail	Fail	A	Fail
	25	46	29	Fail	Fail	Fail	A	Fail
	30	47	23	Pass	Fail	Fail	A	Fail
	35	46	19	Fail	Fail	Fail	A	Fail
	40	40	20	Fail	Fail	Fail	A	Fail
3:1 (G)	10	17	73	Pass	Fail	Fail	A	Fail
	15	28	57	Pass	Fail	Fail	A	Fail
	20	27	53	Pass	Fail	Fail	A	Fail
	25	47	28	Fail	Pass	Fail	A	Fail
	30	48	22	Pass	Pass	Pass	A	Pass
	35	45	20	Fail	Fail	Fail	A	Fail
	40	42	18	Fail	Fail	Fail	A	Fail
4:1 (H)	10	13	77	Pass	Fail	Fail	A	Fail
	15	25	60	Pass	Fail	Fail	A	Fail
	20	31	49	Pass	Fail	Fail	A	Fail
	25	44	31	Pass	Fail	Fail	D	Fail
	30	47	23	Pass	Fail	Fail	D	Fail
	35	46	19	Pass	Pass	Pass	D	Fail
	40	41	19	Pass	Pass	Pass	D	Fail

Table 3: Optimized formulations selected from phase diagram at a difference of 5% w/w of oil having least Smix concentration that passed thermodynamic stability test and dispersion test

Formulation	Smix ratio	Oil%	Surfactant%	Co-Surfactant%	Aqueous%
C15	1:2	15	19	38	28
C20	1:2	20	19.3	38.7	22
G30	3:1	30	36	12	22

Table 4: Data of particle size, zetapotential, polydispersibility index, Viscosity, R.I and % transmission

Formulation	Particle Size(nm)	Zetapotential (mv)	Polydispersibility ndex	Viscosity (cps)	Refractive Index (R.I)	% Transmission
C15	142.8	-2.67	0.581	21.2±0.2	1.46±0.2	97.2±1.6
C20	147.7	-4.7	0.136	24.6±0.6	1.458±0.4	98.7±0.8
G30	156.5	-3.54	0.181	29.3±0.3	1.458±0.3	95.4±1.2

Data are mean ± S.D. (n = 3).

Table 5: Comparative *in vitro* release of optimized formulations

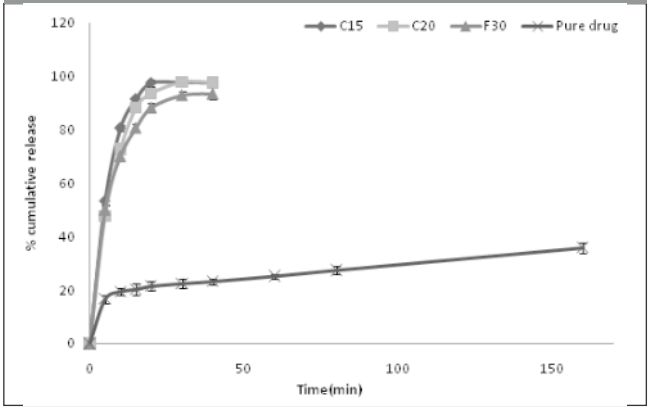
Time(min)	Pure drug	C15	C20	F30
0	0	0	0	0
5	16.6	53.4	47.4	50.2
10	19.4	80.6	72.8	70.2
15	20.24	91.4	88.2	80.8
20	21.4	97.4	93.6	88.4
30	22.4	97.6	97.8	93.0
40	23.2	97.5	97.6	93.5
60	25.2			
80	27.4			
160	35.8			

Table 6: Stability study data of optimized formulation

Testing interval	Description of Formulation	FT-IR Study	Drug content	% cumulative drug release at 10 min
Initial(0 time)	Transparent	Complies	97.42	74.72
1 month	Complies	Complies	97.39	74.70
2 month	Complies	Complies	97.34	74.67
3 month	Complies	Complies	97.29	74.65

Sample name: Efavirenz SNEDDS(C15) **Storage condition:** 40°C /75% RH

Fig. 3: *in-vitro* release profiles of optimized formulations and pure drug



nanoemulsion was selected at 5% intervals (10%, 15%, 20%, 25%, 30%, 35%, 40%) So that, largest number of formulations could be selected covering the nanoemulsion are of the phase diagram (Table no 2). For each percentage of oil selected, only those formulations were taken from the phase diagram which used minimum concentration of Smix. These optimized Oil and Smix concentrations were mixed gently for homogeneity of the formulation. The mixture was stored at room temperature until used.

EVALUATION

Formulations taken from ternary phase diagram(o/w nanoemulsion region) were subjected to thermodynamic

stability and dispersibility tests in order to eliminate metastable formulations in minimum possible time. The results were shown in the Table no 2. The formulations which passed thermodynamic test and dispersibility test were presented in Table no 3 along with their concentrations. The optimized formulations C15, C20, F30 were robust to all dilutions and did not show any phase separation or precipitation. The sequence of viscosity of prepared SNEDDS batches is as follow F30 > C20 > C15 (Table no 4). The viscosity determination shows that as the concentration of surfactant increased, viscosity of formulation also get increased. The mean particle size of the three optimized diluted SNEDDS results were shown in Table 4. All the three formulations show the particle size in nearby range. Of the three formulations C15 shows the lowest particle size when compare to the others, this is because as the concentration of oil decreases the particle size also decreases. Several studies have reported that the zeta potential played an important role in the interactions with mucus of the gastrointestinal tract. According to the reports, the positive charged droplets could have better interaction with the mucus of the gastrointestinal tract, since the intestinal cell interior carry negative charges with the presence of mucosal fluid. Aggregations will not take place due to slightly negative charge of the droplet. Because the droplets have a lower negative potential, they are likely to facilitate the intestinal absorption of efavirenz. The refractive index of the prepared formulation was similar to that of refractive index of the water (1.333). In addition, the developed system showed percent transmittance > 95%. The refractive index and percent transmittance data prove the transparency of the system as shown above. The observed transparency of the system is due to the fact that the maximum size of the droplets of the dispersed phase is not larger than $1/4^{th}$ of the wavelength of visible light. Thus, NE scatters little light and are therefore transparent or translucent. Drug content of the optimized formulations was found to be more than 97%.

Drug Release Studies

The *in vitro* drug release studies were carried in order to ensure the fast release of the drug to the dissolution medium. Furthermore, *in vitro* drug release studies also give an idea about the self-emulsification efficiency of the developed system. Surfactant molecules in the oily solvent create a system of reverse micelles, with the hydrophilic inner core and the external layer formed by hydrophobic groups of the surfactant in the oily medium. Upon mild agitation followed by dilution in aqueous medium, the reverse micellar solution undergoes transformation into a liquid crystalline system. The amount of water solubilized by the reverse micelles depends on the type and concentration of surfactant, type of oil, temperature and co-solvent concentration. The *in vitro* drug release profile of C15, C20, F30 and pure drug were evaluated in 0.1N HCl. It was observed that all the SNEDDS formulations C15, C20, F30 released more than 90% of drug within 30 m (Table no 5). Of the three formulations, C15 shows the fastest release which is due to the less oil concentration in its composition. Whereas the pure drug shows only the release of 22.4% at 30 m.

Stability study

The results of the stability study of optimized formulation stored at 40°C and 75% relative humidity for 3 month are represented in the Table no 6. No significant change in the appearance and content was observed during this period. The FTIR data remains unchanged throughout the study. The drug release behavior of the optimized formulation was remained unchanged during storage.

CONCLUSION

The complete summary of present research work conclude that SNEDDS for lipophilic Efavirenz was successful developed using labrafac PG(oil), tween 80(surfactant), PEG 200(Cosurfactant). The optimized formulation of the SNEDDS consisted of oil 15%, surfactant 19%, cosurfactant 38% which had sufficient drug loading, rapid self-microemulsification in aqueous media, and forming droplet size in the range of nanoemulsion. Significant improvement in drug solubility is achieved and thus overcomes dissolution rate-limited absorption of efavirenz with *in vitro* drug release studies.

ACKNOWLEDGMENTS

The authors are thankful to Shasun labs(Pondicherry, India) for the gift samples of Efavirenz. Further we extend thanks to Gattefosse, France (through Bombay College of Pharmacy, Mumbai) and Abitec Group (USA) for providing gift sample of excipients. Authors are thankful to the Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

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