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Research Article

Pharmacokinetics and Bio-Distribution Properties of a Self-Emulsifying Drug Delivery System Containing Nevirapine

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Abstract

Nevirapine has several dose related side effects. Thus necessitating a formulation with increased bioavailability causing a reduction in dosage. The work was aimed at preparing and evaluating a Self-Emulsifying Drug Delivery System (SEDDS) containing nevirapine. Solubility of nevirapine in various vehicles (oil, surfactant and co-surfactant) was determined and those with the highest solubilizing potential for nevirapine were selected. The pseudo ternary phase diagrams composed of lipid (Soya oil) surfactant-co-surfactant mixture (solutol-cremophor EL) water were mapped and combinations with better micro emulsification properties were chosen. Different batches of nevirapine SEDDS were formulated and assessed. The *in vivo* release profiles of the nevirapine SEDDS were studied using adult albino Wistar rats. The CD4 counts of the animals and biodistribution of nevirapine to various organs was also determined. SEDDS formulation improved the aqueous solubility and bioavailability of nevirapine and resulted in more reproducible blood–time profile. The biodistribution of nevirapine SEDDS was lower to the liver but higher to the brain when compared with conventional nevirapine tablets ($p<0.05$). Nevirapine SEDDS had a higher time-dependent increase in CD4 cells/μ^l than the conventional tablets ($p<0.05$).

Nevirapine SEDDS increases the drug's aqueous solubility, permeability and bioavailability enabling dose reduction.

Keywords: Antiretroviral; Plasma profile; Emulsification; *In vivo* kinetics

Introduction

The oral route is the most convenient means of drug administration to patients. This route however poses problems of absorption for many drugs owing to their poor solubility profiles. Drug discovery data suggest that about 40% of new drug entities introduced into the market have solubility problems [1]. To overcome this challenge, several drug delivery systems have been explored to enhance drug solubility, dissolution in the gastrointestinal tract and, ultimately, absorption into the systemic circulation. Self-Emulsifying Drug Delivery Systems (SEDDS) have great potential in improving drug bioavailability.

SEDDS are mixtures of oils and surfactants, ideally isotropic, and sometimes containing one or more hydrophilic solvents as co-surfactants/co-solvents, which emulsify spontaneously to produce fine oil in-water emulsions when introduced into aqueous media such as the Gastrointestinal Tract (GIT) under gentle agitation [2,3]. Recently, SEDDS have been formulated using medium chain triglyceride oils and non-ionic surfactants, the latter had been less toxic. SEDDS can be orally administered in soft or hard capsules. Some of the advantages of SEDDs include: Improved drug solubilization, long half-life, improved oral bioavailability, consistency in drug absorption, protection against hydrolysis by enzyme in GIT, reduction of gastrointestinal metabolism of drug prior to systemic absorption, by-pass of hepatic first-pass metabolism, selective targeting of drugs toward specific absorption window in GIT, protection of sensitive drug substances, reduced variability including food effects [4,5].

The process of self-emulsification proceeds through formation of Liquid Crystals (LC) and gel phases, the properties of which significantly affect the formation of droplets and interfaces available for partitioning of drug [6-8]. Lipophilic substances with poor solubility are thus candidates for such formulations. Several SEDD formulations have been explored to enhance the solubility of poorly soluble drugs [9-18].

Nevirapine is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) which is one of the drugs used in the first line management of HIV/AIDS as a component of the Highly Active Antiretroviral Therapy (HAART) regimen. Its poor solubility and high permeability makes it a Biopharmaceutics Classification System (BCS) class II drug, thus making it a candidate for SEDDS formulation (Figures 1-4).

This study was aimed at determining the ability of a SEDDs formulation prepared using locally available oils, to enhance the solubility and release profile of nevirapine, as well as determine its effect on the pharmacokinetic parameters of the drug in immune-compromised rats.

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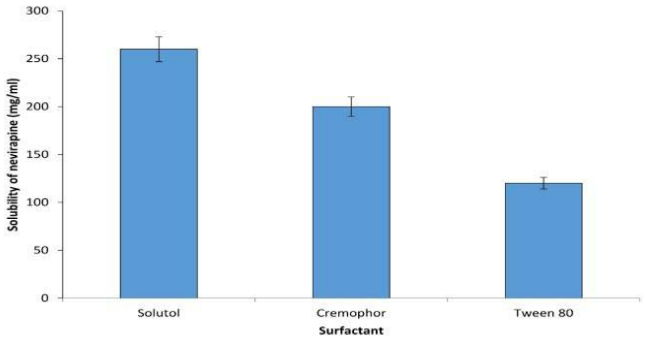

Figure 1: Solubility of Nevirapine in different surfactant solutions.

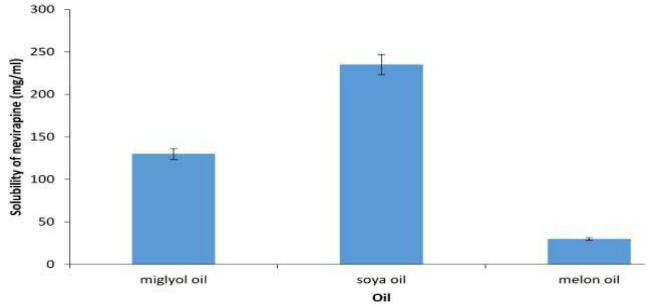

Figure 2: Solubility of Nevirapine in different oils.

Materials and Methods

Materials

The following materials were used as procured from their manufacturers: Nevirapine, a gift from Fid son Healthcare Ltd, Lagos; Solutol® HS 15 (BASF Ludwigshafen, Germany), Cremophor® EL (Ludwigshafen, Germany), cyclophosphamide (Korea United Pharm Inc), soya oil (processed in our Laboratory), ammonia (Merck, England), hydrochloric acid (Merck, Germany), Monobasic potassium phosphate, ethanol (BDH Chemicals Ltd Poole, England), sodium chloride (Merck, England), sodium hydroxide (Avoadale Laboratories, England), distilled water, and water for injection. All other reagents were of analytical grade and were used as received.

Methods

Extraction of soya oil: About 45 kg of soya beans was crushed to powder using a laboratory mill. The resultant powder was soaked in 2.5 L of n-hexane for 48 h and subsequently passed through a muslin cloth to filter it and dried using a rotary evaporator (GmbH, Germany).

Solubility studies of nevirapine in various vehicles: The solubility of nevirapine in various lipids, surfactant and co-surfactants was determined. The method of Shen and Zhong [17] was used with slight modification. An excess amount of nevirapine was introduced into 2 ml of each excipient and the mixture in a capped cuvette was stirred in a water bath at 25°C. A vortex mixer was used to facilitate the solubilization. After standing for 24 h and reaching equilibrium at ambient temperature, each cuvette was centrifuged at 3000 rpm for 10 min using a centrifuge (Sigma 3 k15; Sigma USA). Undissolved nevirapine was removed by filtering in a membrane filter (0.45 μm).

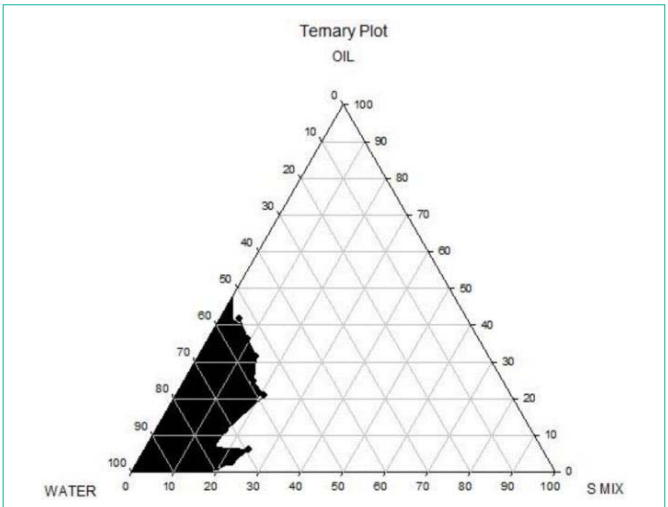

Figure 3: Ternary phase diagram of 1:1 surfactant mix, oil and water.

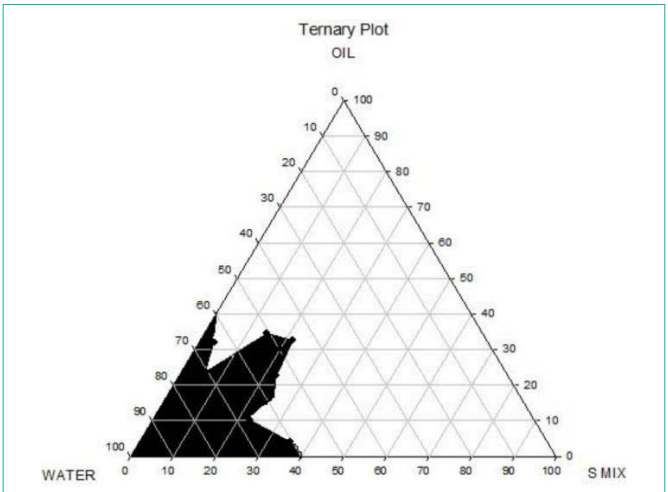

Figure 4: Ternary phase diagram of 2:1 surfactant mix, oil and water.

The concentration of nevirapine was determined using a UV-Vis spectrophotometer (Jenway 6405, USA) from a calibration curve of the drug in the oils at a predetermined wavelength of 311 nm [9,18] (Tables 1-3).

Construction of pseudo ternary phase diagram: Pseudo ternary phase diagrams consisting of lipid, surfactant, co-surfactant and water were constructed according to the method using the titration method [19]. The non-ionic surfactant, Solutol® HS, and the solubilizer, Cremophor® EL, as co-surfactant were selected. The lipid employed was soya oil. The surfactant was blended with co-surfactant in the ratio of 2:1, 1:1, 3:1 and 1:2 using a magnetic stirrer (IKA, Germany) at 200 rpm for 10 min. Volumes of each surfactant and co-surfactant mixture (S_{mix}) were blended with lipid in a ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 w/w also at 200 rpm for 10 min using a magnetic stirrer (IKA, Germany). Water was folded in a drop-wise manner to each lipid-S_{mix} with gentle shaking at 37 °C. After equilibrium, the appearance and dispersibility of the formulation were observed, photomicrographs taken and droplet size distribution was analyzed. The amount of water, lipid, surfactant and co-surfactant folded was noted down, and calculated. The pseudo ternary phase diagrams were

Table 1: The globule sizes of microemulsions.

Globule sizes (µm) ± SD	Globule sizes (µm ± SD)			
	A	B	C	D
1:9	13.12 ± 2.50	20.37 ± 1.00	30.81 ± 2.50	15.31 ± 4.00
2:8	25.03 ± 9.10	10.85 ± 2.00	7.53 ± 4.70	8.09 ± 1.80
3:7	7.32 ± 3.40	8.47 ± 3.00	9.82 ± 5.00	7.54 ± 2.90
4:6	8.85 ± 2.00	8.32 ± 4.60	15.51 ± 2.10	9.38 ± 2.00
5:5	7.28 ± 7.00	30.70 ± 3.90	12.08 ± 4.90	8.53 ± 1.50
6:4	8.57 ± 5.20	12.25 ± 4.00	8.71 ± 2.00	7.35 ± 8.00
7:3	5.82 ± 5.00	8.24 ± 1.00	5.29 ± 5.00	7.28 ± 3.00
8:2	5.35 ± 9.00	7.01 ± 1.50	7.39 ± 5.00	8.93 ± 3.00
9:1	7.48 ± 2.20	8.55 ± 2.00	7.72 ± 2.20	8.85 ± 3.00

Key: A = 1:1 S_{mix}; B = 2:1 S_{mix}; C = 3:1 S_{mix}; D = 1:2 S_{mix}

Table 2: Particle sizes of nevirapine SEDDS formulations.

Formulation	Particle sizes (µm) ± SD	
	3:1 S_{mix} Formulation	2:1 S_{mix} Formulation
A	15.95 ± 2.00	17.50 ± 5.10
B	13.82 ± 1.50	15.94 ± 2.20
C	10.33 ± 4.00	12.22 ± 3.50
D	9.85 ± 3.10	12.00 ± 2.00

Table 3: Emulsification time of nevirapine SEDDS.

3:1 S_{mix} (ml)	Emulsification time test	
	Water volume (ml)	Time (sec)
A	2.3	32 ± 5.0
B	1.9	27 ± 8.0
C	1.7	22 ± 2.9
D	1.5	19 ± 3.4
2:1 S_{mix} (ml)	Water volume (ml)	Time (sec)
A	4.7	60 ± 3.0
B	3.2	44 ± 5.0
C	2.6	30 ± 7.0
D	1.5	26 ± 1.8

mapped using Sigma Plot Window 6.1 (USA). The micro emulsion regions in the diagrams were plotted and the ternary diagrams with wider region indicated the better self-micro emulsification efficiency [20].

Stability analysis

Globule size analysis: The particle size/distribution was analysed by computerized image analysis using a motic image analyzer (Moticam, China) attached to a binocular microscope (Weltzer, Germany). The nevirapine SEDDS formulation was dispersed in water on a microscope slide covered with a cover slip and imaged using the motic.

The stability of the micro emulsion was assessed by analyzing droplet size and distribution. Isotropicity test

Stability of the micro emulsions was assessed visually. Changes in droplet size, phase separation and /or precipitation were noted. This was done 24 h after preparation and repeated three months post preparation.

Photomicrographs of the micro emulsion: The structure, droplet size, and size distribution of particles of the micro emulsion were observed using a motic image analyzer (Moticam, China) attached to a binocular microscope (Weltzer, Germany).

Preparation of nevirapine SEDDS: After the pseudotenary phase diagrams were plotted and compared, optimum surfactant, co-surfactant and lipid combination were selected. Nevirapine SEDDS formulations were prepared by firstly dissolving nevirapine into Solutol® HS-Cremophor® EL mixture (S_{mix}) in a test tube heated to 25°C in a water-bath, then, the required weight of the lipid was added in the test tube and mixed properly using a magnetic stirrer (IKA, Germany) at 200 rpm for 10 min. The mixture was filled into capsules and tightly sealed and stored at a temperature of 25°C until required. Different ratios of S_{mix} to oil were used to formulate different concentration of nevirapine SEDDS. The ratios of S_{mix} to oil used were 8:1, 6:1, 4:1 and 2:1.

Emulsification time test: A 1.0 ml volume of each of the different concentrations of nevirapine SEDDS formulation was titrated with water. The emulsification time was noted and recorded. The volume of water used was also recorded. The photomicrograph of the nevirapine micro emulsion was also taken.

Infinite dilution test: A 1 ml volume from each formulation of nevirapine SEDDS was diluted to 10 ml, 100 ml and 1000 ml with distilled water respectively and the degree of phase separation noted.

Absolute drug content: Beer's calibration curve of nevirapine was obtained fornevirapine in plasma and ethanol at a concentration range of 1 to 5 mg% respectively at a predetermined wavelength of 255 and 291 nm respectively. A 50 mg quantity of nevirapine SEDDS was dissolved in ethanol and analyzed in a spectrophotometer (Jenway 6405, USA) at 291 nm. The determination was replicated

Table 4: Pharmacokinetic evaluation of some selected SEDDS formulation and nevirapine tablet.

Formulations	Cmax (mg/ml)	Tmax (min)	Corr (x;y)	$T_{1/2}$(min)	AUC (mg min/ml)	MRT (min)
3:1ASEDDS	0.4370	300.0000	-0.9876	179.6767	214.2900	373.6161
3:1BSEDDS	0.4100	300.0000	-1.0000	241.1878	201.3900	368.7859
2:1ASEDDS	0.3930	300.0000	-0.9659	306.4380	177.1800	381.2733
2:1BSEDDS	0.4400	300.0000	-0.9954	287.5719	237.9000	396.2421
Nev Tab	0.3600	360.0000	-0.8930	175.6660	189.0900	292.5797

Key: C_{max}= maximum plasma concentration; T_{max}= time to achieve maximum plasma concentration; AUC= Area under Curve; MRT= mean residence time; $T_{1/2}$= half-life

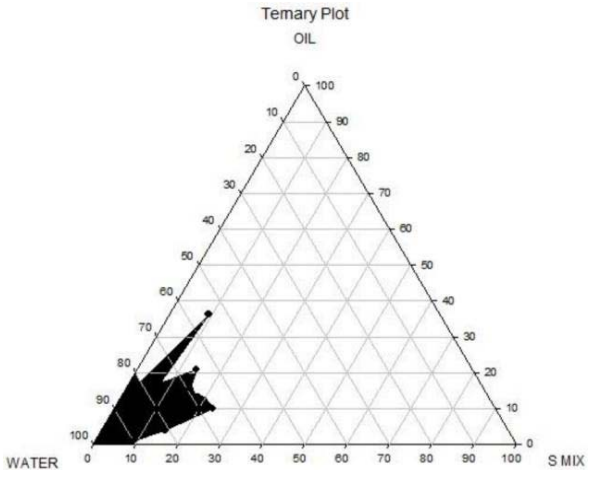

Figure 5: Ternary phase diagram of 3:1 surfactant mix, oil, and water.

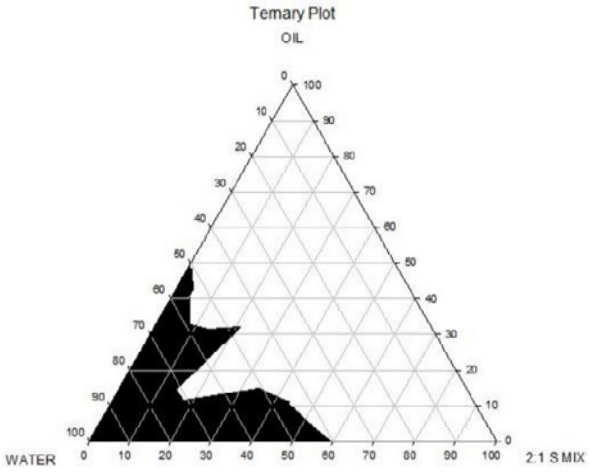

Figure 6: Ternary phase diagram of 1:2 surfactant mix, oil and water.

three times and the mean taken to obtain the absolute drug content for each batch.

***In vivo* drug release studies:** Prior to commencement of this study, ethical clearance was got from the ethical committee of the institution. The animal studies were conducted in line with the revised Helsinki declaration of 2000 and in accordance with the guidelines set forth in the eight edition of the guide for the care and use of laboratory animals published by the National Academy of Sciences, the National Academies Press, Washington, D.C.

In this study, fifteen adult Albino Wistar rats of both sexes (130-160 g) were used. The rats were weighed and divided into groups of threes'. They were allowed access to food and water ad libitum for one week to acclimatize. Blood samples of rats were withdrawn to determine the base line CD4 count (Figures 5 and 6). Afterwards, a single dose of 30 mg/kg of cyclophosphamide was administered to the rats Intraperitoneally (IP) to induce immunosuppression [21,22]. The immune suppressed rats were allowed to starve for 24 h with free access to drinking water. At the end of this period, blood samples were withdrawn from the retro-orbital plexus of the rats at time, t=0. Subsequently, 10 mg/kg of pure nevirapine was administered to the rats in group one (served as control) while the remaining four groups received 10 mg/kg of nevirapine SEDDS preparation. After administration, blood samples were withdrawn from the retro-orbital plexus of the animals at intervals of 1, 3, 5, 8 and 15 h respectively with the aid of heparinized capillary tubes and placed in EDTA bottles. The withdrawn blood samples were analyzed for CD_4 cells using a CD_4 count machine. The blood samples were centrifuged (Abishkar Centrifuge, India) at 5000 rpm for 10 min. The resulting plasma was then carefully collected with the aid of 1 ml syringe and its absorbance read using a UV-Vis spectrophotometer (Jenway 6405, USA)

Biodistribution studies: The distribution of nevirapine from the SEDDS to various organs of the body was checked using healthy albino rats. Three groups of six rats were used. Cyclophosphamide, 30 mg/kg was administered orally to all the rats and denied access to food for 24 h with free access to drinking water. The test group received nevirapine SEDDS dispersed in water and given orally, (equivalent to 10 mg/kg), the control groups received normal saline, while the reference group received nevirapine pure drug (10 mg/kg). After the administration, the rats were sacrificed at intervals from 1 to 1.5 h. The sacrificed animals had their kidneys, livers, brains and spleens harvested. The harvested organs were pulverized, and soaked in ethanol for about 30 min, and filtered. The filtrates were then analysed with a UV-Vis spectrophotometer (Jenway 6405, USA) at a predetermined wavelength of 255 nm for nevirapine content.

Pharmacokinetic and data analysis: For group analysis, Student t-test was used. The pharmacokinetic data was analyzed statistically using the non-compartmental model obtained with the Win Nonlin software (Version 4; Pharsight Inc, Mountain CA). Data from the plasma concentration time curve with 15 h after drug intake were used to obtain the peak plasma concentration (C_{max}, mg/ml), time to peak plasma concentration (T_{max}, min), Mean residence time (MRT, min).

Results and Discussions

Results

Yield of soya oil extract: The results of the yield of soya oil showed that the percentage yield of the soya oil extracted was 66.5%. The results show that soya bean exhibited high yield of oil thus making it a relatively efficient source of oil.

Solubility of nevirapine in surfactant solutions: The results of the solubility of nevirapine in surfactant solution are shown in Figure 1 and show that the drug exhibited solubility of 260, 200 and 120 mg/ml in Solutol® HS, Cremophor® EL and Tween® 80 respectively. These results thus revealed that nevirapine exhibited significantly higher solubility in Solutol® HS ($p<0.05$).

Solubility of nevirapine in the oils: The results of the solubility of nevirapine in different oils as shown in Figure 2 depict that the drug exhibited significantly higher solubility in soya oil than migloyl and melon oil ($p<0.05$). Nevirapine showed a solubility of about 235, 130, and 30 mg/ml in soya oil, miglyol and melon oil respectively.

Pseudoternary Phase diagram: The pseudo ternary phase diagrams (3-6), revealed different micro emulsion regions for the the S_{mix} ratios, with the 3:1 S_{mix} having the widest micro emulsion region followed by S_{mix} 2:1. Thus S_{mix} 3:1 and S_{mix} 2:1 were used for further

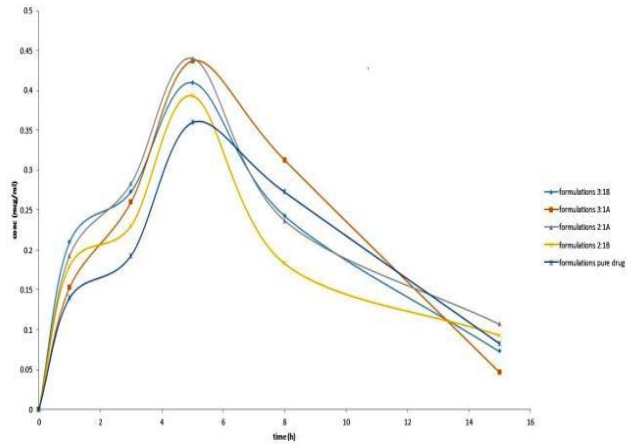

Figure 7: *In vivo* drug release studies.

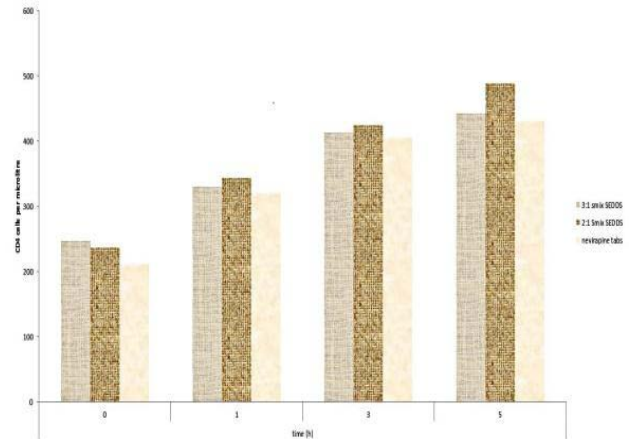

Figure 8: Effect of formulations and conventional nevirapine tablet on CD_4 cell count.

studies.

Particle sizing and stability analysis: The globule sizes of the different micro emulsions were determined. It was observed that the globule sizes increased with increasing oil content (Table I). On the basis of this, different ratios of S_{mix} to oil were used to formulate different concentrations of nevirapine SEDDS. The ratios of S_{mix} to oil used were 8:1, 6:1, 4:1 and 2:1.

The photomicrographs of the optimized formulations revealed a mean particle size of 11.165 ± 2.75 µm and 12.495 ± 1.43 µm for the 2:1 and 3:1 S_{mix} ratios respectively (Tables 1 and 2).

Emulsification time results: The results of the emulsification time test are presented in (Table 3) below. The results showed that nevirapine content and oil ratio affected emulsification times with lower times recorded for lower drug (nevirapine) and oil contents.

***In vivo* drug release studies:** The results of the *in vivo* release studies showed a gradual increase in the plasma concentration of all formulations up to a maximum concentration. Peak values were observed for all the formulations at 5 h. However, the SEDDS-containing nevirapine formulations exhibited higher peak plasma concentration values of 0.437 mg/ml, 0.393 mg/ml for the 2:1 and 3:1 SEDDS formulations respectively, as compared with the pure nevirapine with a C_{max} of 0.360 mg/ml (Figure 7).

Table 5: Biodistribution studies of 2:1 S_{mix} SEDDS.

Organ	Concentration (µg/ml)	
	1h	1.5h
Brain	0.367 ± 0.030	0.400 ± 0.023
Liver	0.467 ± 0.033	0.567 ± 0.025
Kidney	0.167 ± 0.025	0.26 7± 0.045
Spleen	0.133 ± 0.020	0.167 ± 0.037

***n*= 6**

Table 6: Biodistribution studies of conventional nevirapine tablet.

Organ	Concentration (µg/ml)	
	1h	1.5h
Brain	0.300 ± 0.022	0.420 ± 0.034
Liver	0.500 ± 0.025	0.667 ± 0.030
Kidney	0.200 ± 0.020	0.267 ± 0.033
Spleen	0.133 ± 0.035	0.200 ± 0.047

Pharmacokinetic evaluation: Pharmacokinetic parameters evaluated (Table 4) showed that the SEDDS formulations had greater C_{max}, T_{max}, T1/2 and MRT than the conventional nevirapine tablet.

Effect of formulation on CD_4 count: The decrease in CD_4 cells after inducing immune suppression was increased after administration of nevirapine from SEDDS and conventional nevirapine tablet respectively (Figure 8). There was time-dependent increase in the CD_4 cells after nevirapine administration. Nevirapine from 2:1 S_{mix} SEDDS formulation gave the highest CD_4 count after 5 hours followed by 3:1 S_{mix} SEDDS formulation. The lowest CD_4 count was recorded with nevirapine from the conventional tablet. The reason being that the conventional tablet had lower bioavailability than the nevirapine SEDDS.

Biodistribution studies of formulation

The biodistribution studies carried out with one of the optimized formulations-2:1 SEDDS containing nevirapine, and conventional tablets, showed the least drug distribution to the spleen; 0.133 *µg/g* of tissue, 0.167 *µg/g* of tissue at 1h and 1.5 h respectively for the 2:1 SEDDS, and 0.133 *µg/g* of tissue and 0.200 *µg/g* of tissue at 1 h and 1.5 h respectively for the conventional tablets. The highest distribution was to the liver with 0.467 *µg/g* of tissue and 0.567 *µg/g* of tissue at 1 h and 1.5 h respectively for the 2:1 SEDDS and 0.500 *µg/g* of tissue and 0.667 *µg/g* of tissue at 1 h and 1.5 h respectively for the conventional nevirapine tablets (Tables 5 and 6).

Discussions

The concentration of nevirapine in various excipients at 25 °C was determined by UV-Vis spectrophotometry. Preliminary studies were performed for selection of oil and surfactant which are an important and critical requisite for formulation of SEDDS. Solubility studies are conducted to determine the best combination of drug, surfactant and oil. This helps to improve drug loading and decrease production costs *via* a reduction in the quantity of excipient utilized. From the solubility studies conducted, the oils showed varying solubilizing potentials for nevirapine with soya oil exhibiting the greatest

(Figure 2) hence its selection for further studies. Also, preliminary investigation showed that soya oil has better micro emulsification properties when compared the other oils. Among the surfactants studied, Solutol® HS and Cremophor® EL had greater solubilizing potential for nevirapine than Tween 80® (Figure 1). The selection of surfactant was also on the basis of micro emulsification ability for soya oil. All surfactants studied had good mucosal compatibility, but studies have shown that Solutol® HS and Cremophor® EL had better micro-emulsification ability for soya oil as compared to Tween® 80 [23]; this was also confirmed by our studies.

Anionic surfactants are known to cause irritation of the mucosal surfaces [24,25]. Therefore, the non-ionic substances Solutol® HS and Cremophor® EL were selected as surfactant and co-surfactant respectively. An additional important criterion for selection of the surfactants is their HLB values. The William C. Griffin method as cited in Rajinikanth, Keat, Sunjay [11] states that the HLB value to form oil in water (o/w) emulsion should be between 8 and 18. However Konmmuruet al. [26] had earlier stated that HLB values for microemulsion formation should be greater than 10. Whichever method adopted, the surfactant and co-surfactants chosen for this study satisfied the requirement.Solutol® HS 15 and Cremophor® EL have HLB values of 14-16 and 12-14 respectively.The addition of cosurfactant has been shown to increase microemulsion region in Solutol® HS 15 -Cremophor® ELsystem [27]. From the pseudoternary phase diagrams (Figures 3-6), it is evident that all the S_{mix} ratios have good micro emulsion region but the S_{mix} 3:1 had the widest micro emulsion region followed by S_{mix} 2:1. Thus S_{mix} 3:1 and S_{mix} 2:1 were used for the study.

The globule sizes of the different micro emulsion were determined. It was observed that the globule sizes increased with increasing oil content (Table I). On the basis of this, different ratios of S_{mix} to oil were used to formulate different concentrations of nevirapine SEDDS. The ratios of S_{mix} to oil used were 8:1, 6:1, 4:1 and 2:1.

The particle size distribution is one of the most important characteristics of evaluating emulsion stability [3] and also *in vivo* fate of emulsion [28]. The particle size of the nevirapine micro emulsion was decreased with reduction in the oil content of SEDDS. When the S_{mix}: oil ratio was 2:1, bigger particles were formed in comparison with ratio 4:1, 6:1 and 8:1 of S_{mix} to oil (Table 2). The emulsification time of nevirapine SEDDS formulations decreased with decrease in nevirapine concentration and oil content (Table 3). The emulsification time was determined to evaluate or assess the in-vitro self-micro emulsification efficiency, dispersibility, and formulation stability. From the post formulation isotropicity test, it was observed that the micro emulsions showed no phase separation. This continued even after three months of storage. Ten-fold, hundred-fold and 1000-fold dilution of the micro emulsion with water were clear and isotropic as observed visually, showing that serial dilutions showed no separation of phases and indicating that the micro emulsion formed is oil–in-water and very stable.

The higher C_{max}, T_{max}, ¬AUC, and MRT exhibited by the SEDDS formulation over the conventional tablets could be as a result of enhanced solubilization of the drug when formulated as SEDDS leading to an improved bioavailability. SEDDS are known to avoid first pass metabolism due to their uptake by the lymphatic system. This would thus increase their bioavailability. This increased bioavailability shown by higher AUC values for the SEDDS than the conventional nevirapine tablets as well as the increased T1/2 and MRT could be explored in dose reduction of the drug thus reducing the likelihood of dose-related side effects experienced. The increased bioavailability was supported previous studies on nevirapine SEDDS by some authors [29,30]. Cyclophosphamide suppresses the immune system by decreasing the CD4+CD45RA+ suppressor/inducer T cells [31]. The active form of cyclophosphamide, 4-Hydroperoxycyclophosphamide (4-HC) is involved in this action. These results reveal a time-dependent increase in the drug distribution to various organs with nevirapine drug concentrations being higher in the liver than other organs investigated. The lower concentrations of nevirapine in the liver from the nevirapine SEDDS could be as a result of avoidance of first-pass metabolism by the SEDDS formulation. This is one of the notable advantages of SEDDS formulations. This could portend a potential advantage in drug administration since hepatotoxicity of nevirapine SEDDS could be reduced in comparison with the conventional nevirapine tablets.

The studies conducted show that SEDDS possess a remarkable potential in altering the kinetics of orally administered drugs. The solubility of nevirapine was enhanced when administered as SEDDS while its *in-vivo* kinetics was significantly altered. Further studies need to be carried out to determine an optimum SEDDS formulation of the drug aimed at improving its solubility, reducing its dose, and thus reducing the likelihood of dose-related side effects.

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