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Research Article

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Novel Self Micro-emulsifying Drug Delivery Systems (SMEDDS) of Efavirenz

Ashish Deshmukh* and Shirishkumar Kulakrni

Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, (M.S) India Pin: 411001

ABSTRACT

Efavirenz is a poorly water soluble drug with aqueous solubility 4 µg/mL and oral bioavailability 40-45%, having non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral activity. The aim of the present study was to develop a Self-Micro-emulsifying Drug Delivery System (SMEDDS) of EFV with improved dissolution rate for the oral delivery of poorly water-soluble antiretroviral agent. The optimized SMEDDS of EFV was prepared by dissolving EFV in selected vehicles such as PEG-6 Caprylic/Capric Glycerides (Softigen® 767) as oil, Polyoxyl 35 Castor Oil (Cremophor® EL) as a surfactant and Glyceryl Caprylate/Caprate (Capmul® MCM) as co-surfactant. The proportion of oil, surfactant and co-surfactant in liquid SMEDDS of EFV was optimized using ternary phase diagram, phase separation study, droplet size analysis and in-vitro dissolution study. Optimized SMEDDS composition of oil to surfactant/co-surfactant content did not show phase separation in 0.1N HCl and water, with the droplet size varying from 39-46 nm, which indicate the formation of homogeneous stable microemulsion in both the media. In-vitro dissolution data showed surprisingly and significant enhancement of dissolution rate of EFV in form of SMEDDS compared to pure EFV powder.

Keywords: Efavirenz, Oil, Surfactant, Co-surfactant, SMEDDS, S-SMEDDS

INTRODUCTION

Efavirenz (EFV) is non-nucleoside reverse transcriptase inhibitor activity classified as BCS Class IV having highly lipophilic nature **Fig. 1** [1]**.** The low solubility of EFV in aqueous medium alters its bioavailability from the GI tract. The oral bioavailability of the EFV is around 40–45% and the aqueous solubility is around 4.0 µg/ml [2]**.** In recent era much attention was gained by Lipid based drug delivery system (LBDDS) to enhance the solubility and oral bioavailability of poorly water soluble drugs. LBDDS can be designed in many ways, out of that Self-Micro-emulsifying Drug Delivery System (SMEDDS) is one of the promising technique which enhance the solubility and oral bioavailability of poorly water soluble drugs [3-7]. SMEDDS is a isotropic and thermodynamically stable mixture of oil, surfactant/cosurfactant and drug which in contact with aqueous media, spontaneously form microemulsion with peristaltic movement generated by Gastrointestinal (GI) tract [8-12]. The bioavailability was improved by surfactants by various mechanisms, which includes the better drug dissolution and by increasing intestinal epithelial as well as tight junction permeability, [13]**.** All these properties were fulfill by SMEDDS which results in lipophilic drug with improved solubility and bioavailability. In present study attempt was made to enhance the solubility of EFV using SMEDDS technology which was justified by accelerated In-vitro dissolution of EFV compared to pure EFV in water.

EXPERIMENTAL SECTION

2.1 Materials

Efavirenz (EFV) was gifted by Matrix Laboratories, Hyderabad, India. Glyceryl Caprylate (Imwitor® 988), PEG-6 Caprylic/Capric Glycerides (Softigen® 767) were supplied as a gift sample by SASOL, Witten, Germany. Propylene Glycol Dricaprylate/Dicaprate (Captex® 200), Glyceryl Triacetate (Captex® 500), Propylene glycol monocaprylate

(type II) NF (Capryol® 90), Glyceryl Caprylate/Caprate (Capmul® MCM), Propylene Glycol Monocaprylate (Capmul® PG-8) were supplied as a gift sample by Abitec Corporation, Ohio, USA. polyethoxylated castor oil (Cremophor® EL), Polyethylene glycol-15-hydroxystearate (Solutol® HS-15) were supplied as a gift sample by BASF, India Ltd, Mumbai, India. Caprylocaproyl polyoxyl-8 glycerides NF (Labrasol®), Propylene glycol dicaprylate/dicaprate NF (Labrafac®), highly purified diethylene glycol monoethyl ether EP/NF (Transcutol® P), were supplied as a gift sample by Gattefosse India Ltd, Mumbai, India. Other chemicals were of HPLC or analytical grade.

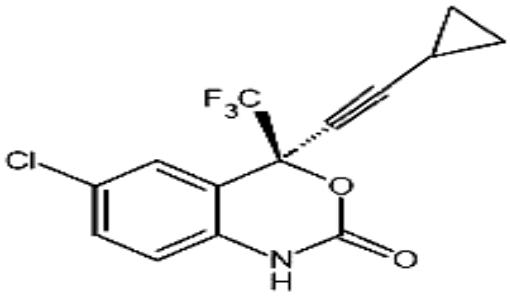


Figure 1. Structure of Efavirenz (EFV)

2.2 Solubility Study

Excipients were screened for their ability to solubilize EFV in oils, surfactants and co-surfactants. In this study, excess amount of EFV (Approximate 500 mg) was added to 2 g each of selected excipient in screw capped glass vials. The drug was gently mixed using vortex mixer for 30 min and further sonicated (Bandelin sonorex RK 514h) for 2 h at room temperature. The sonicated mixture was kept in water bath at room temperature for 48 h for reaching the equilibrium. After 48 h these vials were centrifuged at 3000 rpm for 20 min [12, 14]**.** After centrifugation the amount of drug dissolved in the selected excipients was determined by suitably diluting the supernatant in ethanol and analyzing the supernatant by UV- spectrophotometer ((Varian Cary C50 Conc.) at 252 nm. Solubility of EFV in selected oils, surfactant and cosurfactant was determined in duplicate. The results of solubility determination are presented in **Fig. 2**.

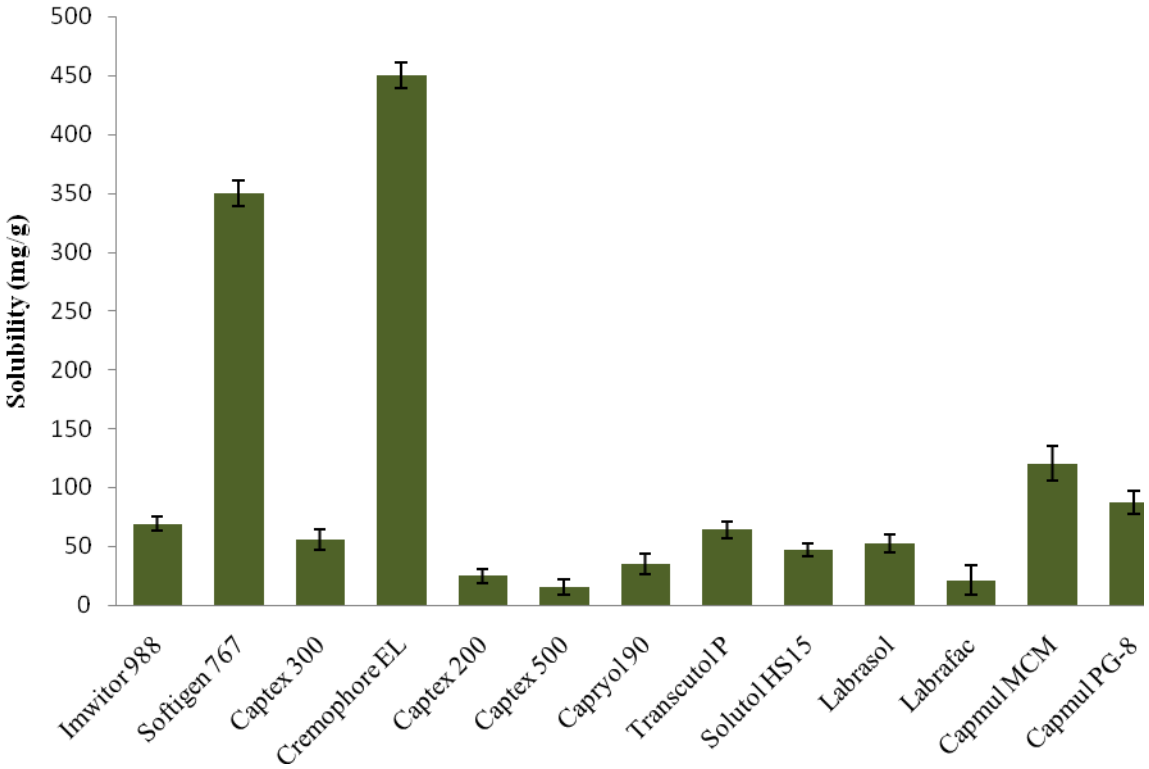
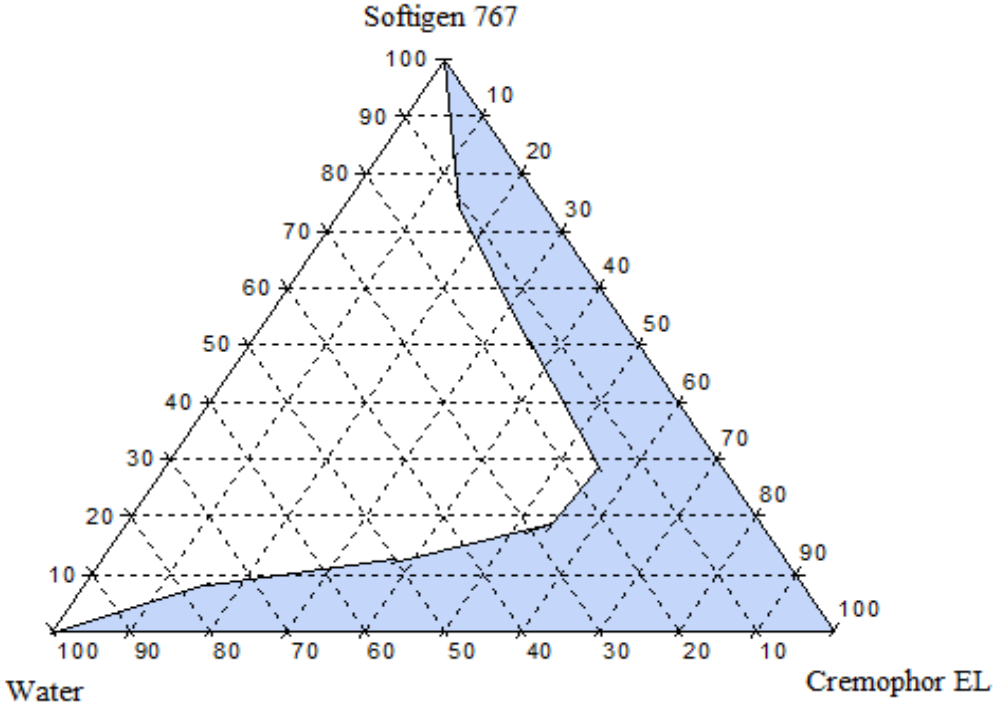


Figure 2. Solubility data of Efavirenz in various oil, surfactant and co-surfactant.



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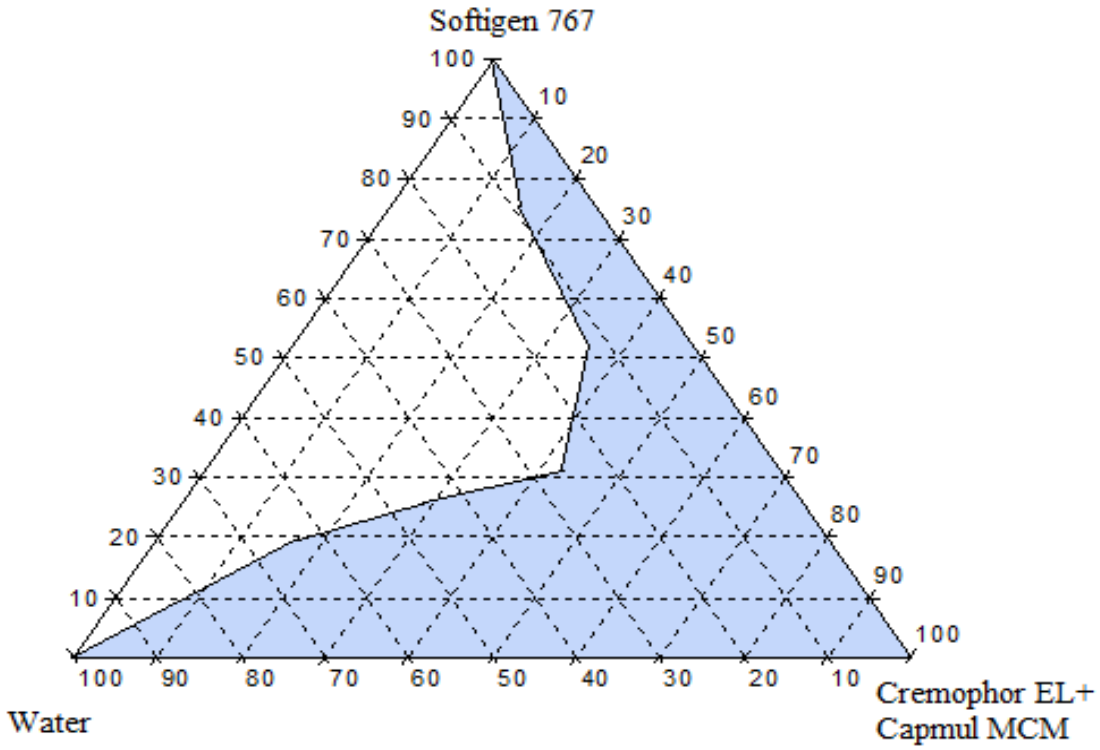

3-II

Figure 3. Pseudo-ternary phase diagram 3-I. Pseudoternary phase diagram with Softigen 767 (oil), Cremophor EL (surfactant) and Water, 3-II. Pseudoternary phase diagram with Softigen 767 (oil),, Cremophor EL (surfactant), Capmul MCM (Co-surfactant) and Water.)

2.3 Construction of Ternary Phase Diagram

A ternary phase diagram was constructed for mixtures of oil, surfactant, cosurfactant and water at room temperature. The mixture of oil and surfactant-cosurfactant in various ratios by weight were diluted with water by drop wise addition method under moderate stirring. At equilibrium, the apparent spontaneity of emulsion formation was

measured by visual observation. Phase diagrams were prepared in the presence of drug to obtain optimum concentration of oil, surfactant and cosurfactant. Various series of pseudo-ternary phase diagrams were constructed to identify microemulsion regions and the size of microemulsion region among the diagrams was compared. For each phase diagram, the ratios of oil: surfactant/co-surfactant were varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 w/w . The data obtained was used to construct pseudo ternary phase diagram using TRIDRAW 4.1 software and are presented in **Fig. 3-I** for Softigen 767 (oil), Cremophor EL (surfactant) and Water and **Fig. 3-II** for Softigen 767 (oil), Cremophor EL (surfactant), Capmul MCM (Co-surfactant) and Water.

2.4 Formulation of Liquid SMEDDS

EFV SMEDDS was formulated using Softigen 767 as a oil, Cremophor EL as surfactant and Capmul MCM as a co-surfactant. In all the SMEDDS formulations, concentration of EFV was fixed at 50 mg and those were prepared by dissolving the EFV into the mixture of surfactant, oil and cosurfactant with heating in a water bath of 37°C and vigorous vortexing until the entire drug was completely dissolved. EFV SMEDDS formulations were stored for 48 hrs in water bath at room temperature to attain equilibrium and then filled in clear Hard Gelatin Capsules Shell Size "0". Compositions of EFV SMEDDS formulations are presented in **Table I**

Table I: Composition of EFV SMEDDS

Sr. No	Ingredients	SE-I	SE-II	SE-III	SE-IV	SE-V
		mg/ Capsule				
1	Efavirenz (EFV)	50	50	50	50	50
2	Softigen 767	200	175	150	125	100
3	Cremophor EL	175	195	215	235	255
4	Capmul MCM	25	30	35	40	45
Total weight		450	450	450	450	450
Hard Gelatin Capsule Shell Size "0"		1	1	1	1	1

2.5 Characterization of Liquid SMEDDS

2.5.1 Determination of Drug Content in the EFV SMEDDS

From the prepared aliquot of EFV SMEDDS of was transferred into 25 mL volumetric flask and the drug was extracted using 25 mL of ethanol under sonication. The supernatant ethanol extract was separated from formulation and suitably diluted with ethanol. The dilutions were analyzed by UV spectrophotometer at 252 nm. The results of drug content are presented in **Table II**.

Table II: Evaluation data of EFV SMEDDS

Formulation Code	Droplet Size Data (nm) in		Drug Content (%)	Phase Separation Observation
	0.1N HCl	Water		
SE-I	350 ± 3.5	340 ± 6.8	94 ± 6.7	No
SE-II	305 ± 4.8	310 ± 3.7	97 ± 3.4	No
SE-III	250 ± 2.6	262 ± 6.2	100 ± 2.8	No
SE-IV	39 ± 1.2	46 ± 1.9	100.4 ± 1.8	No
SE-V	61 ± 1.8	70 ± 2.3	100.7 ± 1.9	No

2.5.2 Phase Separation Study

Approximately 1 mL of EFV SMEDDS was added to 5 mL of a distilled water in a glass test tube at 25°C and vortexed for 1 min. The mixture was stored at 25°C for a period of 2 h and observed visually for any phase separation. The results are presented in **Table II**.

2.5.3 Droplet Size Analysis

Prepared EFV SMEDDS (1 mL) was diluted 100 times with distilled water and 0.1N HCl in beaker with constant stirring on a magnetic stirrer to from a microemulsion [14-15]. The droplet size of microemulsion was allowed to equilibrate for 1 h and distributions of resultant microemulsion were determined by laser scattering particle size analyzer (Beckman Coulter Counter). The results are presented in **Table II**.

2.5.4 In-vitro Dissolution study

In-vitro dissolution of formulation SE-I, SE-II, SE-III, SE-IV, SE-V was carried out in 900 mL of water in USP-II (Paddle) 50 rpm. At predetermined time interval of 5, 10, 15, 20, 30, 45 and 60 min, a 5 mL of sample was collected and replaced with similar volume of fresh dissolution media. The collected samples were suitably diluted and analyzed by UV-Spectrophotometer at 248.0 nm. The in-vitro dissolution profiles are shown in **Fig. 4**.

RESULTS AND DISCUSSION

3.1 Solubility Study

Efficiency of SMEDDS to enhance the dissolution rate and oral bioavailability of poorly water soluble drug is depends upon the solubility of drug in the key components of SMEDDS, i.e., oil, surfactant and co-surfactant. Hence the screening of the excipients for EFV SMEDDS formulation optimization was carried out on the basis of EFV solubility which also permits the optimum EFV loading in SMEDDS. The solubility of EFV in various vehicles was carried out (i.e., Oil, Surfactant and cosurfactant) is presented in **Fig. 2**. The solubility of EFV was found highest in Softigen 767 (350 mg/g), Cremophor EL (450 mg/g) and Campul MCM (120 mg/g) from selected oil and surfactant grades. Thus for further evaluation of EFV SMEDDS formulation Softigen 767 selected as oil, Cremophor EL as a surfactant and Capmul MCM as a co-surfactant.

3.2 Ternary phase diagram

Ternary phase diagram **Fig. 3-I and 3-II**, depicts that Softigen 767 as a oil, Cremophor EL as a surfactant and Capmul MCM as a co-surfactant showed larger microemulsion region Fig. 3-II compared to self emulsifying system without Capmul MCM (Co-surfactant) Fig 3-I. The concentration of surfactant/co-surfactant when increased compared to oil phase, the microemulsion region also gets increased. Hence the SMEDDS of EFV were formulated with the use of 5:5, 4:6, 3:7, 2:8 and 1:9 ratio of oil: surfactant/co-surfactant because of its highest microemulsion formation region **Table 1**. EFV SMEDDS were further evaluated for drug content which complied the limit of NLT 92% and NMT 110% of the labeled amount of EFV **[16]**. From solubility data it was observed that all five formulation (i.e., SE-1 to SE-V) containing varying proportion of excipients could accommodate and solubilize the specified amount of EFV.

3.3 Phase separation study

Phase separation studies revealed that the designed SMEDDS formulation did not show any separation in 0.1N HCl and water for the period of 2 h, which confirmed the ability of formation of stable microemulsion. This observation was further supported by droplet size analysis results.

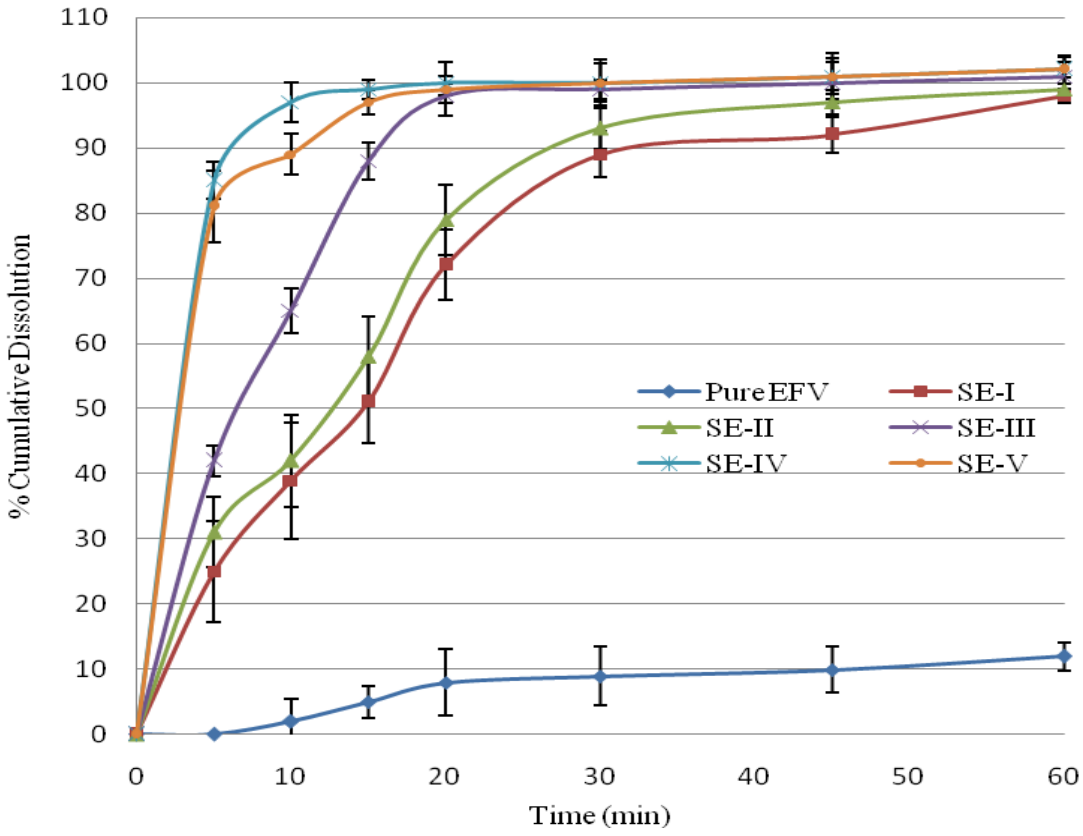

Figure 4. In vitro dissolution profile of Efavirenz SMEDDS of in water.

3.4 Droplet size analysis

Droplet size analysis of all tested five formulations showed resultant droplet size of microemulsion between 39 to 350 nm in 0.1N HCl and water media. Formulation SE-IV showed a droplet size range 39-46 nm in both media (i.e.,

0.1N HCl and water) which confirmed formation of SMEDDS of EFV in both media. SE-IV formulation comprising higher concentration of surfactant compared to other formulations which promotes faster emulsification process and results into finer droplet formation and was independent of the media employed (0.1N HCl and water).

3.5 In-vitro Dissolution study

From In-vitro dissolution study it was observed that when SMEDDS of EFV exposed to water as dissolution media, 10- 15% dissolution of plain EFV achived in 60 min, while all SMEDDS formulation showed complete dissolution within 60 min with significant difference. Formulation SE-IV showed fastest rate of dissolution amongst all SMEDDS formulation as shown in **Fig. 4.**

Faster dissolution rate of EFV SMEDDS formulation with higher concentration of surfactant observed which may be due to formation of finer droplet size during dissolution process. Finer droplet size provides larger surface area for diffusion of solubilized EFV from SMEDDS droplet to dissolution media. The rate limiting factor for dissolution in SMEDDS formulation is the diffusion of solubilized drug in dissolution media which can be control by droplet size formation of resultant microemulsion. Based on the aforementioned results of phase separation, droplet size analysis and in-vitro dissolution studies, the formulation SE-IV was appeared be the optimized SMEDDS of EFV among the tested formulation. All these results confirm the solubility enhancement of EFV by the mechanism of dissolution rate.

CONCLUSION

In this study, we successfully formulate the SMEDDS of Efavirenz by optimizing the various parameters, such as solubility study, ternary phase construction, droplet size analysis, phase separation study, and In-vitro dissolution study. The optimized SMEDDS of Efavirenz confirms the solubility enhancement from dissolution study comprising Softigen 767 as oil, Cremophor EL as surfactant and Capmul MCM as co-surfactant. Droplet size analysis data confirms that the resultant microemulsion droplet size of Efavirenz from SMEDDS are independent of pH, which may reduce the food impact, inter-subject variability and may improve oral bioavailability of Efavirenz with respect to solubility.

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