Research Article

Solubility Enhancement of Poorly Water Soluble Drug Efavirenz by Solid Self Emulsifying Drug Delivery Systems

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ABSTRACT

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which has the poor aqueous solubility of 4-9 µg/ml.Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. One of the promising techniques is Self-Micro Emulsifying Drug Delivery Systems (SMEDDS). Self emulsifying drug delivery system has gained more attention due to enhanced oral bio-availability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT. The main objective of this study is to improve the solubility of efavirenz by formulating in to a self-emulsifying drug delivery system with improved dissolution rate for the oral delivery of poorly water-soluble antiretroviral agent.. Solubility was determined in various oils, surfactants and co surfactants. Ternary phase diagrams were constructed to evaluate the micro emulsification region. Liquid SEDDS were prepared using LLWL 1349, Labrafac PG as oils and cremophor EL, cremophor RH40 as surfactants and labrasol, transcutol HP as co-surfactants. Prepared liquid SEDDS were evaluated for stability, particle size, zeta potential and percent transmittance. Selected liquid formulations were converted to solid SEDDS by adsorbing onto a solid carrier Neusilin. Prepared solid SEDDS were evaluated for flow properties and in-vitro drug release studies. Results proved that prepared solid SEDDS have good flow properties and improved drug solubility and dissolution profiles (99.95%) when compared to pure efavirenz.

Keywords: Adsorption, antiretroviral drug, dissolution rate, neusilin, solid- SEDDS

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INTRODUCTION

Majority of drugs used are lipophillic in nature, but their low solubility and bioavailability limits their use. Thus an attempt has been made to develop a system which could increase solubility, bioavailability and hence reduce the dose. Many researchers, in their diverse work on self emulsifying drug delivery system (SEDDS), have demonstrated the importance, rational and applicability of these systems in delivering lipophillic active moieties. Since SEDDS are systems designed for individual drug candidates, development of an appropriate and optimized system needs careful attention to factors like physico-chemical properties, dose, absorption window, etc., of a drug candidate in question. Hence designing and optimization of SEDDS for selected model drugs was one aspect of this work [1].

Efavirenz is one of the most promising antiretroviral drug belonging to BCS class II, i.e. it has low water solubility and high permeability, it has an oral dose of 600 mg/day and bioavailability of 40 %. Such a high dose of efavirenz causes serious side effects like insomnia, loss of memory and suicidal attempts. Thus there is a need to enhance solubility and bioavailability of drug in order to reduce dose and hence side effects [2,3].

SEDDS or self-emulsifying lipid formulations (SELF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents and co-solvents/ surfactants. Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs.

SEDDS systems act as carriers for drugs by forming fine emulsions, or micro-emulsions, under gentle stirring when diluted in water or physiological media with physiological motion [4, 5].

Conventionally liquid SEDDS are filled in hard or soft gelatin capsules for ease of administration. For oral delivery, solids are always preferred over liquids for many reasons like potential of leaking, leaching, interactions of liquids and patient discomfort. In addition, liquid systems also pose stability and handling problems. Recently a trend has been observed to formulate semisolid and solid SEDDS. But in all these studies, to obtain solids with suitable processing properties, the required ratio of solidifying excipients to SEDDS were very high, and it seems to be practically non-feasible for drugs having limited solubility in oil phase. In the context of present research work, it was envisaged that the transformation of liquid SEDDS to solid dosage forms (with minimum amounts of solidifying aids i.e. adsorbents) would be a significant advancement for reducing the problems encountered with conventional liquid system [6,7].

So there is a need to formulate and evaluate SEDDS of efavirenz to enhance solubility, dissolution and bioavailability and hence reduce dose.

MATERIALS AND METHODS

Materials:

Efavirenz was obtained as a gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India). Labrafac Lipophile WL 1349, Labrafac PG, Labrasol, Transcutol HP, Transcutol 90, Capryol 90, was donated by Gattefosse (Mumbai, India). CremohorRH40, cremophorEL were purchased from BASF chemicals India Ltd (Mumbai, India). HPLC grade Acetonitrile, water was purchased from Merck (Mumbai, India).

Methods:

Solubility studies

The saturation solubility of efavirenz was determined in various oils, surfactants and co-surfactants. The excess amount of drug was added to each screw capped glass vials containing 2 ml of vehicle in a water bath with constant stirring using a vortex mixture to facilitate drug solubilisation. The mixture was kept at ambient temperature for 72 hr to attain equilibrium. The samples were then centrifuged at 2000 rpm for 15 min and then the supernatant was taken. The aliquots of supernatant were diluted and drug assay was performed by using HPLC method [8].

HPLC analysis:

The determination of solubility of efavirenz in the different excipients was made by HPLC analysis. The following conditions were adopted [9].

Column -c18
Mobile phase -Acetonitrile: water-80:20
pH -3.0 (adjusted using ortho-phosphoric acid)
Flow rate -1ml/min
Injection volume -20µl
UV wavelength - 252nm

Construction of pseudo-ternary phase diagram:

The pseudo-ternary phase diagrams of oil, surfactant/co-surfactant, and water were constructed by a water titration method at room Temperature, to investigate the micro-emulsion region. For this different combinations were prepared those are

1. The surfactant (Cremophor EL) was blended with a co-surfactant (Transcutol HP or Labrasol) in a fixed volume ratio 3:1, 2:1, respectively. Aliquots of surfactant/co-surfactant mixture were then mixed with the oil (Labrafac lipophile WL1349) at volume ratios of 9:1, 8:2, 7:3, 6:4, in different vials. The vials were vortexed on a cyclomixer for sufficient time to attain uniformity.
2. The surfactant (Cremophor RH40) was blended with a co-surfactant (Transcutol 90 or Capryol 90) in a fixed volume ratio 4:1, 3:1, respectively. Aliquots of surfactant/co-surfactant mixture were then mixed with the oil (Labrafac PG) at volume ratios of 9:1, 8:2, 7:3, 6:4, in different vials. The vials were vortexed on a cyclomixer for sufficient time to attain uniformity

A small amount of water in 5% increment was added into each vial and mixed with vortex. The samples set aside to attain the equilibrium. The equilibrated samples were evaluated visually, and classified as clear microemulsion, coarse emulsion [10]. The percentage of surfactant, cosurfactant, oil

and water were calculated and pseudo ternary phase diagrams were plotted using TriPlot Version 4.1 Software.

Formulation of SEDDs:

A series of SELF's formulations were prepared using Capryol 90, Transcutol 90, Transcutol HP and Labrasol as the Co-surfactants, Cremophor EL and Cremophor RH40 as Surfactants and Labrafac lipophile WL1349 and Labrafac PG as the oil. In all the formulations, the concentration of Efavirenz was kept constant (i.e., 100mg). Surfactant/Co-surfactants mixture was prepared by mixing in suitable proportions and vortexed. Accurately weighed amount of Efavirenz was dispersed in oil and surfactant/cosurfactant mixtures were added to it. The components were mixed by shaking and vortexing. The mixture was stored at room temperature for further use.

Characterization of liquid self-emulsifying lipid formulations:

Self emulsification time:

Rate of emulsification was taken as an important index for assessment of the efficiency of self-emulsification. Formulations were graded for self-emulsification time, according to the visual assessment criteria for self microemulsion formation [11]. Self emulsifying mixtures should disperse completely and quickly upon aqueous dilution under mild agitation.

Phase separation and stability study of emulsion:

Each SELF formulation (50µL) was added to a glass vial containing 5mL of doubled distilled water at 37C. After 1 minute vortexing, each mixture was stored and observed for phase separation and precipitation of the drug. The observations were made after 2, 4, 6, 8, 12, and 24 hour's period of time. The study was repeated by taking 0.1N HCl (SGF without enzyme).

Effect of Dilution:

Selected formulations were subjected to dilution in different ratios of 1:10, 1:50, 1:100 and 1:1000 fold dilution with distilled water, 0.1 N HCl and phosphate buffer (pH 6.8). The diluted emulsions were stored for 24 hr and monitored for any physical changes (such as precipitation or phase separation).

Droplet size measurement and Zeta potential determination:

SEDDs formulations were diluted to 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. The droplet size distributions and Zeta potential of resultant microemulsion were determined after 1 hr using a Horiba SZ-100 Nanoparticle Analyzer which works on the principle of light scattering and measuring its intensity at 900C. Size analysis was performed at 25ºc by placing the sample in an electrophoretic cell with an angle of detection of 90ºC for measurement [12]. The droplet size and Zetapotential of formulations were obtained.

Percent transmittance:

The percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at particular wavelength using UV spectrophotometer keeping distilled water as blank [13]. The formulation have percent transmittance > 99 %, then formulation has transparent nature.

Thermodynamic Stability Studies:

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SEDDs formulation. Formulations were diluted with deionized water (1:20) and centrifuged at 15,000 rpm for 15 min, and formulation was observed visually for phase separation. Formulations that did not show any sign of phase separation after centrifugation were subjected to freeze thaw cycle [14]. In a freeze thaw study, efavirenz SELF'S was diluted with deionized water (1:20) and two freeze thaw cycle between (−20°C and +25°C) with storage at each temperature for not less than 4 hours were done for formulations.

Preparation of S-SEDDS

From the prepared liquid sedds two formulations LLCT31-2 and LPCC 41-4 are selected for the preparation of solid sedds based on the size and in-vitro drug release. S-SEDDS was prepared by mixing selected liquid SEDDS containing efavirenz with Neusilin in 1:1 proportion. In brief liquid S EDDS was added drop wise over Neusilin contained in broad porcelain dish. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation [15]. Resultant damp mass was passed through sieve no.

120 and dried at ambient temperature and stored until further use.

Evaluation of S-SEDDS

Flow properties of S-SEDDS

Angle of repose

The angle of repose of S-SEDDS was determined by funnel method. Accurately weighed sample were taken in a funnel. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of S-SEDDS powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose calculated using the following equation. $\tan\theta = h/r$ [16].

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of S-SEDDS was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulae [17].

LBD = $Weight\ of\ powder/Volume\ of\ packing$ TBD = $Weight\ of\ powder/Tapped\ volume\ of\ packing$

Compressibility Index

The compressibility of the granules was determined by Carr's Compressibility Index. Carr's compressibility index (%) = $(TBD-LBD)\ /\ TBD \times 100$

Hausner ratio

A similar index like compressibility index has been defined by Hausner. Hausner ratio can be calculated by formula: Hausner ratio = TBD/LBD

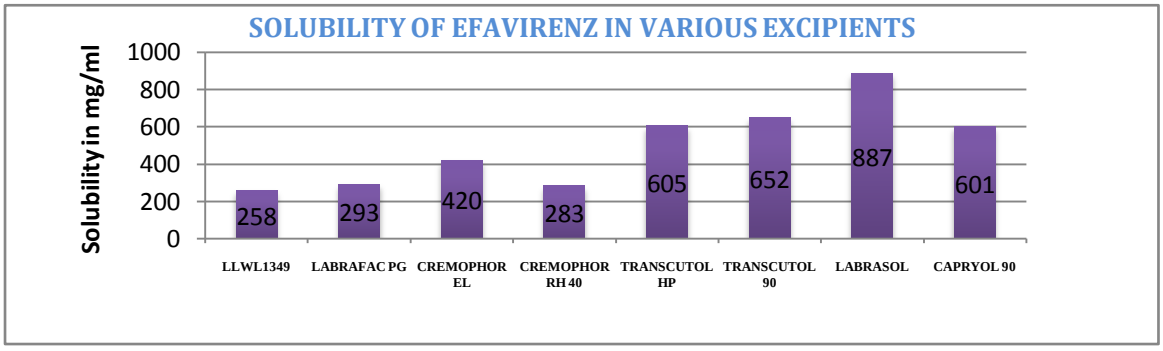
***In vitro* drug release studies:**

In vitro drug release studies of selected liquid SEDDs and solid SEDDs were performed using USP Type II dissolution apparatus (D S 8000 Lab India Dissolution Apparatus). The dissolution medium consisted of 900 ml of 2% SLS. No enzymes were added to the dissolution media Liquid filled Capsules containing 100mg of efavirenz was introduced into the dissolution medium. At predetermined time intervals 5ml of aliquot was withdrawn, filtered using 0.45µm syringe filter and an equivalent volume of fresh dissolution medium was immediately added [18,19]. The amount of drug released was estimated by measuring absorbance at 247 nm using a Double beam spectrophotometer. Dissolution of API was also determined in identical manner.

RESULTS AND DISCUSSION

Solubility studies:

One important consideration when formulating a self emulsifying formulation is avoiding precipitation of the drug. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion [20]. Results of solubility studies are reported in below **Figure**.



Construction of Pseudo-ternary Phase Diagrams:

Pseudo-ternary phase diagrams were constructed to identify the self-microemulsifying regions by water titration method. It has been observed that on increasing the concentration of the Co-Surfactants (Labrasol, TranscutolHP, and Capryol90) within the self-microemulsifying region caused increased spontaneity of self microemulsification process [21].

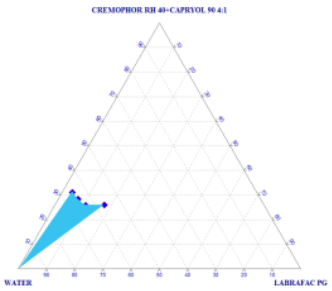


Fig 1: Phase diagram of LPCC 41-4

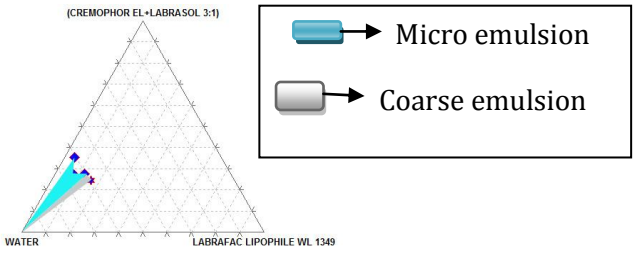


Fig 2: Phase diagram of LLCL 31-2

Formulation of liquid SEDDs

Table 1: Composition of Prepared SEDDs Formulation

S.NO	Formulation name	Drug (mg)	Labrafac lipophileWL1349 (mg)	Cremophor EL (mg)	Labrasol (mg)	TranscutolHP (mg)
1	LLCL 31-2	100	80	240	80	
2	LLCT 31-2	100	80	240	_	80
3	**Formulation name**	**Drug (mg)**	**Labrafac PG (mg)**	**Cremophor RH40 (mg)**	**Transcutol90 (mg)**	**Capryol90 (mg)**
	LPCC 31-4	100	80	180	_	60
4	LPCC 41-4	100	80	192	_	48

Evaluation of liquid SEDDS

Self emulsification time

Rate of emulsification was taken as an important index for assessment of the efficiency of self-emulsification. Formulations were graded for self-emulsification time, according to the visual assessment criteria for self microemulsion formation. Self emulsifying mixtures should disperse completely and quickly upon aqueous dilution under mild agitation. The results of emulsification time were depicted in (**Table 2**). All the formulations were emulsified in 20 to 30 seconds.

Phase separation studies:

Formulations were evaluated for precipitation and phase separation. Formulations were observed for a period of 24 hrs. The data were recorded in (**Table 2**).

All the formulations neither showed precipitation nor the phase separation of the drug in the emulsion for 2, 4, 6, 8, 12, 24 hours after the study, representing that the formulations were stable emulsions [22].

Percent transmittance:

All the four formulations are having more than 99% of transmittance so all the formulations are clear and transparent. Complete solubility of the drug in microemulsion formulations is also supported by this study [23]. Those results are shown in (**Table 3**).

Table 2: Results of Self Emulsification Time & Phase Separation Studies

S.NO	Formulation	Self-emulsification time	Phase separation	Phase precipitation	Formulation
1	LLCT31-2	24.28± 1.23 sec	X	X	LLCT31-2
2	LLCL31-2	29.30± 2.14 sec	X	X	LLCL31-2
3	LPCC31-4	25.47± 1.54 sec	X	X	LPCC31-4
4	LPCC41-4	27.12± 1.26 sec	X	X	LPCC41-4

Table 3: Result of Percent Transmittance

S.NO	Formulation	Percent transmittance
1	LLCT 31-2	99.22
2	LLCL 31-2	99.56
3	LPCC 31-4	99.15
4	LPCC 41-4	99.14

Effect of dilution:

Formulations were diluted with excess of water, 0.1 N HCl and phosphate buffer (pH 6.8) and was stored for 24 hours. No precipitation or phase separation was found which indicate that all the formulations were stable on dilution. Results were shown in (**Table 4**).

Thermodynamic stability:

The formulations were diluted and subjected to stress conditions. The stable formulations were stored at different temperature conditions. The emulsions were stable during centrifugation at 15000 rpm and alternative temperature cycles of -20°C and +25°C. There was no phase Separation and precipitation. Thermodynamic stability study was designed to identify and avoid the metastable formulations [24].

Table 4: Results of effect dilution & Thermodynamic stability studies

S.NO	Formulation	Distilled water	0.1N Hcl	Phosphate buffer (Ph 6.8)	Centrifugation (15000rpm)	Freeze thaw cycle (-20°c to +25°c)
1	LLCT 31-2	√	√	√	√	√
2	LLCL 31-2	√	√	√	√	√
3	LPCC 31-4	√	√	√	√	√
4	LPCC 41-4	√	√	√	√	√

(√ - stable on dilution) (√ - stable on centrifugation and freeze thaw cycle)

Droplet size measurement and Zeta potential determination:

Table 5: Particle size and zeta potential of SEDDs formulations

Formulation	Particle size(nm)	Zeta potential (mV)	Inference
LLCT 31-2	79.2	-34.8	GOOD
LLCL 31-2	71.0	-22.0	GOOD
LPCC 31-4	80.24	-44.4	GOOD
LPCC 41-4	50	-46.2	GOOD

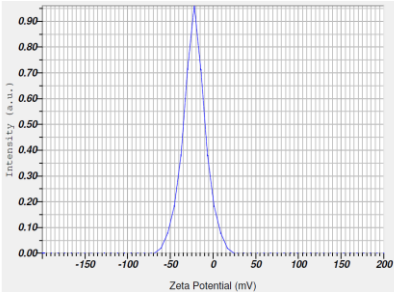


Fig 3: Zeta-potential of LLCL 31-2

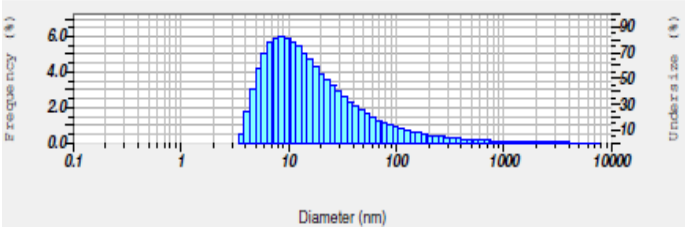


Fig 4: Particle size of LPCC 41-4

Evaluation of solid-SEDDS:

1. Flow properties of solid-SEDDS:

The results of the flow properties of solid-SEDDs showed in (**Table 6**) and those results depicted that the prepared solid-SEDDs having good flow properties.

2. In-vitro drug release studies

The dissolution studies for the selected liquid and solid SEDDS formulations were determined in USP dissolution apparatus containing medium of 2%SLS. The results are shown in (**fig: 5**). At the end of one hour, the dissolution of the solid SEDDS formulation was significantly greater than that of liquid SEDDS formulations and pure API. It suggests that efavirenz solid-SEDDS show better drug release profiles when compared to the API and liquid SEDDS [25].

Table 6: Results of flow properties of solid- SEDDs

S.NO	Micromeritic Properties	S-LLCL 31-2	S-LPCC 41-4
1	Angle of repose	24.45	26.21
2	Bulk density	0.61g/ml	0.68g/ml
3	Tapped density	0.78g/ml	0.83g/ml
4	Carr's index	21.79	18.07
5	Hausner's ratio	1.27	1.22

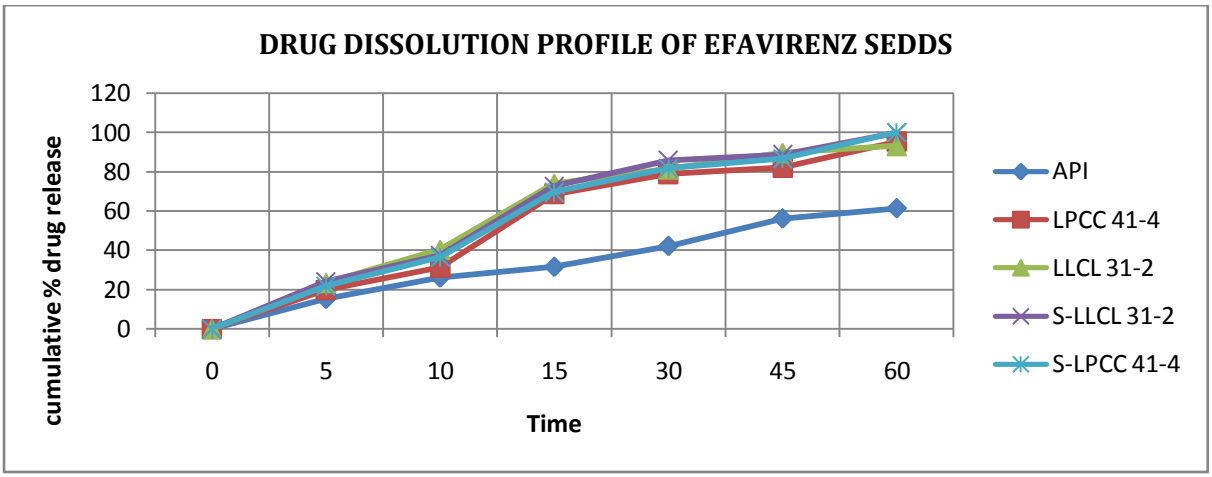


Figure 5: Results of dissolution data of efavirenz SEDDs

CONCLUSION

Self emulsifying drug delivery systems of poorly soluble drug efavirenz were prepared by using Labrafac lipophile WL1349, Labrafac PG (oils), Cremophor EL, Cremophor RH40 (surfactants), labrasol, transcutolHP, transcutol 90, capryol90 (co-surfactants). Prepared formulations were further evaluated for different parameters like self-emulsification time, phase separation studies, robustness to dilution, percent transmittance, droplet size and zeta potential, and thermodynamic stability studies. All the formulations showed satisfactory results for the above parameters. The efavirenz loaded formulations were subjected to *in-vitro* dissolution studies and results showed that the two formulations LLCL 31-2 and LPCC 41-4 were good. They showed a significant increase in dissolution, when compared with the plain API. Two liquid SEDDs formulations (LLCL 31-2, LPCC 41-4) were selected based on the droplet size, zeta potential and *in-vitro* dissolution profiles. Those selected formulations are further formulated into solid SEDDs by adsorption method using Neusilin as carrier. The prepared solid SEDDs are characterized for their flow properties like angle of repose, Carr's index and hausner's ratio and those formulations showed good flow properties. Then the drug loaded solid SEDDs were filled into capsules and performed *in-vitro* dissolution studies. The two formulations showed higher drug release compared to the liquid SEDDs formulations.

From the entire study it was concluded that there was an increase in both the solubility and dissolution rate of drug efavirenz in S-

SEDDS as compared to dissolution rate of pure efavirenz. The significant increase in solubility and dissolution were observed in formulations S-LLCL 31-2 and S-LPCC 41-4.

REFERENCES

1. Bhupinder singh, shanthan bandopadhyaya et..al., Self-Emulsifying Drug Delivery Systems (SEDDS): Formulation Development, Characterization, and Applications, Critical Reviews™ in Therapeutic Drug Carrier Systems, 26(5), 427–521 (2009).
2. Manoj Narkhede, Smita S. Pimple*, Archana D. Gawade, Pravin D. Chaudhari, development of microemulsion system for poorly water soluble drug efavirenz: International Journal of Universal Pharmacy and Life Sciences 2(3): May-June 2012.
3. Alejandro Sosnik, Angel M. Carcaboso. Drug delivery systems in HIV pharmacotherapy: What has been done and the challenges standing ahead. J Controlled Rel.2009; 138: 2-15.
4. Gursoy RN and Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacotherapy. 2004; 58(3): 173-82.
5. Patel D and Sawant KK. Self micro-emulsifying drug delivery system: formulation development and biopharmaceutical evaluation of lipophilic drugs. Curr Drug Deliv. 2009; 6(4): 419-24.
6. Preethi Sudheer *, Nishanth Kumar M , Satish Puttachari , Uma Shankar MS, Thakur RS, Approaches to development of solid- self micron emulsifying drug delivery system: formulation techniques and dosage forms – a review; Asian Journal of Pharmacy and Life Science Vol. 2 (2), April-June,2012.
7. Tao Yi, Jiangling Wan, Huibi Xu and Xiangliang Yang.,A new solid self microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2008;70:439-444.
8. M. Sunitha Reddy*, P. Srinivas Goud and S.S. Apte, solubility enhancement of candesartan cilexetil by self emulsifying drug delivery systems: IJPSR, 2012; Vol. 3(7): 2098-2104.
9. Osnir de Sá Viana1, Flávia Patrícia Morais Medeiros, Development and validation of a HPLC analytical assay method for efavirenz tablets: a medicine for HIV infections, Brazilian Journal of Pharmaceutical Sciences vol. 47, n. 1, jan./mar., 2011.
10. Balakrishnan P, Beom-Jin Lee, Dong Hoon Oh, Jong Oh Kim, Young-Im Lee, Dae-Duk Kim, Jun-Pil Jee, Yong-Bok Lee, Jong SooWoo, Chul Soon Yong, Han-Gon Choia. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. Int J Pharm 2009; 374:66–72.
11. H. Shen, and M. Zhong. Preparation and evaluation of self-microemulsifying drug delivery system containing atorvastatin, Journal of Pharmacy and Pharmacology, 58: 1183–1191 (2006).
12. Ashish Deshmukh and Shirishkumar Kulakrni, Novel Self Micro-emulsifying Drug Delivery Systems (SMEDDS) of Efavirenz, Journal of Chemical and Pharmaceutical Research, 2012, 4(8):3914-3919.
13. Huabing C, Xueling C, Xiangliang Y, et. Al. Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. Int. J. Pharm. 315 (2006); 52–58.
14. Paul BK, Uses and applications of microemulsions. Current science.2001; 80:997-1000.
15. Durgacharan Arun Bhagwat, John Intru D'Souza, Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier, International Current Pharmaceutical Journal 2012, 1(12): 414-419.
16. More H. N., Hazare A. A. (2004): Practical Pharmaceutics (Physical pharmacy), Manas Prakashan, Kolhapur, 1st Ed., 86-105.
17. Patel P. A., Patravale V. B. (2010): International Journal of Pharma Sciences and Research (IJPSR), 1(8): 282-292.
18. Gupta AK, Mishap DK, Mahajan SC. Preparation and in-vitro evaluation of self emulsifying drug delivery system of antihypertensive drug valsartan. Int J Pharm & Life Sci 2011; 2 (3):633-39.
19. V. Kiran kumar*, m. Aruna devi, and d.v.r.n.bhikshapathi, development of solid self emulsifying drug delivery Systems containing efavirenz: in vitro And in vivo evaluation, Int J Pharm Bio Sci 2013 Jan; 4(1): (P) 869 – 882.
20. Shivani sharma*, himani bajaj, piyush bhardwaj, anshul dutt Sharma and ranjeet singh. Development and characterization of self emulsifying Drug delivery system of a poorly water soluble drug using Natural oil. Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 69 No. 4 pp. 713-717, 2012.
21. Rajendra chouksey*, Harish pandey, A. K. Jain, Himesh soni, G. K. Saraogi, Preparation and evaluation of the self emulsifying drug delivery system Containing Atorvastatin HMG CO-A Inhibitor. International Journal of Pharmacy and Pharmaceutical Sciences, Vol-3, issue 3, 2011.

22. Shafiq F, Shakeel S, Talegaonkar F, Ahmad J, Khar RK and Ali M Design and development of oral oil in water ramipril nanoemulsion formulation: In vitro and in vivo assessment, J. Biomed. Nanotech., 2007, vol-3, 28-44.
23. Manoj Narkhede, Smita S. Pimple, Archana D. Gawade, Pravin D. Chaudhari, development of microemulsion system for poorly water soluble drug efavirenz: International Journal of Universal Pharmacy and Life Sciences 2(3): May-June 2012.
24. M. Sunitha Reddy*, P. Srinivas Goud and S.S. Apte, solubility enhancement of candesartan cilexetil by self emulsifying drug delivery systems: IJPSR, 2012; Vol. 3(7): 2098-2104.
25. Vijaykumar Nekkanti, Pradeep Karatgi, Raghavendra Prabhu, and Raviraj Pillai, Solid Self-Microemulsifying Formulation for Candesartan Cilexetil. AAPS PharmSciTech, Vol. 11, No. 1, March 2010.