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Research Article **Novel drug delivery system**

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DEVELOPMENT OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEMS CONTAINING EFAVIRENZ: IN VITRO AND IN VIVO EVALUATION

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ABSTRACT

Efavirenz is a drug with an absorption window. Its oral bioavailability is 40-50%. The aim of this work was to formulate solid self-emulsifying drug delivery system to improve the solubility and bioavailability of efavirenz. Solubility of Efavirenz was determined in various vehicles like oils, surfactants and co surfactants. Which, upon dilution with aqueous media, spontaneously form fine oil in water (micro) emulsion with less than 300 nm in droplet size. Pseudoternary phase diagrams were constructed to identify the self (micro) emulsifying region. Seven S(M)EDDS formulations were prepared. The optimized liquid self-emulsifying drug delivery system formulation (F3) was converted into solid S(M)EDDS with free flowing powder by adsorbing onto a solid carrier like Neusilin US2 for encapsulation. X-ray diffraction studies showed no physicochemical interaction. The in-vitro dissolution characteristics and in-vivo bioavailability studies of optimized formulation and reference standard confirmed that better systemic absorption and bioavailability also found to be increased with optimized formulation.

KEY WORDS: Adsorbent, Efavirenz, Neusilin US2, Solid self- emulsifying drug delivery system.

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INTRODUCTION

Oral route has been the major route of drug delivery for the chronic treatment of human diseases. However, oral delivery of 50% of the drug compound is hampered because of the high lipophilicity of the drug itself[1]. In drug discovery, about 40% of the new drug candidates display low solubility in water, which leads to poor bioavailability, high intra subject/inter subject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity. Therefore producing suitable formulations is very important to improve the solubility and bioavailability of such drugs[2]. Self-emulsifying systems are a useful means of improving the bioavailability of poorly water soluble drugs[3], particularly the self micro emulsifying drug delivery systems are well known for their potential as alternative strategies for delivery of hydrophobic drugs[4]. SEDDS are isotropic mixtures of drug, oil/lipid, surfactant and/or co-surfactant, which form fine emulsion/lipid droplets on dilution with physiological fluid. The drug therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state[5]. However, there exist a few limitations associated with this delivery system, including stability, manufacturing methods, interaction of the fill with the capsule shell and storage temperature. The researchers now focused on solid S(M)EDDS area were increasing. Solid S(M)EDDS prepared by solidification of liquid or semisolid selfemulsifying ingredients into powders, have gained popularity[6]. These solid S(M)EDDS were prepared by extrusion/spheronization method or wet granulation in a high shear mixer and adsorption to solid carriers involves addition of the liquid formulation onto carriers by mixing in a blender[7]. Efavirenz is a non-nucleoside reverse transcriptase inhibitor and is used as a part of highly active anti retroviral therapy for the treatment of human immunodeficiency virus type I infection[8]. Efavirenz is a class II drug according to the biopharmaceutical classification system. The site of absorption of efavirenz is stomach. It often demonstrates poor gastrointestinal absorption due to inadequate drug solubility in GI fluids. Efavirenz is a hydrophobic drug with low density and high flow resistance[9]. In the present study we intend to prepare Efavirenz Solid S(M)EDDS by adsorption to solid carriers with an inert solid carrier Neusilin US2 and evaluating its in-vitro and In-Vivo potential.

MATERIALS AND METHODS

Materials

Efavirenz was obtained as a gift sample from Matrix laboratories (Hyderabad, India). Tween80 was obtained from Merck specialties Private Limited (Mumbai, India), Labrafac PG, Maisine, Labrasol and Peceol were obtained from Gattafosse (Mumbai, India). Soybean oil and Oleic acid were obtained from Croda (India), Cremophore EL35 was obtained from BASF (Mumbai, India), Miglyiol 812 was obtained from Sasol (Germany) and Neusilin US2 (Magnesium aluminium silicate) obtained from Fuji chemicals (Japan). All other chemicals and solvents were of analytical grade.

Animals

Male Wistar rats (weighing approximately 250±25 g) were procured from institutional the animal house. The animals were maintained at a temperature of 25^0C and humidity 60% and were supplied with food and water. The study protocol was approved by the institutional animal ethics committee (IAEC) with No. IAEC/22/UCPC/KU/2011.

Methods

Solubility Studies

The solubility study was used to find out the suitable oil, surfactant and co-surfactant that possess good solubilizing capacity for

Efavirenz. An excess amount of Efavirenz was introduced into 2 ml of each excipient and the mixture was kept in a mechanical shaker for 24hrs and centrifuged at 10,000 rpm for 20 min using a centrifuge. Undissolved Efavirenz was removed by filtering with a membrane filter (0.45µm). The concentration of Efavirenz was determined by HPLC[10].

Particle size reduction and distribution of Efavirenz

Particle size reduction, leading to increased surface area, is a very promising approach to enhance solubility of poorly water- soluble compounds. As such Efavirenz particle size was d (0.9) having 208 microns. Particle size reduction of efavirenz was done by two stages. In first stage (Cycle 1) un micronized efavirenz was milled using Air Jet Mill (Promas Engineering, Mumbai), milling was performed by using primary and secondary pressures of 4.8 kg/cm^2, 4.2 kg/cm^2 and screw feeder speed was adjusted to 5 rpm. Cycle 1 sample was analyzed for particle size using Malvern laser diffraction instrument. (Malvern Laser Diffraction Master Sizer'2000') In second stage micronized efavirenz (obtained after first stage process) was again milled using Air Jet Mill with same conditions as mentioned above. Particle size distribution was determined using laser diffraction instrument with measuring cell (Scirocco 2000). 2-3 gm of the sample was transferred, with the aid of a dry spatula, into the dry powder (accessory). Spread the sample in the feeder evenly. Set the software parameters and run the equipment as specified.

Pseudo ternary phase diagram

To determine the concentration of components for the existing range of S(M)EDDS, pseudo ternary phase diagram was constructed using water titration method at ambient temperature (25^{0}C). Surfactant and co surfactant was mixed in different volume ratios (1:1 and 2:1). Oil and surfactant/co-surfactant mixture (S/CoS) were mixed thoroughly in different volume ratios 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 w/w. The mixture of oil, surfactant and co-surfactant at certain weight ratios were titrated with water by drop wise addition under gentle agitation. Deionized water was used as diluting medium and added into the formulation. The proper ratio of one excipient to another in the S(M)EDDS formulation was analyzed. Pseudoternary plots were constructed using Chemix software[11].

Development of S(M)EDDS Formulations

A series of S(M)EDDS formulations for Efavirenz were prepared based on Solubility studies, Pseudo ternary phase diagram and visual observation. Here, Labrafac PG used as oil phase and Labrasol and Tween 80 were used as surfactant and co-surfactant respectively. The compositions were given in the Table 1. In brief, accurately weighed Efavirenz was placed in a glass vial, to this oil, surfactant and cosurfactant were added. Then the components were kept in a sonicator until Efavirenz was completely dissolved.

Table 1
Development of S(M)EDDS formulations

	Formulation						
Components (%wt/wt)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Efavirenz	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Labrafac PG	40.01	60.01	80.00	100.00	120.01	80.00	80.00
Labrasol	106.70	93.34	80.00	66.68	53.32	60.00	70.00
Tween80	53.29	46.67	40.00	33.34	26.66	60.00	70.00
Total	250.00	250.00	250.00	250.00	250.00	250.00	250.00

Freeze Thawing

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variations on S(M)EDDS formulations. Centrifugation was performed at 10,000 rpm for 20 minutes and observed visually for phase separation. Formulations were subjected to freeze cycle (-20°c for 2days followed by 40°C for 2days). Only stable formulations were selected for further studies[12].

Determination of Droplet Size

The average droplet size of Efavirenz S(M)EDDS formulations were determined by Photon correlation spectroscopy using Malvern Zetasizer (Malvern Instrument UK) able to measure sizes between 10 and 5000 nm. The selected formulations were diluted with deionized water and placed in an electrophoretic cell for measurement[13].

In Vitro Dissolution studies of SMEDDS

The release of drug from liquid S(M)EDDS formulations filled in capsules and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. The dissolution media is 1% Sodium Lauryl sulfate in water (900ml), and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined intervals 5, 10, 15, 20, 30 and 45 min and filtered through 0.45-µm pore size membrane filters. The removed volume was replaced each time with 5 ml of fresh medium. The amount of drug dissolved was determined using an HPLC method.

HPLC Analysis of Efavirenz

The amount of Efavirenz in the samples was determined by HPLC system. The HPLC analysis system consisted of Agilent 1200 separation module and 1200 diode array detector (Agilent 1200 series). The chromatographic column was a 4.6 mm X 250 mm; 5 µm packing L1 (SS WAKOSIL C 18 RS). The chromatographic conditions were mobile phase Acetonitrile and Solution A (3:2), flow rate 1mL/min, loop size 100 µL, detection at 252 nm and retention time 6.5±0.5 minutes.

Preparation of Solution A: 0.8mg/mL of ammonium acetate in water. Adjust with 2% ammonium hydroxide solution to a pH of 7.50±0.05. Pass the solution through a suitable 0.45 - µm filter.

Oil adsorption study

The objective of this study was to select adsorbent for preparing free flowing solid Self emulsifying formulation for Efavirenz. Microcrystalline cellulose, colloidal silicon dioxide, Neusilin US2, dicalcium phosphate and tricalcium phosphate were used as adsorbents. They were added separately to the optimized liquid S(M)EDDS formulation i.e F3 under stirring (adsorbents were added to 100gms of oil phase until free flowing blend was formed). Neusilin US2 showed higher oil adsorption capacity when compared to microcrystalline cellulose and colloidal silicon dioxide[6].

Conversion of S(M)EDDS to Solid S(M)EDDS

The optimized liquid S(M)EDDS formulation (F3) based on droplet size and dissolution study was converted into free flowing powder by adsorption onto solid carriers. The solid carrier used for adsorption comprised of materials that provided a high surface area with good disintegration characteristics. 100 mg Neusilin US2 (magnesium aluminum silicate) was used as a solid carrier. It can adsorb at high levels up to 70% (w/w). The conversion process involved addition of liquid formulation onto carriers under continuous mixing. The powder was dried and filled directly into capsules[14].

CHARCTERIZATION OF SOLID S(M)EDDS

Dissolution studies of Solid S(M)EDDS

The release of drug from solid S(M)EDDS formulations filled in capsules and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. The dissolution media 1% Sodium Lauryl sulfate in water (900ml), and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. A 10ml sample of medium was withdrawn

at predetermined intervals 5, 10, 15, 20, 30 and 45 min and filtered through 0.45-µm pore size membrane filters. The amount of drug dissolved was determined using an HPLC method.The solid-state properties of Efavirenz in the solid S(M)EDDS was investigated using X-ray powder diffraction (XRPD) technique since this would influence the *in vitro* and *in vivo* dissolution characteristics.

XRD (X-Ray diffraction) studies

XRPD diffractograms of drug, placebo (Oil surfactant, co-surfactant are mixed according to the ratio's of finalized formulation of S(M)EDDS without drug) and solid SMEDDS formulations were recorded using a Bruker D8 advanced Diffractometer with a Cu line as the source of radiation. Standard runs using a 40-kv voltage, a 40-mA current, and a scanning rate of 0.02° min^{-1} over a 20 range of 3-40° were used.

Pharmacokinetic study

The pharmacokinetic characteristics for pure drug suspension and solid SMEDDS of efavirenz was evaluated using eight healthy Wistar rats weighing 250±25 g were used in the study. All rats were dosed following an overnight fast, food was returned 4h after dose was given. Rats were divided in two groups at random. First group was administered Efavirenz suspension was prepared in 0.5% methocel. Second group was administered solid S(M)EDDS suspension prepared in 0.5% methocel. Blood samples (approximately 0.5ml) were obtained with syringes predose and at 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 24.00, 52.00 hrs post dose. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min and stored frozen at −20°C until analysis. The concentration of Efavirenz in plasma was determined by validated liquid chromatography–mass spectrometry (LC-MS).

Pharmacokinetic Data Analysis for Solid SMEDDS formulation and pure drug suspension:

The area under the drug concentration-time curve from zero to 52h (AUC) was calculated using the trapezoidal rule. The maximum plasma concentration of the drug (Cmax and the time to reach Cmax (T_{max}) were obtained directly from the plasma profiles. The relative bioavailability (BA) of the Solid S(M)EDDS to the reference (pure drug suspension) was calculated as follows:

$$\text{Relative Bio Availability (\%)} = \frac{AUC_{test}}{AUC_{reference}} \times \frac{Dose_{reference}}{Dose_{test}}$$

Where, AUC_{test} and $AUC_{reference}$ are AUCs obtained after the oral administration of the Solid S(M)EDDS formulation and the reference (pure drug suspension), respectively. $Dose_{test}$ and $Dose_{reference}$ are the doses of the two products. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values were expressed as the mean±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The solubility of Efavirenz in various surfactants and oils are presented in Figure 1. The Efavirenz showed good solubility in surfactants (Tween 80 and Labrasol) and oil (Labrafac PG). Based on drug solubility, Tween 80, Labrasol and Labrafac PG were selected as surfactant, co-surfactant and as oil phase respectively. The

components selected were miscible with each other and form a homogenous mixture. The particle size reduction was observed during the process of micronization using Air Jet Mill, Particle size distribution of efavirenz with different sizes were illustrated in Figure 2a-2c.

Figure 1
Solubility of efavirenz in various components

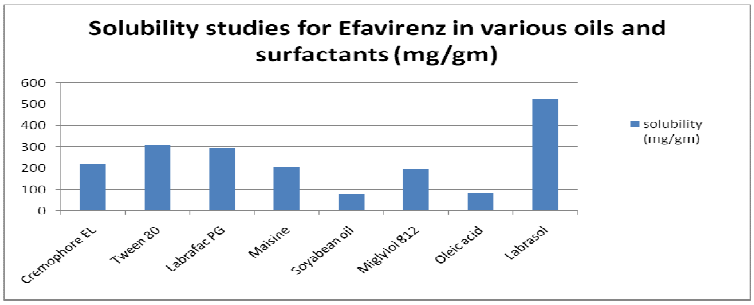


Figure 2a
Unmicronized particle size distribution

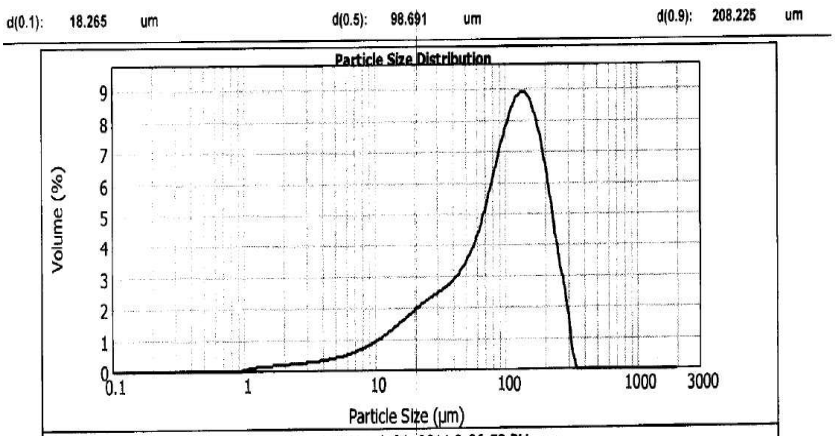


Figure 2b
Micronized (Cycle 1) particle size distribution

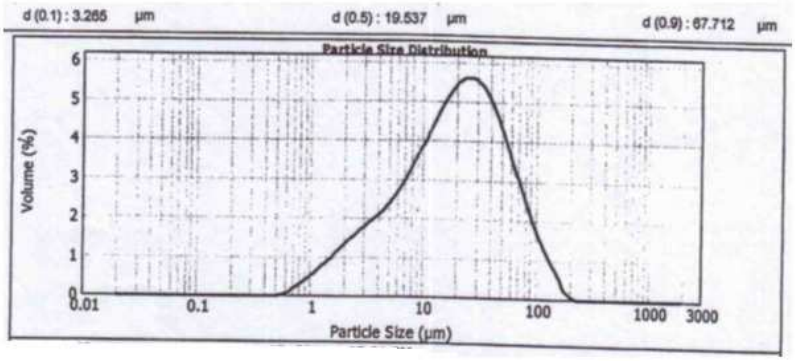
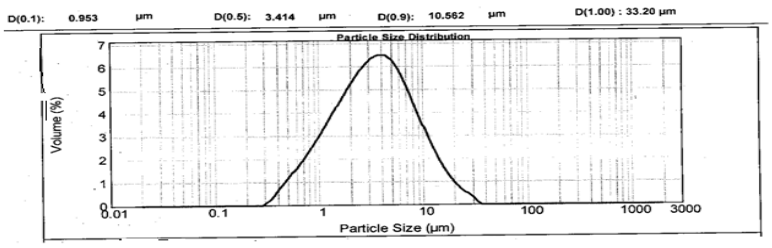


Figure 2c
Micronized (Cycle 2) particle size distribution



Particle size distribution of Micronized Efavirenz after Cycle 2

Pseudoternary phase diagram of system with Labrafac PG gave a wider microemulsion region, it was selected as a lipid phase. Labrasol and Tween 80 were used as a surfactant and co-surfactant respectively. From the phase diagrams shown in Figure 3a & 3b, it was observed that self emulsifying region was enhanced with increasing concentrations of surfactant and co surfactant with oil (Labrafac PG). Efficiency of self-emulsification was good when the surfactant concentration increased.

Figure 3a
Pseudoternary phase diagram of system with the following components: Oil=Labrafac PG, surfactant= Labrasol and cosurfactant Tween 80. S/CoS ratio is 1:1

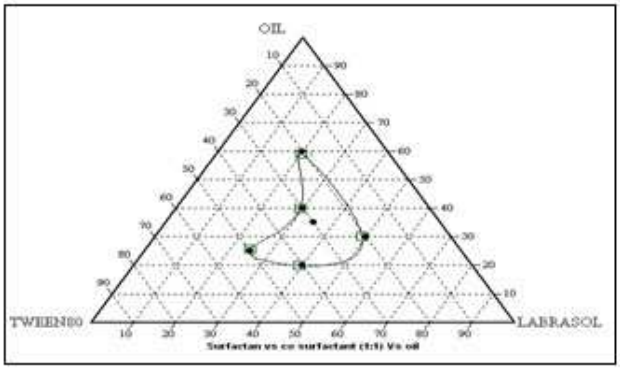
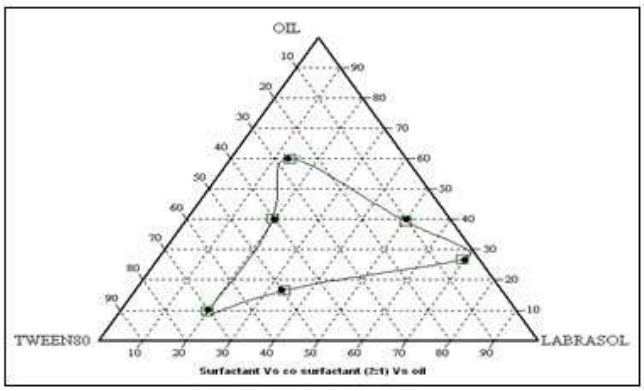


Figure 3b
Pseudoternary phase diagram of system with the following components: Oil=Labrafac PG, surfactant= Labrasol and cosurfactant Tween 80. S/CoS ratio is 2:1



In thermodynamic stability study, no phase separation and effect of temperature variations on prepared formulations were observed. There was no change in the visual description of samples after centrifugation freeze-thaw cycles. Formulations which are thermodynamically stable only those were selected for further characterization and results are summarized in Table 2.

Table 2
Thermodynamic stability studies

Formulations	Centrifugation	Freeze thaw method	
		-20°C for 2 days	+40°C for 2 days
Formulation 1	No phase separation	No change	No change
Formulation 2	No phase separation	No change	No change
Formulation 3	No phase separation	No change	No change
Formulation 4	No phase separation	No change	No change
Formulation 5	No phase separation	No change	No change
Formulation 6	No phase separation	No change	No change
Formulation 7	No phase separation	No change	No change

The effect of different compositions of S(M)EDDS on droplet size was shown in Table 3. The mean droplet size was relatively very smaller in formulation F3 compared with other formulations. Size distribution by intensity of all formulations was shown in Figure 4a-4e.

Figure 4a)
Particle size distribution of Formulation 1

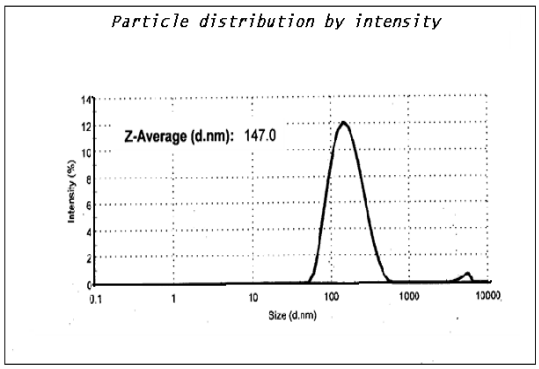


Figure 4b)
Particle size distribution of formulation 2

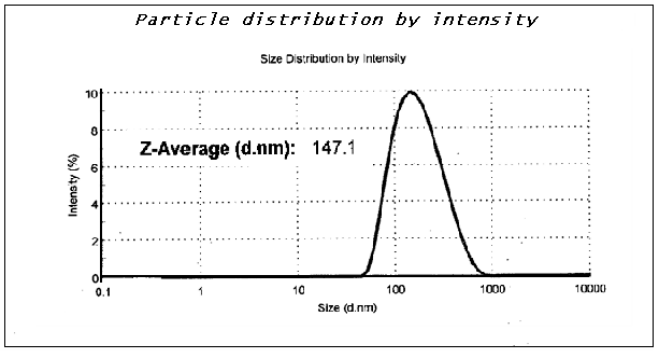


Figure 4c)
Particle size distribution of Formulation 3

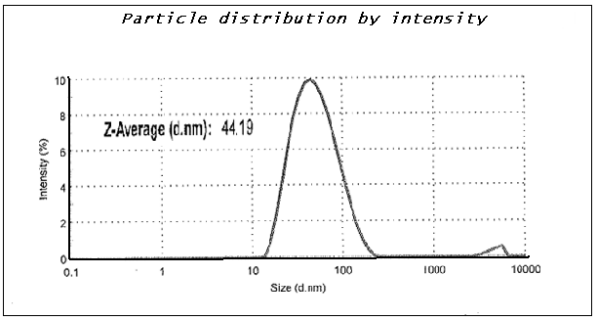


Figure4d)
Particle size distribution of Formulation 4

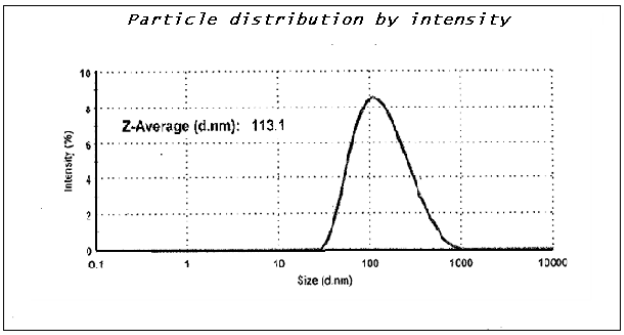


Figure4e)
Particle size distribution of formulation 5

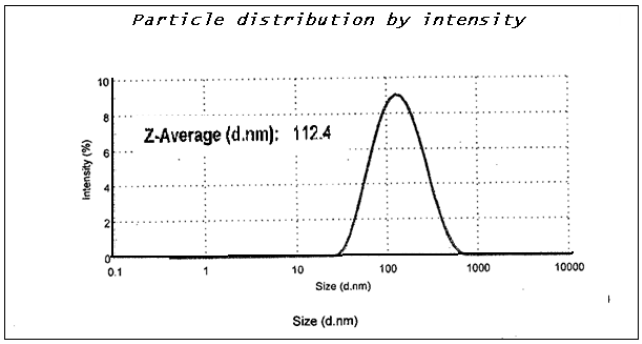


Table 3
Droplet sizes of different formulation

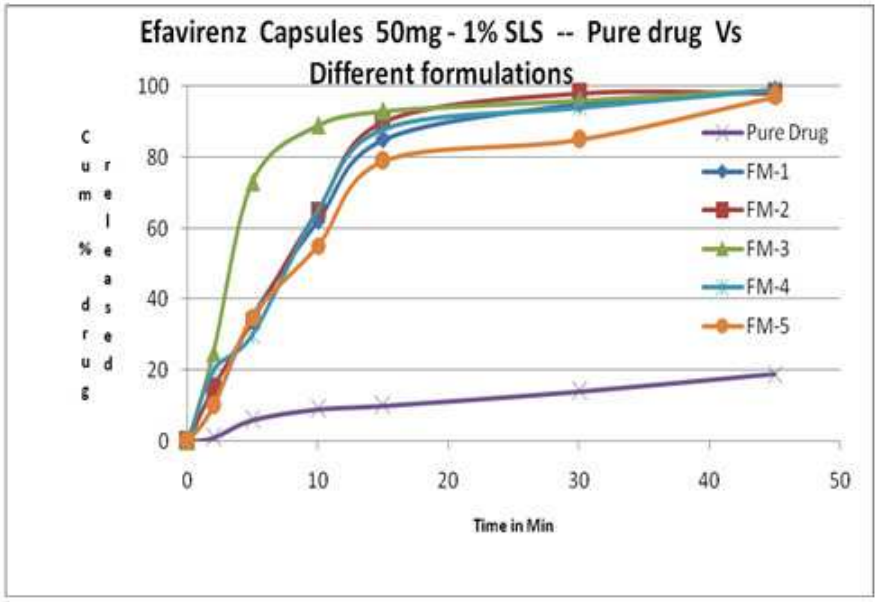
Different Formulation	Droplet size
Formulation 1 (F1)	147.0
Formulation 2(F2)	147.1
Formulation 3 (F3)	44.19
Formulation 4 (F4)	113.1
Formulation 5 (F5)	112.4

The results of *in vitro* dissolution comparisons of S(M)EDDS formulations are summarized in Table 4 & Figure 5. The faster dissolution from S(M)EDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplet that can dissolve rapidly in the dissolution medium. The release from liquid S(M)EDDS formulation F3 (mean droplet size 44.19 nm) was faster than S(M)EDDS formulations 1, 2, 4, 5 and pure drug substance indicating influence of droplet size on the rate of drug dissolution. On the basis of mean droplet size and faster and complete dissolution rate formulation F3 was selected as optimized formulation and this formulation was converted into solid S(M)EDDS by adding required quantity of Neusilin US2 as adsorbing agent.

Table 4
Dissolution profiles of various formulations

Time in Min	Dissolution media - 1% SLS in water					
	Pure Drug	F-1	F-2	F-3	F-4	F-5
0	0	0	0	0	0	0
2	1	10	15	25	20	10
5	6	35	34	73	30	35
10	9	62	65	89	65	55
15	10	85	90	93	88	79
30	14	95	96	98	94	85
45	19	99	98	99	99	97

Figure 5
Dissolution profiles of selected formulations with pure drug



Oil adsorption study was performed for efavirenz by using different adsorbents and results are depicted in Figure 6. Neusilin US2 showed higher oil adsorption capacity when compared to microcrystalline cellulose and colloidal silicon dioxide. From oil adsorption study Neusilin US2 was used for the preparation of Solid SMEDDS from optimized SMEDDS formulation (F3) by adsorption and composition for both the formulations were mentioned in Table 5.

Figure 6
Adsorption studies of efavirenz with different adsorbents

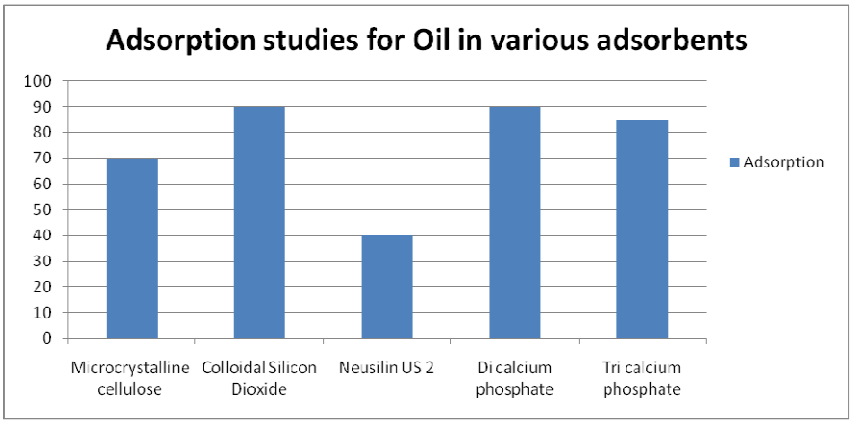
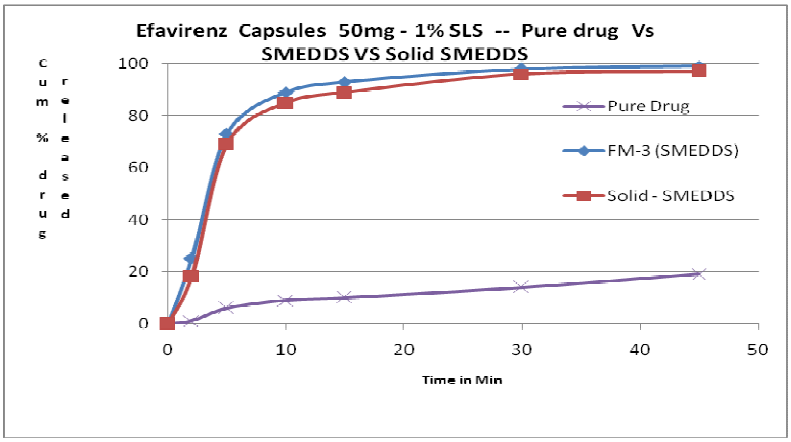


Table 5
Composition of Solid – SMEDDS and SMEDDS

Components (%wt/wt)	Formulation	
	FM-3 (SMEDDS)	Solid - SMEDDS
Efavirenz	50.00	50.00
Labrafac PG	80.00	80.00
Labrasol	80.00	80.00
Tween80	40.00	40.00
Neusilin US2	-	100.00
Total	250.00	350.00

The release of drug from solid, liquid S(M)EDDS formulations filled in capsules and pure drug was determined. The amount of drug released was determined using an HPLC method. Comparative dissolution profiles of Solid and liquid S(M)EDDS formulations with pure drug was shown in **Figure 7**. Solid and liquid S(M)EDDS shown better and equal release profiles when compared with pure drug.

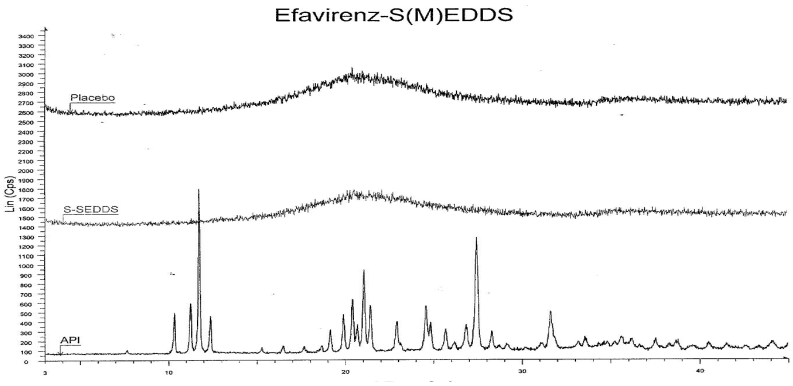
Figure 7
Comparative results of drug release from SMEDDS, Solid SMEDDS and Pure drug



XRD (X-Ray diffraction) studies

The X-ray diffractograms of pure drug, placebo, and solid S(M)EDDS formulations are shown in Figure 8. The results show absence of obvious peaks, representing crystals of Efavirenz in solid S(M)EDDS indicating that the drug was in amorphous or disordered crystalline phase in the lipid matrix.

Figure 8
X-ray Diffraction analysis of efavirenz



In-Vivo studies

Pharmacokinetic parameters comparison for pure drug suspension and Solid SMEDDS formulation:

Figure 9 shows the plasma concentration–time curve in Wistar rats after a single oral dose of Efavirenz solid SMEDDS formulation as compared to efavirenz pure suspension. At all the indicated time points, the efavirenz plasma concentrations in rats treated with Solid SMEDDS formulation were significantly higher than those treated with pure drug suspension. Pharmacokinetic parameters of efavirenz after oral administration of the two formulations to Wistar rats are shown in Table 6.

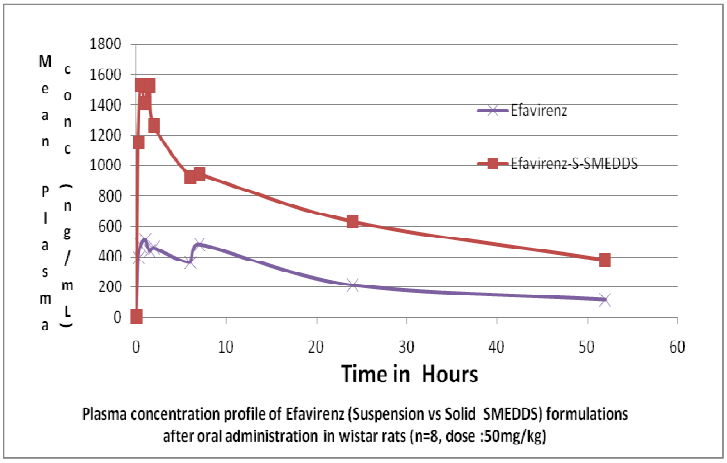
Table 6
Pharmacokinetic parameters of efavirenz pure drug and solid SMEDDS

Pharmacokinetic parameters	Efavirenz	Efavirenz- S(M)EDDS
Dose (mg/kg)	50.00	50.00
C max (µg/ml)	0.52	1.68
AUC 0-t (µg.hr/ml)	2.62	8.06
AUC 0-inf (µg.hr/ml)	2.65	8.11
T max (h-1)	1.50	1.13
t 1/2 (h)	4.22	7.26
K el (h -1)	0.16	0.10

As can be seen from the above table, the test preparation shows the increased AUC and Cmax values, which are about 8.06 and 1.13 times, respectively, as high as those in the reference formulation. Accordingly, it can be identified that the efavirenz of the Solid SMEDDS formulation is significantly increased in comparison with that of the pure drug (efavirenz suspension). C_{max} of the Solid SMEDDS formulation 1.68 µg mL−1 was significant ($p<0.05$) as compared to the pure drug suspension formulation 0.52 µg mL−1. T_{max} of both Solid SMEDDS formulation and pure drug suspension was 1.13 and 1.50 h, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage

form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0-\infty}$ for Solid SMEDDS formulation was higher (8.11 µg hmL−1) than the pure drug suspension formulation 2.65 µg hmL−1. Statistically, $AUC_{0-\infty}$ of the Solid SMEDDS formulation was significantly higher ($p<0.05$) as compared to a pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of efavirenz from Solid SMEDDS formulation as compared to the pure drug suspension formulation.

Figure 9
Plasma concentration profiles of efavirenz solid SMEDDS and pure drug



Plasma concentration profile of Efavirenz (Suspension vs Solid SMEDDS) formulations after oral administration in wistar rats (n=8, dose :50mg/kg)

CONCLUSION

A SMEDDS formulation of a poorly water-soluble drug, Efavirenz was developed for direct filling into hard gelatin capsules for oral administration. The formula composition of SMEDDS for capsule filling was obtained based on solubility evaluation, pseudo ternary phase diagram, and droplet size analysis. The optimized formulation (F3) showed a small droplet size, fast dissolution rate and rapid self microemulsification in an aqueous media. The SMEDDS formulation converted into solid SMEDDS using Neusilin US2 as adsorbent for capsule filling showed faster rate of drug release than the pure drug and equal drug release was found with liquid SMEDDS in a discriminating dissolution media. The results from this study demonstrate the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like Efavirenz which may result in improved therapeutic performance. After oral administration of efavirenz (50 mg kg^{-1}) to either sex Wistar rats, showed superior absorption profile than the suspension of pure drug. The relative bioavailability of S-SMEDDS formulations was enhanced in comparison with pure drug suspensions. It can be concluded that efavirenz SMEDDS formulations offer more predictable and more extensive drug release/absorption than the corresponding conventional formulations. The present exploratory work successfully illustrates the potential utility of S-SMEDDS formulation for the delivery of poor water-soluble compounds such as efavirenz. The comparison of in vivo bioavailability studies of optimized formulation F3 and that of a pure suspension in Wistar rats confirmed that the higher amount of drug concentration in blood indicated better systemic absorption and bioavailability also found to be increased with optimized formulation.

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