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Formulation & *In vivo* Evaluation of Self Nano Emulsifying Drug Delivery System of Doravirine

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Abstract:

The study is an attempt to improve the solubility and bioavailability of doravirine by employing self-nanoemulsifying drug delivery technique (SNEDDS). Based on the components' effectiveness at solubilizing and emulsifying one another, preliminary screening was done to choose the oil, surfactant, and co-surfactant. The region of nanoemulsification was found using pseudo ternary phase diagrams. In terms of globule size, globule size distribution, zeta potential, and surface shape of the resulting nanoemulsions, the created self-nanoemulsifying drug delivery systems (SNEDDS) were assessed. The optimized SNEDDS formulation (F8) contained drug (100 mg), neobee M5 (22.2%), caproic acid (58.2%) and PEG 600 (19.4%). The SNEDDS was further evaluated for its turbidity, robustness, entrapment efficiency, % drug content, droplet size and zeta potential. The optimized formulation of drug-loaded SNEDDS exhibited 98% entrapment efficiency, 99% drug content and 99% *in vitro* drug release in 60 min as compared with the plain drug, which had a limited dissolution rate (31%). The particle size for the optimized formulation of SNEDDS (F8) was found to be 67.8 nm with PDI 0.173.In vitro drug release from SNEDDS was significantly higher ($p < 0.005$) than pure drug. Furthermore, area under the drug concentration time-curve of drug from SNEDDS formulation revealed a significant increase ($p < 0.005$) in Doravirine absorption compared to pure drug alone. The increase in drug release and bioavailability as compared to drug suspension from SNEDDS formulation may be attributed to the nanosized droplets and enhanced solubility of drug in the SNEDDS.

Keywords —Doravirine, anti-HIV drug,Self-nanoemulsifying drug delivery systems, in vitro and in vivo studies, bioavailability

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I. INTRODUCTION

The application of nanotechnology has been recognized in the provision of many benefits of drugs including enhancing the solubility of hydrophobic drugs, increasing the permeability or transport of poorly permeable drugs, improving drug stability, controlling drug distribution and disposition in the body, and targeting drug delivery to the site of action. Additionally, a number of nanoparticle strategies have been created, including polymeric micelles, polymeric nanoparticles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and inorganic nanocarriers. Moreover lipid-based drug delivery systems; such as, nanoemulsions have shown the successful potential in enhancing the solubility of poorly water soluble drugs, which have been categorized as drugs in the Biopharmaceutical Classification System (BCS) classes II and IV[1]To make the lipid-based drug delivery systems more suited for both hydrophilic and hydrophobic actives, different components and quantities can be added or subtracted. They have the mechanism to enhance

drug bioavailability by extending the drug retention time in the stomach, changing in the biophysical barrier[2], improving drug solubilization, decreasing drug metabolism, stimulating lymphatic transport , and having less toxicity in vivo[3]. As colloidal dispersions, nanoemulsions are the most well-known lipid-based drug delivery methods. They are optically isotropic, transparent, thermodynamically unstable, and kinetically stable systems of oil, surfactant, and water with a nanoscopic droplet size. The ability of nanoemulsions to improve the oral bioavailability of poorly water soluble drugs has been recognized for many decades. However, the use of nanoemulsions in oral delivery was limited due to some drawbacks; such as, poor palatability according to their lipidic composition. Moreover, nanoemulsions are usually consumed in a large volume to achieve the therapeutic concentration of the drugs which might limit the patient compliance. Furthermore, nanoemulsions cannot be given by soft gelatin, hard gelatin, or HPMC capsules due to their high water content. The water content in nanoemulsions would promote hydrolysis and precipitation of drugs during storage, which would affect their utility in oral delivery. To solve the limitation of nanoemulsions, the approach of spontaneous self-nanoemulsification has been developed for oral drug delivery.

The SNEDDS 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 that have the ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media such as gastric fluids. SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification.[4,5]

A non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV-1, doravirine is provided along with other antiretroviral drugs. It is a BCS class II drug that exhibit low solubility across the physiological pH range. The compound has one pKa of 9.47 that does not affect solubility in the physiological pH range. LogD was measured to be 2.26 at pH 7. Hence, the aim of this study was to develop a SNEDDS of a poorly water-soluble doravirinedrug.

II. MATERIAL AND METHODS

A. Materials

Doravirine drug was purchased from AurobindoPharma Ltd, Hyderabad. Miglyol 810, capryol 90, triacetin, caprylic acid, imwitor, castor oil, akomed E, neobee M5, oleic acid, acconon E, acconon sorb20, brij 35, tween 20, tween 40, tween 85, lauroglycol 90, cremophor RH 40, triton-9100, labrafac, span 80, cremophor EL, caproic acid, transcutol p, propylene glycol, lauro glycol fcc, ethanol, PEG 600 and capmul MCM were purchased from Gattefosse, Mumbai. All the reagents used were of analytical grade.

B. Solubility of Doravirine in vehicles

Various oils, surfactants and co-surfactants were studied for doravirine solubility in order to identify the components for construction of ternary phase diagrams. [6,7]

C. Construction of Pseudo-ternary phase diagrams

Ternary phase diagrams comprising surfactant, co-surfactant and oil were plotted, each of them, representing an apex of the triangle. Neobee M5 as oil phase and Caproic acid as surfactant and PEG600 as co-surfactant were selected (based on the solubility studies) [8]. The transmittance value more than 90 indicated nano size droplets formation hence these ratios were noted and used for plotting pseudo-ternary phase diagram [9]. Pseudo ternary phase diagram is constructed using CHEMIX software.

Effect of Doravirine loading on all 15 formulations with varying ratios of Neobee M5 - Caproic acid-PEG600 was evaluated[10].

D.Preparation and evaluation of doravirine SNEDDS

The formulations that displayed transmittance> 90 were chosen from 100 mg drug loaded system and prepared as described above. About 1ml of the formulation (equivalent to 100 mg of the doravirine) was filled in size '00' hard gelatin capsules, sealed and stored at ambient temperature (25° C). These SNEDDS were evaluated for visual observations, turbidity, and robustness to dilution and in vitro dissolution study and were optimized [11].

TABLE 1
COMPOSITION OF DORAVIRINE SNEDDS

Formulation code	Doravirine drug (mg)	Ratios of Oil: S_{mix}	Oil (Neobee M5)	Smix 3:1	
				Surfactant (Caproic acid)	Co-surfactant (PEG 600)
F1	100	1:01	50	37.5	12.5
F2	100	1:02	33	49.5	16.5
F3	100	1:03	25	56.25	18.75
F4	100	3:01	75	18.75	6.25
F5	100	2:01	66	24.75	8.25
F6	100	2:03	40	45	15
F7	100	2:05	28.5	53.25	17.75
F8	100	2:07	22.2	58.2	19.4
F9	100	5:02	71	21.3	7.1
F10	100	3:02	60	30	10
F11	100	3:04	42.6	42.6	14.8
F12	100	3:07	30	52.5	17.5
F13	100	8:03	72.7	20.25	6.75
F14	100	7:03	70	22.5	7.5
F15	100	5:03	62.5	28.12	9.3

E.Evaluations of Doravirine SNEDDS

All the formulations were subjected to visual observation physically[12,13],Turbidity measurement[14] and checked for robustness to dilution with 50, 100 and 1000 mL of distilled water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer [14].

The percentage drug content [15] and entrapment efficiency [15] of all the doravirine -loaded SNEDDS was recorded as per the refereed method.

***F.In Vitro* Dissolution Study**

In vitro dissolution studies were conducted for doravirine pure drug, marketed formulation (Nexavar) and doravirine SNEDDS formulations (F1-F15) was performed using USP dissolution Apparatus II (Lab india DS 8000, Mumbai, India). Hard gelatin capsules, size "1" filled with doravirine SNEDDS formulation were introduced into 900 mL of freshly prepared pH 6.8 phosphate buffers with 3% W/V plysorbate 80 maintained at 37 ± 0.5° C and the speed of the paddle was set at 75 rpm (followed FDA dissolution method). Copper sinkers were used to secure capsules to the bottom of the vessel. At pre-determined time intervals, 5 mL of samples were withdrawn by means of a syringe and immediately replaced with 5 mL of fresh medium maintained at 37 ± 0.5° C. The samples were suitably diluted and analyzed for doravirine using UV method spectrophotometrically at 270nm [16].For comparison, similarly dissolution studies of pure drug and marketed product were also performed. All measurements were done in triplicate.

G.Characterization Of Optimised Doravirine SNEDDS Formulation

The globule Size and zeta potentialwere determined by a Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern Instruments, Malvern, and Worcestershire, UK) [16].

TheFTIR of pure drug and optimised formulation scanned and compared to check any incompatibility between the drug compound and excipients used.Scanning electron microscopy studies (JEOL JEM 2100 F, USA) were carried out for optimized formulation by diluting the same with distilled water to 1000 times and then plunging on a 2% uranyl acetate solution stained carbon grid [17].

H.Accelerated Stability Studies

All formulations filled in hard gelatin capsules were packed in HDPE screw capped bottles and kept in humidity chambers maintained at 40 ± 2°C/ 75 ± 5% RH as per ICH guidelines for Zone III and stored for 6 months.[18,19]

I.In Vivo Pharmacokinetic Studies Of Doravirine SNEDDS

Animal preparation

For this investigation, healthy Wistar rats (weighing 150–180 g) were chosen; all of the animals remained healthy throughout the experiment.All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25^0C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with standard diet and *waterad libitum.* The protocol of animal study was approved by the institutional animal ethics committee (IAEC NO:1477/PO/Re/S/11/CPCSEA-54A)**.**

Study Design[20]

Rats were divided in to two groups at random. Each group containing six rats. The treatments as given below were administered to the rabbits.Prior to the tests, the rats fasted for 24 hours. Foods were offered again 4 hours after the last dose.First group was administered with pure Doravirine (as such) made suspension with 0.5% methocel and second group was administered Prepared Doravirine optimisedSNEDDS diluted in 0.5% methocelby oral route at a dose of 0.625 mg.

Blood sampling

200 µL blood samples were collected at regular time intervals from the femoral artery at times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24h post dose and transferred into Eppendrof tubes containing heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at −20°C until analysis.

Pharmacokinetic analysis

Maximum plasma concentration (C_{max}), time to reach C_{max} (i.e., T_{max} and C_{max} t ½values), area under the plasma concentration-time curve from zero to the last sampling time (AUC_{0-t}), and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) were the pharmacokinetic parameters used to evaluate.

III. RESULTS AND DISCUSSION

A. DeterminationOf Doravirine Solubility In Various Excipients

Based on solubility studies neobee M5 was selected as oil phase due to its higher solubilization (1.92±0.56 mg/ml) of Doravirine compared to other oils. The surfactant cremophor CO 60and co-surfactant PEG600 was selected for further studies due to their higher solubilizing capacity towards Doravirine.

B. Construction of Ternary Phase Diagrams

The region of nano emulsification was indicated as shadow area encircled by a solid line and the points indicate the compositions of the system explored.Neobee M5 - Caproic acid- PEG600 system with S_{mix} ratio in 3:1 exhibited larger nanoemulsification region (figure 1) as compared to 1:1 and 2:1 S_{mix} ratio.The mean globule size was decreased with increase in surfactant concentration. Hence the systems containing Neobee M5 - Caproic acid- PEG600 with 3:1 Smix ratio were selected forfurther studies due to their larger nanoemulsifying area, greater capacity for incorporation of oily phase with uniformity of dispersion and high transmittance values.

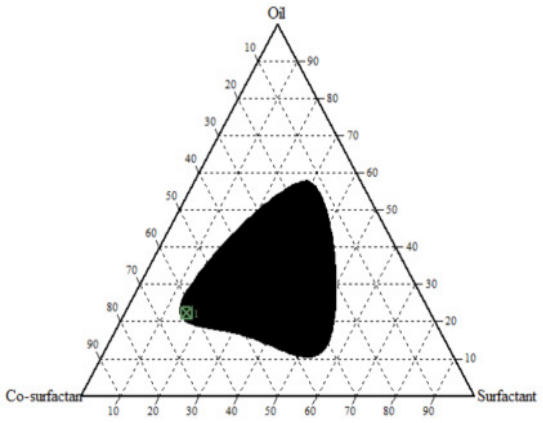

Figure 1:Ternary phase diagram for Neobee M5 - Caproic acid- PEG600 with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

C. Effect of Doravirine Loading

Incorporation of Doravirine (100 mg, 200 mg and 300 mg) led to a considerable decrease in transmittance values. This behaviour could be thought that undissolved drug in the compositions affected the clarity and thereby transmittance value

to decrease with increased Doravirine amount. Oil globules were observed on the surface after dispersion on standing for majority of the compositions containing high Doravirine. The area of nano emulsification was considerably reduced with increase in Doravirine loading in to the Neobee M5 - Caproic acid- PEG600 system with 3:1 S_{mix} ratio (figure2) hence for the stability reasons of the SNEDDS, system containing 100 mg of Doravirine was chosen for formulation of Doravirine SNEDDS and further studies.

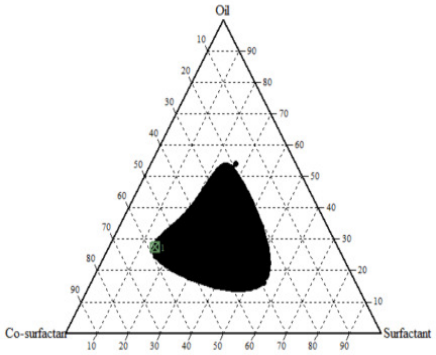

Figure 2: Ternary phase diagram for 100 mg of doravirine loaded in Neobee M5 - Caproic acid- PEG600 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

D. Preparation and Evaluation of Doravirine SNEDDS

From the above results it was found that Neobee M5 concentration in the range of 22-75% w/w, Caproic acidin the range of 18-60% w/w and PEG 600 in the range of 7-20% w/w in 3:1 of oil: S_{mix} ratio with 100mg loaded doravirine drug produced the SNEDDS having the transmittance greater than 90, with good stability. A series of SNEDDS were prepared in the abovementionedrangesofoil-surfactant-co-surfactantratiosandwereevaluated.

Visual observations indicated that at higher levels of surfactant, the spontaneity of the self- emulsification process was increased.

Turbidity values (NTU) have been reported to be of use in SNEDDS characterization [20]. From these results it can be generalized that the formulations that have low turbidity (<20) gave a transmittance values of more than 90 indicating rapid and spontaneous emulsification within 1min, hence it gives a good correlation between transmittance and turbidity values (table 2).

All the formulations of Doravirine SNEDDS (F1-F14) were found to be robust to all dilutions and no separation or drug precipitation was observed even after 24 hours of storage.

The drug content of all formulations ranged between 95.40±1.26 to 99.14±1.15% with maximum value exhibited by F8 The entrapment efficiency of all formulations varies between 94.69±1.15 to 98.89±1.79% with maximum value displayed by F8 (table 2)

TABLE 2

EVALUATION PARAMETERS OF DORAVIRINE SNEDDS

Formulation code	Visual Observation	Turbidity (NTU)	%Entrapment efficiency	% Drug content
F1	A	18.65	96.86±1.43	97.21±1.21
F2	A	17.39	97.52±1.51	98.07±1.19
F3	A	16.32	98.23±1.69	98.95±1.65
F4	B	24.68	94.69±1.15	95.40±1.26
F5	B	20.06	95.88±1.22	96.53±1.19
F6	A	17.87	97.38±1.67	97.93±1.49
F7	A	17.03	98.08±1.53	98.63±1.78
F8	B	15.65	98.89±1.79	99.14±1.15
F9	A	22.95	95.30±1.73	96.05±1.66
F10	A	18.87	96.49±1.35	97.04±1.45
F11	A	18.05	97.06±1.39	97.81±1.13
F12	B	17.24	97.87±1.95	98.32±1.62
F13	B	23.29	95.16±1.84	95.71±1.89
F14	A	21.16	95.51±1.70	96.27±1.39
F15	B	19.16	96.11±1.71	96.97±1.40

Above parameters are communicated as Average ± Standard Deviation; (n=3)

E.In Vitro Dissolution Tests

Faster release rates were observed for Doravirine SNEDDS than the pure drug. Doravirine SNEDDS F1-F15 released more than 80% of drug within 45min, whereas, pure drugreleased 31.91% of drug in 60min. Formulation F8 exhibited highest drug release of 99.87% in 60min. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration and hence F8 exhibited high drug release.(figure 3).

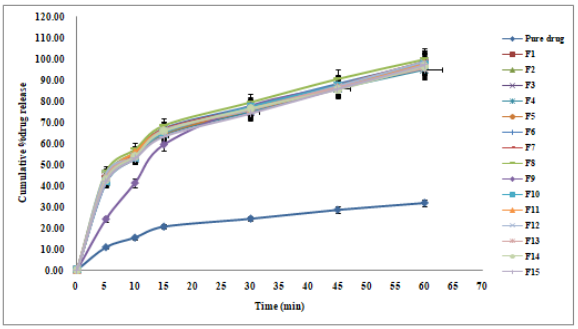

Figure 3: Comparative dissolution profile of doravirine pure drug and doravirine SNEDDS formulation (F1-F15)

F.Characterization Of Optimised Doravirine SNEDDS

FTIR Studies

The spectrum is responsible for the presence of chemical functional groups at different frequencies. The pure Doravirine spectrum showed the main characteristic bonds of Doravirine. The presence of prominent characteristic peaks in optimized formulation F8 spectra confirms the compatibility between drug and excipients used.(figure 4,5)

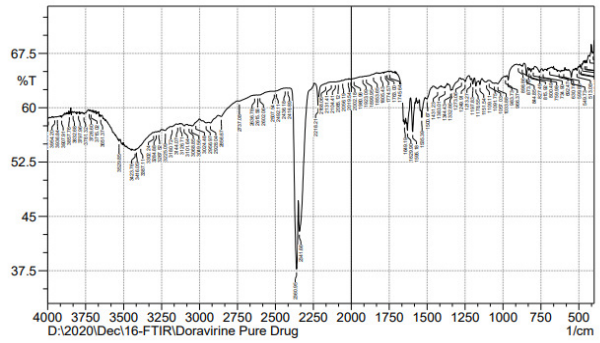

Figure 4:FTIR of Doravirine pure drug

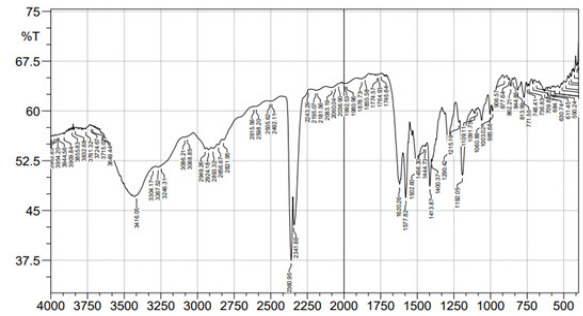

Figure 5:FTIR of optimized Doravirine SNEDDS formulation F8

Globule size and zeta potential

Droplet size distribution following self-nanoemulsification is a critical factor to evaluate a self-nanoemulsion system. The particle size for the optimized formulation of SNEDDS (F8) was found to be 67.8 nm with PDI 0.173. The negative value of zeta potential of -23.2mV might be due to the presence of anionic groups of free fatty acids, and glycols present in the oil, surfactant and co-surfactant.The zeta potential value > 5 mV provide an excellent stability.(figure 6,7)

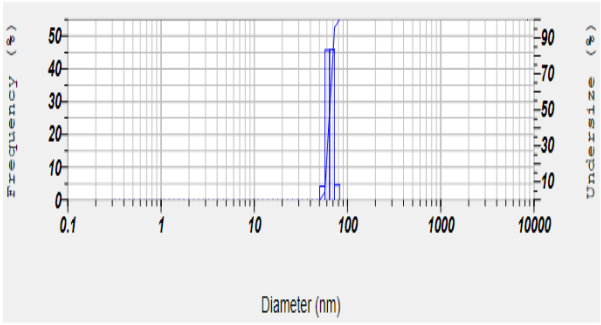

Figure 6: Particle size of optimized SNEDDS formulation of doravirine (F3)

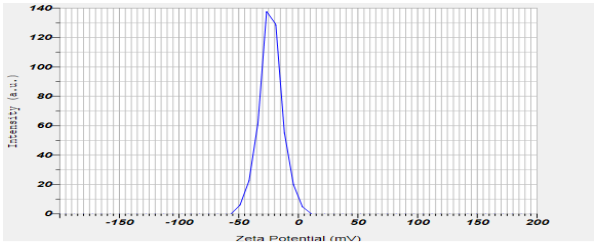

Figure 7: Zeta potential of optimized SNEDDS formulation of doravirine (F8)

G.SEM studies

The SEM results were in accordance to that of globule size analysis and were observed that the size of all droplets of SNEDDS F8 was less than 100 nm as furnished in Figure 8A and 8B. However, the shape of droplets was found to be spherical.

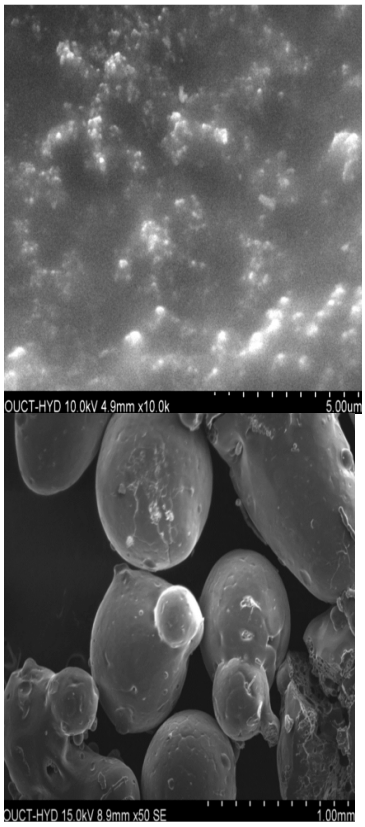

Figure 8: SEM images of optimized formulation of Doravirine SNEDDS F8 (A and B)

H. Accelerated Stability Studies

The purpose of stability testing is to demonstrate how a drug substance's or product's quality changes over time under the effect of various environmental elements, including temperature, humidity, and light, and to enable suggested storage conditions.

All of the formulations that were removed from the humidity rooms showed no discernible physical alterations.

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The samples were assayed for %entrapment efficiency, % drug content and in-vitro drug release and the results are shown in Table 4. No significant difference was observed after storage at accelerated conditions at 40±2° C/75±5% RH for a period of six months.

TABLE 4
STORAGE AT 40±2° C/75±5% RH FOR 6 MONTHS

Retest time for optimized formulation F8	**%Entrapment efficiency**	**% Drug content**	***In-vitro* drug release (%)**
0 days	98.89±1.79	99.14±1.15	99.85±1.75
30 days	98.43±0.45	99.05±0.78	99.42±1.56
60 days	98.15±0.78	98.74±0.23	99.08±1.34
180 days	98.92±0.84	98.26±0.54	98.93±1.95

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Doravirine concentrations in plasma following oral administration of pure drug and optimized Doravirine SNEDDS administered oral and respective plasma concentration-time curves are shown in Figures 9.The plasma concentration–time curve in Wister rats after a single oral dose of Doravirine SNEDDS formulation as compared to Doravirine pure. At all the indicated time points, the Doravirine plasma concentrations in rats treated with SNEDDS formulation was significantly higher than those treated with pure drug.

Pharmacokinetic parameters of Doravirine after oral administration of the two formulations in Wister rats are shown in Table 5.C_{max} of the SNEDDS 3.02±2.85ng/ml was significant ($p<0.05$) as compared to the pure drug 0.97±0.57 ng/ml. T_{max} of both SNEDDS formulation and pure drug was 1.0±0.53 and 2.0±0.72 h respectively. AUC, which indicates the total integrated area under the blood concentration time profile and the total amount of drug that enters the systemic circulation following oral delivery, is a crucial measure in assessing the bioavailability of a medication from a dose form. $AUC_{0-\infty}$ infinity for SNEDDS formulation was higher (55.09±2.48ng. h/ml)) as compared to pure drug (18.2±1.73ng h/ml). Higher amount of drug concentration in blood indicated better systemic absorption of Doravirine from SNEDDS formulation as compared to the pure drug.

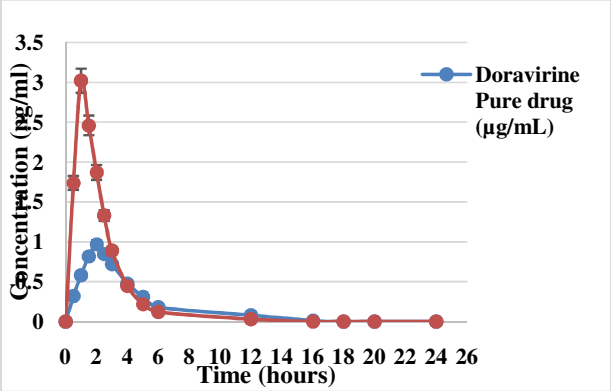

Figure 9:Mean plasma concentration-time profiles for doravirine pure drug and doravirine optimized SNEDDS formulation in rats (n=6)

TABLE 5
MEAN PHARMACOKINETIC PARAMETERS OF DORAVIRINE PURE DRUG AND DORAVIRINE OPTIMISED SNEDDS FORMULATION

Pharmacokinetic parameters	Doravirine Pure drug	Doravirine optimised SNEDDS
C_{max} (µg/ml)	0.97±0.57	3.02±2.85
AUC_{0-t} (µg. h/ml)	16.5±1.02	50.76±3.21
AUC_{0-inf} (µg. h/ml)	18.2±1.73	55.09±2.48
T_{max} (h)	2.0±0.72	1.0±0.53
$t_{1/2}$ (h)	15.0±0.02	9±0.05

III. CONCLUSION

In the present studyDoravirine SNEDDSwere preparedusing Neobee M5(oil), Caproic acid(surfactant), and PEG 400 (co-surfactant) and optimized using ternary phase diagram. The formulation comprising of 100 mg of drug displayed minimum turbidity, maximum % transmittance and drug content. The particle size for the optimized formulation of SNEDDS (F8) was found to be 67.8 nm with PDI 0.173 and zeta potential of -23.2mV.The compatibility study carried out by comparing FTIR spectra of pure drug and optimised formulation. In vitro drug dissolution values obtained at 60 min was 98% with minimized pH dependent degradation when compared to pure drug. Based on in vivo studies carried out in rats the AUC_{0-t} of the SNEDDS formulation was found significantly higher ($p<0.05$) as compared to pure drug. Higher amount of drug concentration in blood indicated better systemic absorption of Atazanavir from SNEDDS formulation as compared to the pure drug.

REFERENCES

1. C. Lipinski, “Poor Aqueous Solubility - an Industry Wide Problem in Drug Discovery,” *Am Pharm Rev.*, vol.5,pp.82-5,2002.
2. K. Cerpnjak, A. Zvonar, M. Gasperlin and F. Vrecer, “Lipid-based Systems as a Promising Approach for Enhancing the Bioavailability of Poorly Water-soluble Drugs,” *Acta pharm.,*vol.63,pp.427-45,2013.
3. K. Mohsin, F. Alanazi,”Lipid based self emulsifying formulations for Poorly Water Soluble Drugs-an Excellent Opportunity,” *Indian J Pharm Educ Res*., vol.46,pp.88-196,2012.
4. S. Ren, MJ Park, A. Kim and BJ Lee, “In Vitro Metabolic Stability of Moisture-sensitive Rabeprazole in Human Liver Microsomes and Its Modulation by Pharmaceutical Excipients,”*Arch Pharm Res.,* vol.31,pp.406-13,2008.
5. RB. Vemula,”Lipid based Self-emulsifying Drug Delivery System (SEDDS) for Poorly Water-Soluble Drugs: a Review,” *J Global Pharma Technol.,* vol.2, pp.47-55, 2010.
6.RI.Sanchez, KL.Fillgrove, KL.Yee, Y.Liang, B.Lu, A.Tatavarti,R.Liu,MS. Anderson, M.Behm , L.Fan, Y.Li, JR.Butterton,M Iwamoto and SG. Khalilieh,”Characterisation of the absorption, distribution, metabolism, excretion and mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans,” *Xenobiotica.,* vol.1,pp.18-25,2018.
7. S.Yosra, A.Magda, and YA.Ossama,“Self-nanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization,” *Int J Pharm.,* vol.380, pp.133-41, 2009.
8. G.Feng, Z. Haijun, and H. Jing, “Self-microemulsifying drug delivery system for improved oral bioavailability of dipyridamole: preparation and evaluation,” *Arch Pharm Res.,* vol.34,pp.1113-23,2011.
9. A.Czajkowska-Kośnik, M.Szekalska, A. Amelian, E. Szymańska and Winnicka K, “Development and Evaluation of Liquid and Solid Self-Emulsifying Drug Delivery Systems for Atorvastatin.” *Molecules,vol.20,pp.* 21010–21022,2015.
10. M. Shiva Kumar, P. Shailaja, and M. Ramana, “Development and Characterization of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) of Atorvastatin Calcium,” *Current Drug Deli.*, vol.9,pp.182,2012.
11. R. Sunny, H. Rajesh, and R. Jayant, “Chavda.Self-Nanoemulsifying Drug Delivery System of Glimepiride: Design, Development, and Optimization,” *PDA J Pharm Sci and Tech.,vol.1,pp.* 67201-213,2013.
12. SM. Khoo, AJ. Humberstone, CJ. Porter, GA. Edwards and WN. Charman, “Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine,” *Int. J pharm*., vol.167, pp.155-64,1998.
13. TR. Kommuru, B.Gurley, MA. Khan, and IK.Reddy, “Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment,” *Int J Pharm.,* vol.212, pp.233-246,2001.
14.J. Patel, G. Kevin, A. Patel, M. Raval, and N. Sheth, “Design and development of a self- nanoemulsifying drug delivery system for telmisartan for oral drug delivery,” *Int J Pharm Investig.,vol.1,pp.*112□118,2011.
15. H. Rachmawati, IS. Soraya, NF. Kurniati, and A. Rahma, “In Vitro Study on Antihypertensive and Antihypercholesterolemic Effects of a Curcumin,” *Nanoemulsion. Sci Pharm.*, vol.84,pp.131□140,2016.
16. T. Hanuman, T. Sivakkumar, and S. Sridhar, “Analytical method development and validation for the estimation of doravirine in bulk and pharmaceutical dosage form by RP-HPLC,” *IAJPS.,* vol.07,pp.33-39,2020.

17. VV. Chopade, and PD. Chaudhari, "Development and evaluation of self-emulsifying drug delivery system for lornoxicam," *IJRDPL.,* vol.2,pp.531-537, 2013.
18. ICH Harmonized Tripartite guideline on "Stability Testing of New Drug Substances and Products Q1A (R2)", 6 February2003.
19. CW. Pouton CW, "Formulation of self-emulsifying drug delivery systems," *Adv Drug Del Rev.,* vol.25, pp.25:47–58, 1997.
20. S. Nazzal, II. Smalyukh, OD. Lavrentovich, and KA. Khan KA, "Preparation and invitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiqui-none: mechanism and progress of emulsion formation," *Int J Pharm.,* vol.235, pp.247-265, 2002.

