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Mixed surfactant based (SNEDDS) self-nanoemulsifying drug delivery system presenting efavirenz for enhancement of oral bioavailability

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ABSTRACT

This study aims to develop a self-nanoemulsifying drug delivery system (SNEDDS) based on non-ionic surfactant mixtures to improve the oral bioavailability of efavirenz (EFZ) categorized as a class II according to the BCS, for HIV- therapy. The result of solubility studies of EFZ in various excipients utilized for construction of the pseudo ternary phase diagram containing surfactant mixtures. Surfactants in 1:1 combination are used with different co-surfactants in different ratio to delineate the area of monophasic region of the pseudo ternary phase diagram. Different accelerated physical stability studies and self-emulsification assessment were performed on the formulations. The formulations clearing the above studies are considered for percentage transmittance and turbidity analysis. The globule size distributions of post diluted SNEDDS having percentage transmittance above 90 were estimated. The TEM analysis of two optimized post diluted SNEDDS formulations further confirm the size in nanometric range (below 50 nm). FT-IR studies showed the retention of the characteristic peaks of EFZ in the preconcentrate. The *in vitro* dissolution profile of SNEDDS established advantages of SNEDDS over plain drug as more than 80% drug was released within 30 min in case of optimized SNEDDS while it was approximately 18.3% in the case of plain drug powder. Pharmacokinetic parameters were calculated after performing the *in vivo* studies of best optimized formulation in rats. The Pharmacokinetic data reveal a 2.63 fold increase in $AUC_{(0-\infty)}$ in comparison to plain EFZ suspension. The designed delivery system showed the faith in generating an effective formulation of EFZ for HIV treatment.

1. Introduction

The Human Immunodeficiency Virus (HIV) causes the most deadly infectious disease acquired immune deficiency syndrome (AIDS) infecting approximately 40 million people globally. HIV is a retrovirus of the lentivirus family, which mainly destroys CD^{4+} T cells a vital component of immune system essential for proper functioning of the immune system. The highly active antiretroviral treatment or HAART has saved some 2.9 million lives since 1996 proving its innovation [1]. Three main classes of antiretroviral (ART) drugs are recommended in HAART regimens. Efavirenz (EFZ) is one of the widely used first line non-nucleoside reverse transcriptase inhibitors (NNRTI) employed in the pharmacotherapy of both children and adults [2]. EFZ has a more favorable resistance profile in comparison to other approved NNRTIS often taking two or more mutations in reverse transcription (RT) to create a higher level drug resistance [3]. It shows high lipophilicity (log P = 5.4) and poor aqueous solubility (4 μg/ml) which comes under BCS class II drug, having an oral bioavailability (40–45%) and relatively high intra (55–58%) and inter (19–24%) subject variability [4]. EFZ is available with flexible doses as a tablet (600 mg), capsules (50 mg and 200 mg) and oral solution (30 mg/ml) (Sustiva®) suffering from solubility/dissolution related problems. The inadequate aqueous solubility and dissolution of dosage form play the major role in lowering oral absorption and adversely affecting the oral bioavailability. Reduced bioavailability pertaining to solubility/dissolution of EFZ is one of the most remarkable hurdles towards a highly compliant pharmacotherapy. Hence there is a need of delivery system having the potential to overcome the solubility and bioavailability issues with scalable and cost-viable rights.

Extensive survey of literature shown some approaches have been investigated to improve solubility, bioavailability and other related problems of EFZ. This includes EFZ-cyclodextrin inclusion complexes [5], polymeric micelles [6], solid dispersion and

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PEGylation [7], surface stabilized nanoparticles [8] and EFZ-nanoemulsion [9]. However, these systems have certain advantages with some limitations of lack of desired enhancement in solubility, use of higher amount of complexing agent, high concentration of cosolvents used for solubilization causes toxicity. The present simple approach was aimed to develop SNEDDS of EFZ for achieving enhanced oral bioavailability.

Self-emulsifying drug delivery system (SEDDS) has been exploited as a popular approach in enhancing aqueous solubility as well as oral bioavailability of hydrophobic drugs in recent years [10]. SNEDDS is a preconcentrate comprise isotropic mixtures of drug, natural or synthetic oil(s), surfactant(s), usually with one co-surfactant or co-solvent. When such system introduced into the aqueous environment of the GIT, spontaneously emulsify to form fine oil-in-water nanoemulsion with a nanometric droplet size less than 200 nm with the aid of GI motility [11]. Apart from thermodynamic stability, SNEDDS could be considered as an efficient, convenient and more patient compliant approach in comparison to submicronic emulsions and metastable emulsions as SNEDDS can be filled directly into soft or hard gelatin capsules for convenient oral administration as unit dosage form [12]. Furthermore the drug can be absorbed after in-situ solubilization of SNEDDS by lymphatic pathways, bypassing hepatic first-pass effect leading to higher bioavailability [13]. Experienced with a few SNEDDS-based products cyclosporin (sandimmun Neoral, Novartis Pharmaceutical Ltd.), and subsequently for ritonavir (Norvir®, Abbott Laboratories), and saquinavir (Fortovase®, Roche Pharmaceuticals) on the pharmaceutical market since 1997, the craze for the best utilization of this pharmaceutical formulation strategy is still on its way.

Eucalyptus oil (EO) a pale yellow volatile liquid chiefly contains eucalyptol (1,8 cineole) 1.3,3-trimethyl-2-oxabicyclo[2,2,2]-octane a monoterpenoid which is used without purification as its boiling point, density and refractive index agreed nicely with literature values [14]. EO commonly used in the treatment of cold and other symptoms of respiratory infections. The multifunctional content of the oil is useful as bactericidal, antifungal as well as analgesic and anti-inflammatory agent [15,16]. EO possesses some surfactant like properties [17,18]. Furthermore EO employed as oil phase for formulating microemulsion based drug delivery system [19,20]. In the current research work EO has used as the vehicle phase in the accepted limit of oral administration [21,22]. Combined use of surfactants has gained attention in the formulation of micro-emulsions and SNEDDS [23–25]. In our work we utilized cremophor EL (Cr EL) (polyoxy 35 castor oil), a GRAS (generally-recognized-a-safe) approved excipient and Brij 35 (polyoxy 23 lauryl ether) included in non parenteral medicines licensed in the USA and UK [26] as nonionic surfactant mixer.

In the present research, a SNEDDS of EFZ designed with EO in its limit of oral use. A mixed surfactant system containing Cr EL and Brij 35 is used with different co-surfactant for making a pool of formulations. Various in vitro assessments including globule size analysis and dissolution profile endeavors to prepare an optimal SNEDDS system. The optimized formulation with a particle size of 31.2 nm evaluated for oral bioavailability in male adult Wistar rats.

2. Materials and methods

2.1. Materials

EFZ was obtained as a gift sample from Hetero Drugs Ltd. (Hyderabad, India), Cr EL, Solutol HS-15 were gift samples BASF India (BASF, Mumbai, India), Transcutol P, Labrafil M 2125CS, Labrafil M 1944CS, Labrasol and Lauroglycol 90 were gifted samples from Gattefosse India (Mumbai, India). Polyoxyethylene (23) lauryl ether (Brij-35) was obtained from Fluka (a subsidiaries of Sigma-Aldrich, USA), Capmul MCM (Glyceryl Caprylate) were gift samples from Abitec corporation (USA), EO was purchased from B.D. Pharmaceutical Works (India), Ethanol, 1-Propanol, 1-Butanol, Polyethylene glycol 400 (PEG 400), Propylene glycol, Tween 20 and Tween 80 and SLS were purchased from S.D. Fine Chemicals (Mumbai, India). Methanol, Acetonitrile and Water of HPLC grade was used in HPLC study procured from Merck (Mumbai, India). All the reagents of analytical grade were used as received. Freshly prepared double distilled water was used whenever required.

2.2. Solubility studies

Determination of drug solubility in various oils, surfactants and co-surfactants were carried out by adding an excess amount of EFZ to 2 ml of the vehicle contained in a screw-capped vial. The drug was solubilized by heating the mixture in a water bath at 50 °C with vortexing. The mixture was shaken at 25 ± 1 °C in a water-bath shaker (Remi, Mumbai, India) for 48 h followed by keeping them for equilibrium for 24 h. The equilibrated mixture was centrifuged at 5000 rpm for 10 min and excess insoluble EFZ was removed by filtration. The filtrate was analyzed for the amount of EFZ by UV–vis spectrophotometer (UV-1800, Shimadzu, Japan) at 247 nm.

2.3. Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams were constructed by titration of homogeneous mixture of oil, surfactants and co-surfactant with water at ambient temperature [27,28]. The oil (EO), binary mixture of surfactants (1/1,w/w ratio of Cr EL and Brij 35) with co-surfactant at different ratios (1:1, 2:1, 3:1) were dispersed at weight ratios of 10:0,9:1,8:2,7:3,6:4,5:5,4:6,3:7,2:8,1:9 and 0:10 into different vials. Each vial containing the liquid mixtures were titrated with water. Following each water addition the

Table 1
Composition of SNEDDS formulations.

Vehicle (mg)	Sample ID											
	FT1	FE1	FP1	FB1	FT2	FE2	FP2	FB2	FT3	FE3	FP3	FB3
	1:1(Smix:Co-surfactant)				2:1(Smix:Co-surfactant)				3:1(Smix:Co-surfactant)			
Efavirenz	10	10	10	10	10	10	10	10	10	10	10	10
Eucalyptus oil	12	12	12	12	12	12	12	12	12	12	12	12
Cremophor EL	12	12	12	12	16	16	16	16	18	18	18	18
Brij 35	12	12	12	12	16	16	16	16	18	18	18	18
Transcutol P	24	–	–	–	16	–	–	–	12	–	–	–
Ethanol	–	24	–	–	–	16	–	–	–	12	–	–
1-Propanol	–	–	24	–	–	–	16	–	–	–	12	–
1-Butanol	–	–	–	24	–	–	–	16	–	–	–	12