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DEVELOPMENT OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF DORAVIRINE: SOLUBILITY AND DISSOLUTION RATE IMPROVEMENT

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Keywords:

Doravirine, Anti-HIV drug, Self-nanoemulsifying drug delivery systems, Solubility, Particle size

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ABSTRACT: Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). The aim of the present investigation was to develop a self-nanoemulsifying drug delivery system (SNEDDS) to enhance the solubility and dissolution of poorly water-soluble doravirine. The solubility of doravirinein various oils was determined to identify the oil phase of SNEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oil. A ternary phase diagram was constructed to identify the efficient self-emulsifying region. 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 robustness, turbidity, % drug content, entrapment efficiency, 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. The negative value of zeta potential of -23.2 mV might be due to anionic groups of free fatty acids and glycol present in the oil, surfactant, and co-surfactant. The degradation of doravirine from optimized doravirine SNEDDS formulation was significantly less when compared to the pure drug degradation. These results suggest the potential use of SNEDDS to improve dissolution and stability of poorly water-soluble doravirine.

INTRODUCTION: The oral route is the easiest and most convenient way of noninvasive administration. However, oral drug delivery may hamper drug molecules that exhibit poor aqueous solubility. Approximately 40% of the new chemical entities exhibit poor aqueous solubility and present a major challenge to the modern drug delivery system, which leads to poor oral bioavailability, high intra-, and inter-subject variability and lack of dose proportionality.

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These drugs are classified as class II drugs by the Biopharmaceutical Classification System (BCS), drugs with poor aqueous solubility and high permeability [1, 2]. Various approaches like solid dispersion and complexation with cyclodextrins have already been utilized to resolve the poor aqueous solubility [3, 4].

Complexation with cyclodextrin techniques is not applicable for drug substances that are not soluble in both aqueous and organic solvents. The realization that the oral bioavailability of poorly water-soluble drugs may be enhanced when co-administered with a meal rich in fat has led to increasing the recent interest in the formulation of poorly water-soluble drugs in lipids. Lipid suspension, solutions, and emulsions have all been used to enhance oral bioavailability, but, more

recently, there has been increasing focus on the utility of self-nano-emulsifying drug delivery systems (SNEDDS). Being hydrophobic, *i.e.*, more lipophilic, a lipid-based drug delivery system would ideally work for a poorly water-soluble drug [5].

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 can form fine oil-in-water (o/w) microemulsions 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.

Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) intended to be administered in combination with other antiretroviral medicines. It is a BCS class II drug that exhibits 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 doravirine drug.

MATERIAL AND METHODS:

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.

Solubility of Doravirine in Vehicles: Various oils, surfactants, and co-surfactants were studied for doravirine solubility in order to identify the components for the construction of ternary phase diagrams. An excess amount of doravirine was placed in screw-capped glass vials containing 1 g of vehicle (*i.e.,* oil or surfactant or co-surfactant). Glass vials were sealed with caps and vortexed for 10 min using a cyclomixer in order to facilitate proper mixing of doravirine with the vehicles. Then vials were shaken reciprocally using a mechanical rotary shaker for 48 h at 25 °C and allowed for another 24 h to attain equilibrium conditions without shaking at the same temperature. The vials were centrifuged at 3000 rpm for 10 min using a centrifuge to obtain a clear supernatant liquid. The supernatant (100 mg) was collected, extracted for doravirine and filtered through a millipore membrane filter (0.45 µm), diluted suitably with methanol, and analyzed for doravirine using UV spectrophotometer at 270 nm. The amount of doravirine dissolved in various vehicles was calculated [6, 7].

Construction of Pseudo-ternary Phase Diagrams: Ternary phase diagrams comprising a 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). Varying ratios of oil: S_{mix} were filled in 2 ml eppendr of tubes shaken and kept aside. These mixtures were gently mixed with 100 ml of water taken in a beaker and checked for phase separation and turbidity. The ratios with no phase separation and clear appearance with no turbidity were separated and checked for transmittance using UV spectro-photometer [8]. The transmittance value of 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: Fifteen compositions of varying ratios of Neobee M5 - Caproic acid- PEG600 were taken, and in 1ml composition of each ratio were 100 mg, 200 mg, and 300 mg of doravirine was added (*i.e.*, 15*3=45 formulations). Contents vortexed at 40°C in a water bath for complete solubilization. The oil was added to the mixture and vortexed for 2 min. 25 mg of the formulations diluted using 50 mL distilled water and evaluated for % transmission spectro-photometrically [10].

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 1 ml 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

Evaluations of Doravirine SNEDDS:

Visual Observation: The doravirine SNEDDS (25 mg) was mixed with 50 mL of distilled water in a glass Erlenmeyer flask at 37° C and stirred manually [12]. After equilibrium, time of self-emulsification, dispersibility, and appearance were observed and rated according to grading system [13].

Turbidity Measurement: Turbidity of the prepared dispersions was measured using Nephelo Turbidity Meter using 30 mL of the dispersion [14].

Robustness to Dilution: Robustness of doravirine SNEDDS to dilution was studied by diluting 25 mg of SNEDDS with 50, 100, and 1000 mL of distilled water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The diluted nanoemulsions were stored for 24 h and observed for any signs of phase separation or drug precipitation [14].

Percentage Drug Content: All the formulations of doravirine -loaded SNEDDS were subjected to assay analysis in order to determine their percentage drug content. Accurately weighed samples were dissolved individually in 10 mL of methanol and stirred by a vortex mixer for a period of 10 min. Each of the solutions was filtered, and the drug content of each filtrate was estimated UV spectrophotometrically against blank at 270 nm [15].

Entrapment Efficiency: A known quantity of doravirine loaded SNEDDS mixed with 100mL phosphate buffer (pH 6.8) and kept in the dark for 24h.the contents were filtered, filtrate diluted, and analyzed for drug content by UV for the drug content at 270nm [15]. Entrapment efficiency was calculated by formula

Drug entrapment efficiency = Experimental drug content / Theoretical drug content × 100

***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 buffer 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). Capsules were held to the bottom of the vessel using copper sinkers. 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 spectro-

photometrically at 270nm [16]. For comparison, similarly, dissolution studies of pure drug and marketed products were also performed. All measurements were done in triplicate.

Characterization of Optimised Doravirine SNEDDs Formulation:

Globule Size and Zeta Potential: The globule Size and zeta potential of optimized formulation was determined by a Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern Instruments, Malvern, Worcestershire, UK) at a wavelength of 270 nm, a scattering angle of 90°and at 25 °C [9].

Drug Compatibility Studies: The FTIR of pure drug and optimized 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].

Forced Degradation Studies: All solutions for use in forced degradation studies were prepared by dissolving optimized SNEDDS and pure drug in small volume of methanol and diluted with the respective forced degradation medium i.e., with methanol or distilled water for neutral degradation, with simulated gastric fluid (aqueous 0.1N HCl was adjusted to pH 1.2 with NaCl) without pepsin for gastric degradation and with simulated intestinal fluid (aqueous pH 6.8 phosphate buffer) without pancreatin for intestinal degradation to achieve a concentration of 100 g/mL of each solution. All solutions were stored at room temperature. At different time intervals (0, 4, 6, 12 and 24 h) aliquots of these solutions were diluted suitably to yield 10 g/mL concentrations and analyzed for drug-using UV method. The percentage degradation of doravirine was calculated (ICH Harmonized Tripartite guideline on "Stability Testing of New Drug Substances and ProductsQ1A (R2)", 6 February2003) [18].

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.

RESULTS AND DISCUSSION:

Determination of 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 **Fig. 1**. The surfactant cremophor CO 60and co-surfactant PEG600 was selected for further studies due to their higher solubilizing capacity towards doravirine **Fig. 2** and **3**.

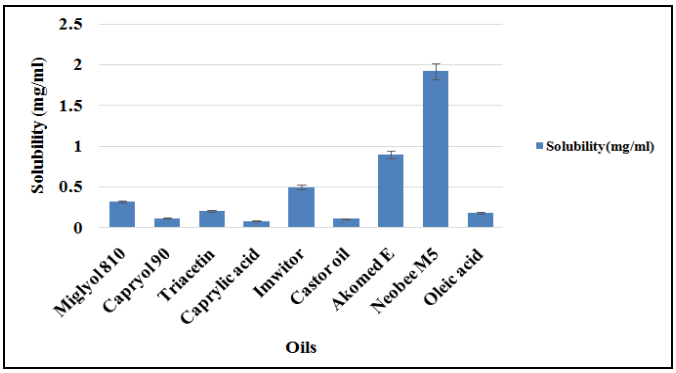

FIG. 1: SOLUBILITY OF DORAVIRINE IN VARIOUS OILS

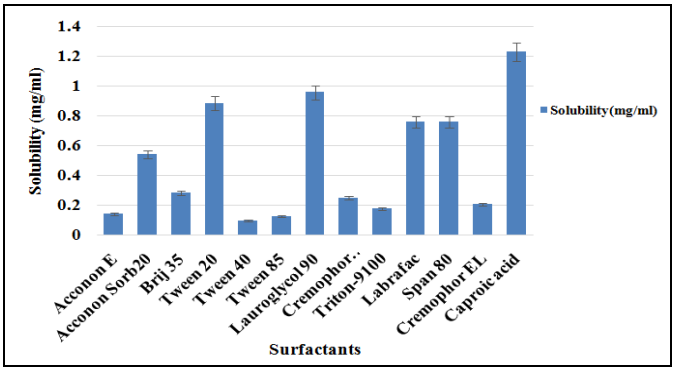

FIG. 2: SOLUBILITY OF DORAVIRINE IN VARIOUS SURFACTANTS

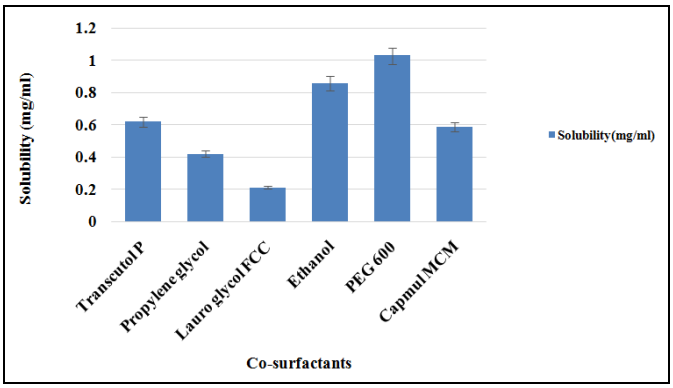

FIG. 3: SOLUBILITY OF DORAVIRINE IN VARIOUS CO-SURFACTANTS

Construction of Ternary Phase Diagrams: The region of nano emulsification was indicated as a 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 nano-emulsification region **Fig. 4** as compared to 1:1 and 2:1 S_{mix} ratio.

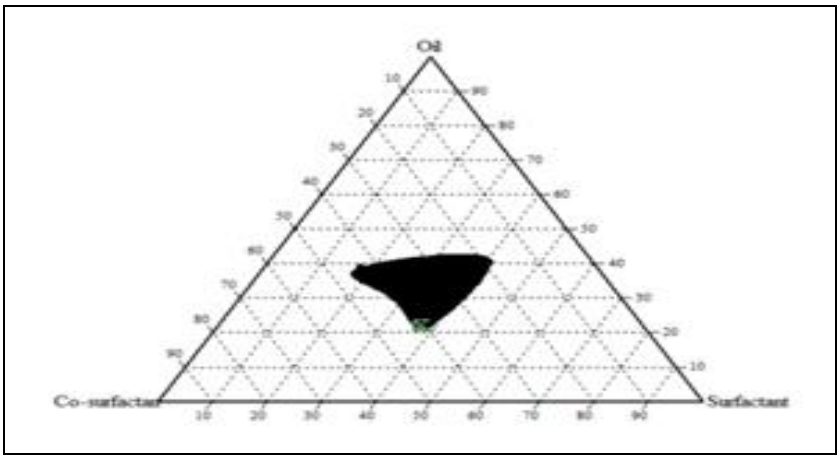

FIG. 4: TERNARY PHASE DIAGRAM FOR NEOBEE M5 - CAPROIC ACID- PEG600 WITH S_{MIX} IN 1:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO-EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

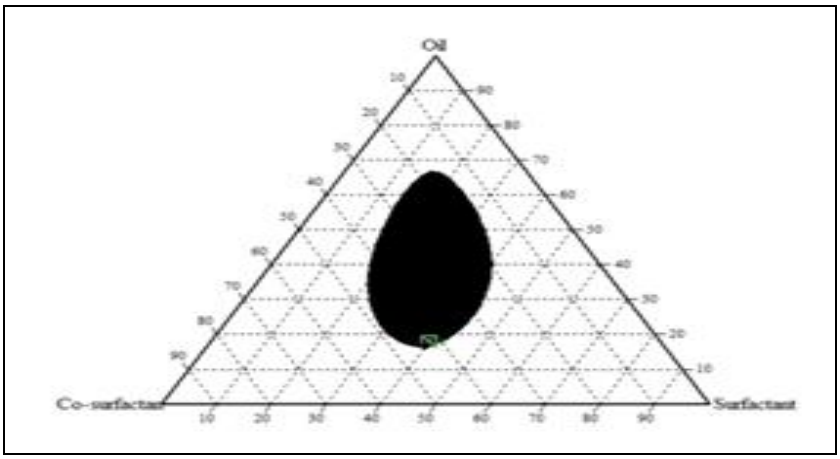

FIG. 5: TERNARY PHASE DIAGRAM FOR NEOBEE M5 - CAPROIC ACID- PEG600 WITH SMIX IN 2:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

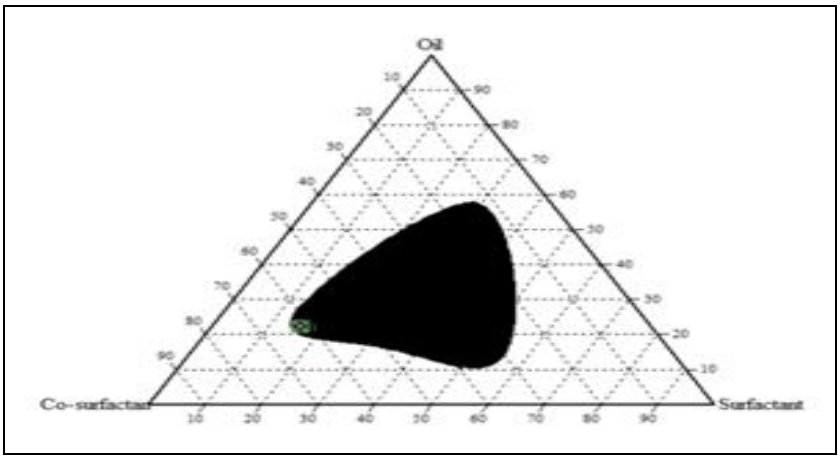

FIG. 6: TERNARY PHASE DIAGRAM FOR NEOBEE M5 - CAPROIC ACID- PEG600 WITH SMIX IN 3:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

The mean globule size was decreased with an increase in surfactant concentration. Hence the systems containing Neobee M5 - Caproic acid- PEG600 with 3:1 S_{mix} ratio were selected for further studies due to their larger nanoemulsifying area, greater capacity for incorporation of oily phase with uniformity of dispersion, and high transmittance values.

Effect of Doravirine Loading: Incorporation of doravirine (100 mg, 200 mg, and 300 mg) **Fig. 7** and **9** and 10) 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.

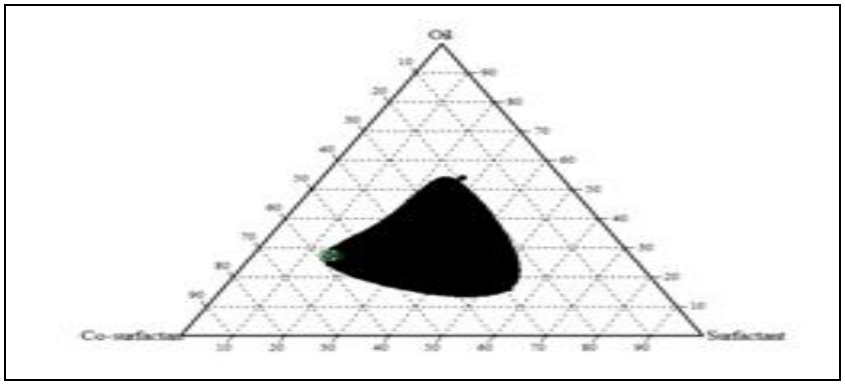

FIG. 7: TERNARY PHASE DIAGRAM FOR 100 MG OF DORAVIRINE LOADED IN NEOBEE M5 - CAPROIC ACID- PEG600 SYSTEM WITH SMIX IN 3:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

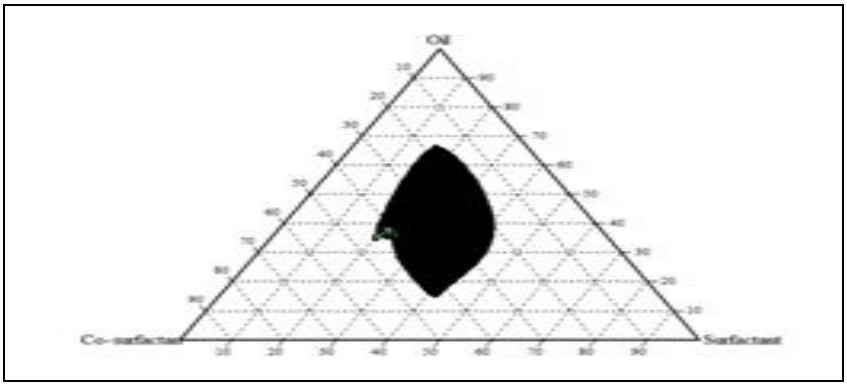

FIG. 8: TERNARY PHASE DIAGRAM FOR 200 MG OF DORAVIRINE LOADED IN NEOBEE M5 - CAPROIC ACID- PEG600 SYSTEM WITH SMIX IN 3:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

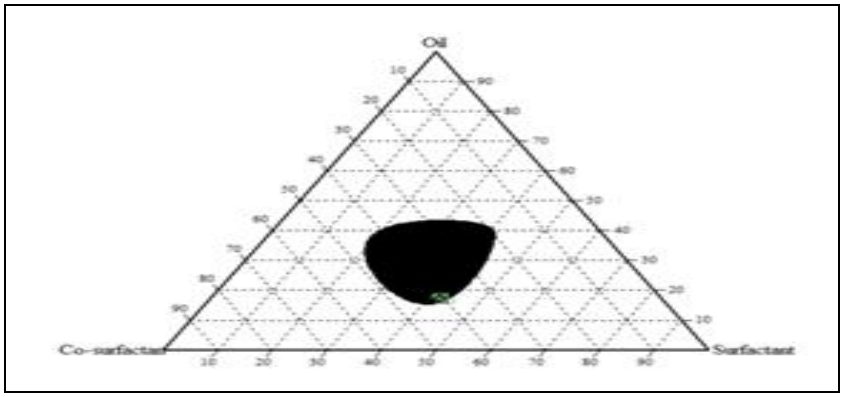

FIG. 9: TERNARY PHASE DIAGRAM FOR 300 MG OF DORAVIRINE LOADED IN NEOBEE M5 - CREMOPHOR CO 60- PEG600 SYSTEM WITH SMIX IN 3:1 RATIO (KEY: THE FILLED REGION WITHIN THE TERNARY PHASE DIAGRAM INDICATES NANO EMULSIFICATION AREA WHERE THE TRANSMITTANCE IS GREATER THAN 90)

Oil globules were observed on the surface after dispersion on standing for most compositions containing high doravirine. The area of nano emulsification was considerably reduced with an increase in doravirine loading into the Neobee M5 - Caproic acid- PEG600 system with 3:1 S_{mix} ratio **Fig. 10** hence for the stability reasons of the SNEDDS, a system containing 100 mg of doravirine was chosen for the formulation of doravirine SNEDDS and further studies.

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 acid in the range of 18-60% w/w, and PEG 600 in the range of 7-20% w/w in 3:1 of oil: Smix ratio with 100mg loaded doravirine drug produced the SNEDDS having the transmittance greater than 90, with good stability. A series of SNEDDS was prepared in the above-mentioned ranges of oil-surfactant-co-surfactant ratios and were evaluated

Visual Observations: Visual observations indicated that at higher surfactant levels, the spontaneity of the self-emulsification process was increased. This may be due to excess penetration of water into the bulk oil causing massive interfacial disruption and ejection of droplets into the bulk of aqueous [19].

When a co-surfactant, PEG 600, was added to the system, it further lowered the interfacial tension between the o/w interfaces and also influenced the interfacial film curvature.

Turbidity Measurement: 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 value of more than 90, indicating rapid and spontaneous emulsification within 1min; hence it gives a good correlation between transmittance and turbidity values **Table 2**.

Robustness to Dilution: Nanoemulsions resulting from the dispersion of doravirine SNEDDS (F1-F14) with distilled water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer were found to be robust to all dilutions, and no separation or drug precipitation was observed even after 24 hours of storage.

Percentage Drug Content and Entrapment Efficiency: 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 the 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)

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 the drug within 45 min, whereas pure drugs released 31.91% of the drug in 60 min. Formulation F8 exhibited the highest drug release of 99.87% in 60min. The release of the drug from SNEDDS formulation was increased proportionally with the increase in surfactant concentration, and hence F8 exhibited high drug release **Fig. 10**.

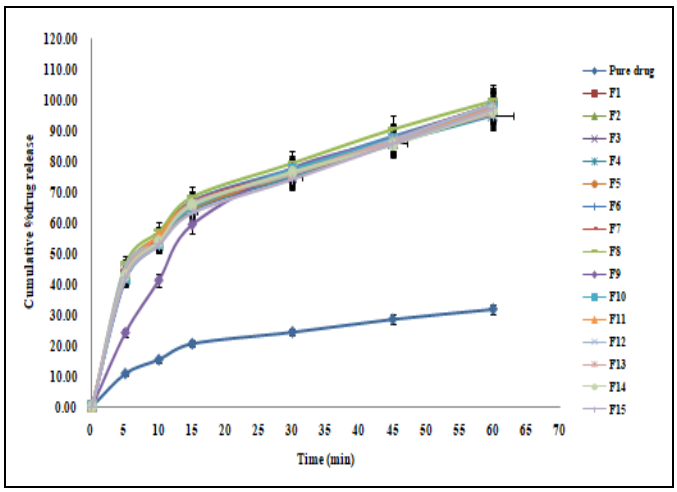

FIG. 10: COMPARATIVE DISSOLUTION PROFILE OF DORAVIRINE PURE DRUG AND DORAVIRINE SNEDDS FORMULATION (F1-F15)

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 at 630 cm^{-1} (C-F Bending) 1033.88 cm^{-1} (Alcohol C-O stretching), 1178.55 cm^{-1} (C-F stretching), 1284.63 cm^{-1} (acid C-O stretching), 1555.16 cm^{-1} (aromatic C=C stretching), 1629 cm^{-1} (C=Ostretching), 1649 cm^{-1} (C=C stretching), 1745 cm^{-1} (C=0 stretching), 3024 cm^{-1} (C-H stretching), 3416 cm^{-1} (Alcohol: O-H stretching), 3416 cm^{-1} (N-H stretching), 3423 cm^{-1} (Amine: N-H stretching).

The presence of prominent characteristic peaks in optimized formulation F8 spectra confirms the compatibility between drug and excipients.

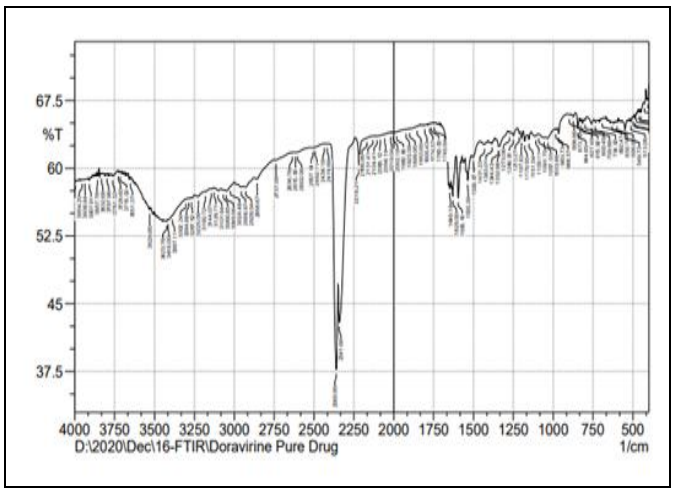

FIG. 11: FTIR OF DORAVIRINE PURE DRUG

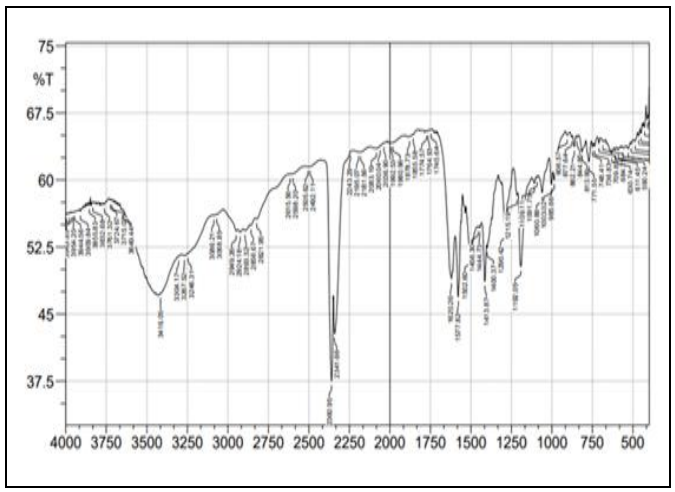

FIG. 12: FTIR OF OPTIMIZED DORAVIRINE SNEDDS FORMULATION F8

Globule Size and Zeta Potential: Droplet size distribution following self-nanoemulsification is a critical factor in evaluating 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 anionic groups of free fatty acids and glycol present in the oil, surfactant, and co-surfactant. The zeta potential value > 5 mV provide excellent stability.

SEM Studies: The SEM results were in accordance with 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 **Fig. 10**. However, the shape of droplets was found to be spherical.

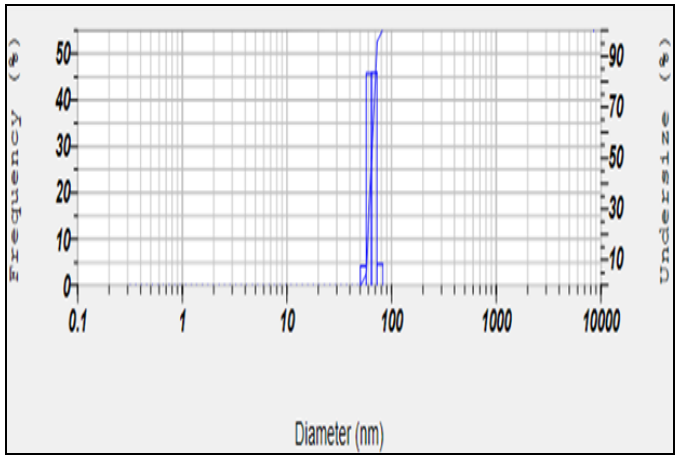

FIG. 13: PARTICLE SIZE OF OPTIMIZED SNEDDS FORMULATION OF DORAVIRINE (F3)

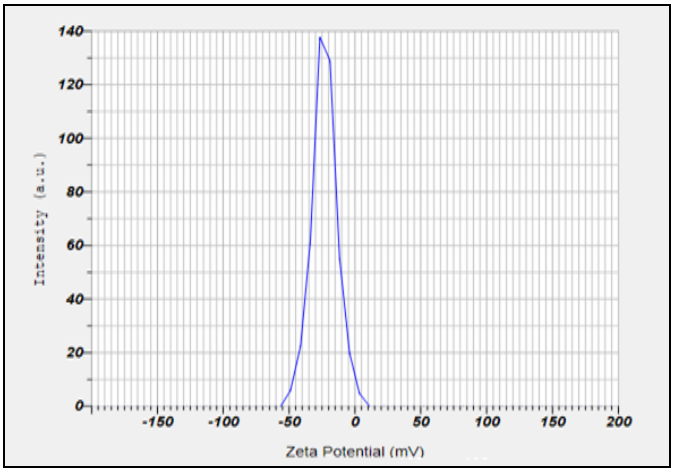

FIG. 14: ZETA POTENTIAL OF OPTIMIZED SNEDDS FORMULATION OF DORAVIRINE (F8)

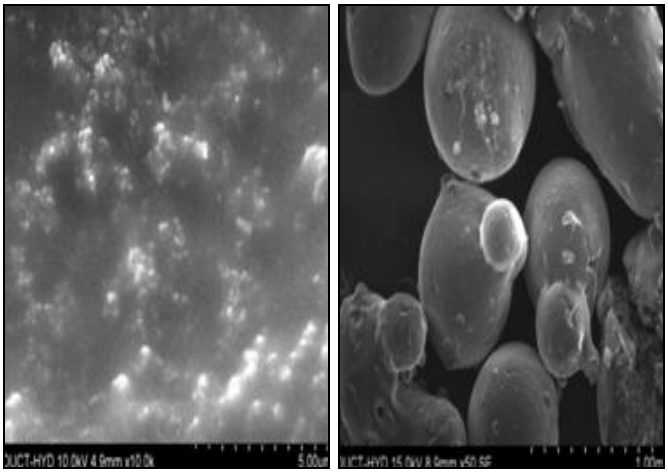

FIG. 15: SEM IMAGES OF OPTIMIZED FORMULATION OF DORAVIRINE SNEDDS F8 (A AND B)

TABLE 3: PERCENT DEGRADATION OF DORAVIRINE FROM PURE DRUG AND OPTIMIZED DORAVIRINE SNEDDS IN FORCED DEGRADATION STUDY

Formulation code	Time (hr) / Diluting Solvent	%Drug Degraded (%, mean ± s.d, n=3)				
		0 Hour	4th Hour	6th Hour	12th Hour	24th Hour
Pure drug	Methanol	0.02 ± 0.63	0.010 ± 0.28	0.01 ± 0.82	0.011 ± 1.38	0.11 ± 1.67
	Water	0.02 ± 1.83	0.03 ± 0.19	0.01 ± 1.93	0.04 ± 1.75	0.05 ± 0.57
	0.1 N HCl	0.07 ± 0.28	23.63 ± 0.85	31.18 ± 0.61	42.01 ± 1.52	61.57 ± 0.09
	pH 6.8 phosphate Buffer	0.02 ± 1.13	0.03 ± 1.84	0.13 ± 0.32	0.06 ± 1.95	0.07 ± 1.13
F8	Methanol	0.02 ± 1.52	0.14±1.48	0.18 ± 1.54	0.03 ± 1.21	0.02 ± 1.09
	Water	0.01 ± 0.59	0.30 ± 0.36	0.01 ± 1.29	0.13 ± 1.29	0.08 ± 1.96
	0.1 N HCl	0.01 ± 0.94	0.06 ± 1.23	12.85 ± 1.46	28.59 ± 0.33	33.44 ± 1.15
	pH 6.8 phosphate Buffer	0.01 ± 0.38	0.06 ± 1.04	0.07 ± 1.35	0.03 ± 1.84	0.10 ± 0.16

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

Forced Degradation Studies: Pure drug present in 0.1N HCl solution showed 23.63% degradation within 4 h and the degradation was increased with time (61.57% degradation was found at 24th h).

Doravirine showed minimal decomposition (<1% degradation) for up to 4 h and then decomposed with the time in the 0.1N HCl solution. Doravirine SNEDDS optimized formulation F8 showed 12.85, 28.59, and 33.44% degradation in 6th, 12^{th,} and 24th h, respectively.

The degradation of doravirine from optimized doravirine SNEDDS formulation was significantly less when compared to the pure drug degradation.

From these results it can be concluded that the pH-dependent degradation of doravirine could be minimized to some extent by formulating the drug into SNEDDS. Moreover, under normal physiological conditions, gastric emptying occurs from the stomach within 4 h, and hence SNEDDS may be considered as a suitable formulation approach for improving the therapeutic efficiency of doravirine.

Accelerated Stability Studies: Stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and enables recommended storage conditions.

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 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

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

CONCLUSION: In the present study doravirine SNEDDS was prepared using Neobee M5 as oil, Caproic acid as a surfactant, and PEG 400 as a co-surfactant optimized using a ternary phase diagram.

Optimum values obtained at the physical evaluation involved drug loading of 100 mg of drug SNEDDS, turbidity of 15.6 NTU, transmittance value of 98%, and % drug content of 99%.

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 anionic groups of free fatty acids and glycol present in the oil, surfactant, and co-surfactant.

The compatibility study was carried out by comparing FTIR spectra of pure drug and optimized formulation. *In-vitro* drug dissolution values obtained at 60 min was98% with minimized pH-dependent degradation compared to pure drug. Hence a highly soluble SNEDDS formulation of doravirine was developed with enhanced stability and dissolution rates.

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CONFLICTS OF INTEREST: Nil

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