OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences

Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Pharmaceutical Sciences**

Formulation and Evaluation of Solid-Self Nano Emulsifying Drug Delivery System of Darunavir

Nara Aishwarya[1*], Shaik Muhammad Fazal ul Haq[1]

[1]Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad (JNTUH), Kukatpally, Hyderabad - 500085, Telangana, India

DOI: 10.36348/sjmps.2022.v08i10.010 | **Received:** 28.08.2022 | **Accepted:** 09.10.2022 | **Published:** 21.10.2022

***Corresponding author:** Nara Aishwarya
Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad (JNTUH), Kukatpally, Hyderabad - 500085, Telangana, India

Abstract

The main aim of this research article is to Formulate and Evaluate the S-SNEDDS of Darunavir. Darunavir is an anti-retroviral protease inhibitor which is in use from long time, but it has poor bioavailability because of poor aqueous solubility and extensive first pass metabolism, when used in the form of conventional dosage form. As it is a BCS Class II drug, which shows low solubility and high permeability. The S-SNEDDS of Darunavir was prepared to improve its oral bioavailability and its release rate was evaluated by in vitro release. The solubility of Darunavir in various oils was to decide and identify the oil phase of formulations. Different oils, surfactants and co-surfactants were screened for their ability to emulsify the selected oil. The pseudo ternary phase diagram was used to know the self -emulsification region of formulation. The optimized S-SNEDDS formulation contain Darunavir (150mg), Caproyl®90(50mg), Labrasol® and Transcutol® mix (45 mg). The data of the FTIR confirms that there is no interaction observed and the drug and excipients was compatible with each other. The developed SNEDDS formulations were examined for nano emulsifying capabilities, and the resulting nano emulsions were investigated for self-emulsification efficiency, dispersibility and in-vitro dissolution. Centrifugation tests, particle size distribution, heating cooling cycle, zeta potential, and freeze thaw cycling were performed on the optimised formulations to establish the stability of the produced SNEDDS formulation. Further produced S-SNEDDS micromeritics studies were done. The formulation was shown to significantly improve drug release, with total drug release occurring within 60 minutes. Darunavir self-emulsifying formulation was thus effectively produced.

Keywords: Solubility, S-SNEDDS, Darunavir, BCS class II, Caproyl 90, Labrasol & Transcutol.

1. INTRODUCTION

T-immune cells (CD4 cells) are rendered inactive by the human immunodeficiency virus (HIV), which also affects the body's overall Immune system. Acquired Immuno Deficiency Syndrome, an advanced illness stage, could results from untreated HIV infection. The antiretroviral therapy combats HIV and slows the virus's ability to spread through the body. Treatment for, HIV /AIDS is successfully carried out using Combination Antiretroviral Therapy, also known as highly active Antiretroviral Therapy. In this Protease inhibitors constitute a new class for HIV infection. Protease inhibitors prevent HIV from producing the protein and protease necessary for the cleavage of the protein into the individual components it needs to form viral particles. Protease inhibitors have shown to reduce viral RNA concentration (viral load), increase the CD4 count and improve survival when used in combination with other agents and compound against placebo. They are extensively metabolised by isoenzymes of the cytochrome P450 system, notably by CYP3A4 which is involved in the metabolism of many drugs. Plasma t1/2 for each of these in the range 2-4 hrs. The drugs have broadly similar therapeutic effects and include Indinavir, lopinavir Ritonavir, Saquinavir and Darunavir.

Among these, Darunavir is the one of the latest drugs in this 2nd generation class approved by USFDA. Due to its poor aqueous solubility and good permeability characteristics it belongs to the Biopharmaceutical Classification System (BCS) II.

Bio-pharmaceutical Classification System

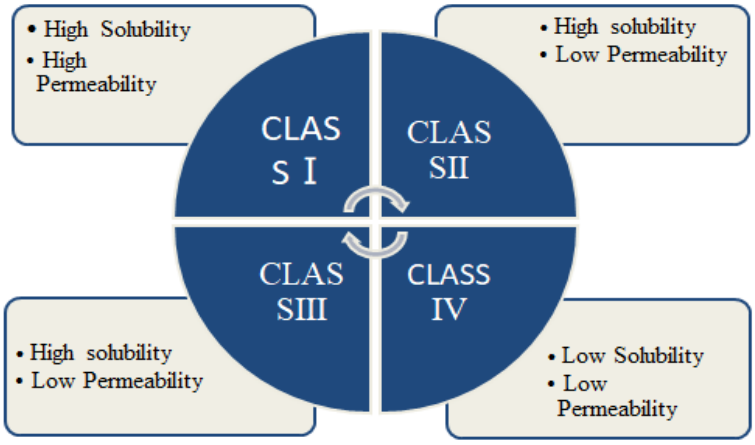

Fig-1: BCS Classification

These characteristics leads to poor oral bioavailability and lack of dose proportionality and high intra and inter subject variability. The use of surfactants, lipids, permeation enhancers, micritization, salt formation, cyclodextrins, nanoparticles, and solid dispersions are just a few of the techniques that have been used to overcome these problems. The bioavailability of class II drugs can be increased using a variety of formulation techniques, such as enhancing the rate of dissolution or delivering the drug in solution and keeping it there throughout the intestinal lumen. In the current study, an effort has been made to increase the drug's solubility properties by changing to a lipid-based drug delivery method (LBDDS). One of the most promising LBDDS is the self-emulsifying drug delivery (SEDDS) system, which may increase the solubility properties of DRV and promote oral bioavailability.

SEDDS are lipid-based formulations, which are isotropic mixtures of oils, surfactants and cosurfactants converts into micro/nano self- emulsion (SNEDDS & SMEDDS) in the presence of gastro intestinal fluids under the gentle agitation. This self-emulsification is also called as in-situ emulsification as it emulsifies inside the body.

Formulation Ingredients of SNEDDS:

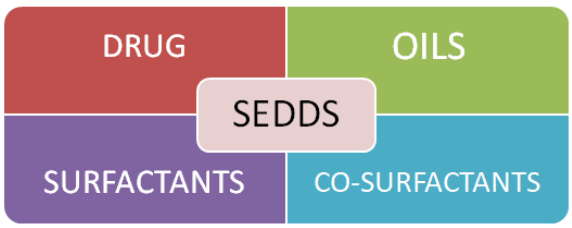

Fig-2: Formulation Ingredients of SEDDS

This emulsified Darunavir drug further solubilised and up taken into lymphatic pathway. And this lymphatic system can be target for treatment of many diseases such as cancer and AIDS. The lymphoid organs like the spleen, thymus, and lymph nodes are colonised by HIV, the virus that causes AIDS. In the early stage of infection and throughout the latent stage, the virus replicates vigorously in lymphoid organs, meaning that lymphatic drug delivery can be advantageous in the treatment of AIDS [1]. Drugs absorbed by the lymphatic system discharge into the bloodstream more quickly than those metabolised by Cyp3A. SNEDDS has been demonstrated to improve the solubility of poorly soluble drugs, and it has been widely reported in previous years that it can target the lymphatic system. These SNEDDS systems advantageously present the drug in dissolved from and the small droplet size provides a large interfacial area for the drug absorption [2]. SNEDDS are physically stable formulations that are less sensitive than emulsions, which are sensitive and meta-stable dispersed forms, simple to produce. Consequently, for drug molecules that are lipophilic show absorption that has a limited dissolution rate, these systems could an increase in the rate and extent of absorption will lead to blood time profiles that are more repeatable [3].

2. MATERIALS & METHODS

Darunavir Ethanolate (Hetero laboratories), Captex, Capmul MCM C8 EP, Capmul MCM (glyceryl caprylate/caprate), Captex 355 EP/NF, Caproyl90

(Propylene glycol monocarprylate, type II), Masine CC, Labrafil CC, Labrafac Liphophile WL 1349 (medium chain triglyceride), Labrafac PG, Tween 80 (Polyoxyethylene Sorbitan mono-oleate), KoliphorRH 40, Cremophor EL, Labrasol(caprylocaproyl macrogol-8 glycerides), Transcutol P (diethylene glycol monoethyl), Lauroglycol 90, LaurylGlycol FCC (propylene glycol monolaurate type I), (PEG 400 polyethylene glycol 400), Simusol, Gelusire-44/14, methanol, HCl and distilled water are used throughout the experiment.

2.2. METHODS

UV-SPECTOSCOPIC ANAYASIS OF DARUNAVIR

2.2.1 Determination of λmax of Darunavir Ethanolate

100 mg of Darunavir Ethanolate was weighed and transferred into 100 ml volumetric flask containing methanol. From this solution take 1µg/ml, 10µg/ml solution. The absorption maxima of Darunavir Ethanolate in methanol were deliberate in range of 200-700nm.

2.2.2. Construction of Calibration Curve

Preparation of standard stock solution using Methanol:

The Standard stock solution of Darunavir sample was prepared by transferring 10 mg of drug in 10 ml of volumetric flask and add 10 ml of methanol. The solution was sonicated for 2-3 min to dissolve drug and the solution was then diluted to volume with methanol.

PREPRATION OF TEST SOLUTION

To prepare test solution pipette out 0.1 ml of stock solution into 10 ml volumetric flask and dilute up to the mark with methanol.

2.1. CALIBRATION CURVE OF DARUNAVIR IN METHANOL

From the above reserved solution, a linear range of concentrations of 1, 2, 3, 4and 5 µg/ml were prepared from the above mentioned solution, and the absorbance was measured at 200-700nm in comparison to a blank using an Ultra-Violet spectrophotometer.

2.2 FTIR Spectroscopy

To know any significant interactions between Darunavir and excipients FTIR Spectroscopy studies were conducted. FTIR ranges from 4000-400 $cm^{-1.}$

2.3. SOLUBILITY STUDIES

An excess amount of Darunavir was added to various oils, surfactants and co- surfactants and mixed by using cyclo-mixer. The mixture was kept at ambient temperature for 72 hours to attain equilibrium. The equilibrated sample was centrifuged at 3200 rpm for 10 min to remove the insoluble drug. And aliquot of the supernatant was diluted with diluted with methanol and Darunavir Ethanolate was quantified by using UV Spectrophotometer.

2.4. PSEUDO TERNARY PHASE DIAGRAM

The components utilised to build the phase diagram from the solubility studies are Caproyl 90, an oil, Labrasol, a surfactant, and Transcutol, a co-surfactant. To identify self-emulsifying regions and choose the proper amounts of oils, surfactants, and co-surfactants for the formulation of SEDDS, pseudo ternary phase diagrams were produced using the water titration method at room temperature.

In each group, the weight ratio of the surfactant to co-surfactant (S mix) was mixed (3:1,4:1). Oil is thoroughly combined with particular S mix ratios in weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. Each mixture underwent titration with water, a 2-minute vortex, and an equilibration period. On the three-component ternary phase diagram, where each axis represents oil, S mix, and water, the transition from transparent to turbid was visually noted. Plots of phase diagrams were made.

2.5. FORMULATION OF LIQUID-SEDDS

In order to create SEDDS formulations, different ratios of Capryol 90, Labrasol and Transcutol HP were used based on Ternary Phase Diagram. Numerous formulations with mixtures of various components are described in detail. The three various formulations (F1-F3) were made by combining 150 mg of Darunavir with Capryol 90, Labrasol and Transcutol HP and allowing the mixture to dissolve. The mixture was then heated in a water bath to 40°C. Vortex mixture was used to vortex the mixture until it was translucent and clear. Prior to usage, all formulations were kept at room temperature.

2.6. FORMULATION OF SOLID-SNEDDS

The formulation C90L3T1 with good stability, good self-nano emulsification property, and showing reduced particle size and fewer PDI was chosen to formulate as solid SNEDDS from the evaluation studies done on several Darunavir SNEDDS. S-SEDDS was made by combining liquid SNEDDS containing Darunavir in a 1:2 ratio with nuselin as a carrier. Over the nuselin that was enclosed in the porcelain dish, liquid SNEDDS was applied drop by drop. For a consistent dispersion of the formulation, the ingredients were stirred using a glass rod after each addition. The resulting wet mass was put through sieve 120, dried at room temperature, and then put away for later use.

3. EVALUATION OF S-SNEDDS

Emulsification Time

In this test, a predetermined volume of each formula (1ml) was introduced into 300mL of distilled water maintained at 37±0.5°C in a glass beaker and the contents were mixed gently using a magnetic stirrer rotating at constant speed (100 rpm). The emulsification

time (the time required for a pre-concentrate to form a homogeneous mixture upon dilution) was mentioned by visually observing the disappearance of SNEDDS and the final appearance of the nano emulsion [3].

Dispersibility Test

To evaluate SNEDDS's ability to dispense into emulsion and classify the size of the resultant globules, the dispersibility test is conducted. 250 ml of distilled water and 0.1 ml of SNEDDS preconcentrate were combined, and the mixture was swirled using a magnetic stirrer at a speed of about 100 rpm for the specified amount of time until an emulsion had formed. The SEDDS formulation creates a variety of mixtures following titration with water, depending on which the formulation's in vitro performance can be graded.

Grade A: An emulsion that forms quickly and has a clear or bluish appearance (within 1 min).

Grade B: A rapidly forming, slightly less clear, and bluish-white looking emulsion.

Grade C: Within two minutes, a fine milky emulsion formed.

Grade D: A dull, greyish-white emulsion that is slow to emulsify and has a faint greasy appearance (longer than 2 min).

Grade E: The formula has either minimal or poor emulsification, and there are visible large oil globules on the surface [3].

Globule size Measurement, Zeta Potential and Polydispersity Index:

Globule size analysis, and PDI, Zeta potential Darunavir formulated SNEDDS of 0.1 ml (1:100) of SNEDDS in 10ml of double distilled water, vortex for 5 minutes to form a uniform solution, kept stand by overnight followed by analyze the sample double distilled water. To analyse fluctuations in light scattering brought on by the motion of the particles, photon correlation spectroscopy was used to measure the mean globule size and polydispersity index (P.I.) of the resulting emulsions (Malvern Instruments Worcestershire, UK) Monitoring of light scattering took place at 25°C and a 90°angle11 [4].

Thermal Stability Studies:

Due to the possibility of drug precipitation in an excipient matrix, the formulation's physical stability is crucial to its effectiveness. Poor formulation physical stability can cause excipient phase separation, which can have an impact on both therapeutic efficacy and excipient bioavailability. Additionally, incompatibilities between the formulation and the capsule's gelatin shell may result in brittleness, softness, delayed disintegration, or insufficient drug release. These studies go through the following cycles:

Freeze Thaw Stress Cycle

Formulation of Darunavir SNEDDS and Distilled water mixed in the ratio (1:10) then these formulations were subjected to three cycles of freeze-thaw between 21 and 25 °C with storage at each temperature for not less than 48 h. Phase separation, cracking, or creaming are not present in formulations that pass this test, which indicates strong stability. The formulations that pass this test are subsequently subjected to a dispersibility test to estimate their ability to produce emulsions on their own.

Heating and Cooling Cycle

The formulation of Darunavir SNEDDS and distilled water are mixed in the ratio of (1:50) and the subjected to six cooling and heating cycles between the refrigerator temperature (4°C) and the higher temperature (45°C) are carried out, with exposure to each temperature lasting no longer than 48 hours. Centrifugation testing is then performed on those formulations that pass the stability test.

Centrifugation

After completing the heating-cooling cycle, the formulation of Darunavir SNEDDS and distilled water are mixed together in ratio of (1:10) then are centrifuged at 3500 rpm for 30 minutes. The freeze-thaw stress test is performed on formulations that do not exhibit any phase separation [5].

Effect of Dilution

Darunavir formulations were diluted 50, 100, 1000, and 3,000 times with distilled water, 0.1M HCl, and simulated intestinal fluid (pH 6.8). After 24 hours of storage, the resulting diluted emulsions were manually examined for any physical alterations, such as droplet coalescence, precipitation, or phase separation.

Phase Separation and Stability Test:

In a beaker 20ml of distilled water is taken and heated to a steady 37°C. Darunavir liquid formulation was mixed with distilled water, 1ml of Darunavir SNEDDS was added, and the mixture was then diluted by agitation before being left alone for 24 hours. Next, the formulation is visually examined for any signs of phase separation.

Drug loading efficiency:

Drug content in Darunavir SNEDDS formulations was determined using UV spectroscopy. The SNEDDS were taken and dissolved in a little amount of methanol, equal to 100 mg of DARUNAVIR. In order to make the quantity 100 ml, double distilled water was used. From the stock solution, 0.2 ml was taken out and diluted with double-distilled water to a final concentration of 10 ml. Utilizing a UV spectrophotometer, the solution's absorbance was measured at 266nm (UV 1800, Shimadzu). The drug content stdy was conducted three times.

Drug Loading

$$Efficiency = \frac{Amount\ of\ Drug\ in\ known\ amount\ of\ foarmulation}{Initial\ Drug\ load} \times 100$$

In-Vitro Drug Release Studies

The USP II dissolution test apparatus is used for the in-vitro drug release studies. The liquid SNEDDS formulation and Solid SNEDDS of Darunavir capsules are dissolved in 900 ml of buffer medium, which contains 0.1 NHCL. The conditions are kept at 37±5°c, PH 1.2, and 50RPM. The samples (5ml) are taken out at predetermined intervals—5, 10, 15, 30, 45, 60, 90, and 120 minutes—and filtered through a 0.45um filter before being subjected to UV spectrophotometer analysis. The calibration curve is used to calculate the drug release.

Angle of repose

The funnel method was employed to determine the angle of repose of S-SNEDDS. The height of the funnel was adjusted such that the tip just touches the top of the powder heap. An exact weighted sample was permitted to freely flow through the funnel and onto the surface. The powder cone's diameter was measured, and the equation was employed to determine the angle of repose.

Tan θ = h/r

h=height of the powder cone
r = radius of the powder cone

Bulk density and tapped density

In a 10mL measuring cylinder, 2gm of S-SEDDS were added. Initial volume was recorded first before cylinder was allowed to descend at regular intervals of two seconds from a height of 2.5 cm onto a hard surface. The tapping continued until there was no longer any loudness change. The following equations were used to calculate the bulk density and the tapped density.

$$\textbf{Bulk denisty}(BD) = \frac{\textbf{weight of powder blend}}{\textbf{volume of the packing}}$$

$$\textbf{Tapped Density}(TD) = \frac{\textbf{Weight of the powder blend}}{\textbf{Tapped volume of the packing}}$$

Compressibility Index:

$$\textbf{Carr's Compressibilty Index}(\%) = \frac{(TD - BD)}{TD} \times 100$$

Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flowability of a powder (or) granular material. Hausner's ratio can be calculated by the equation.

Hausner's Ratio= $\frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$

4. RESULTS AND DISCUSSION

Determination OF λmax of Darunavir:

Observation: The spectrum of Darunavir showed maximum absorption at
wavelength 266nm in methanol.

UV Calibration of Darunavir Ethanoate:

Correlation coefficient was found to be R^2=0.9478

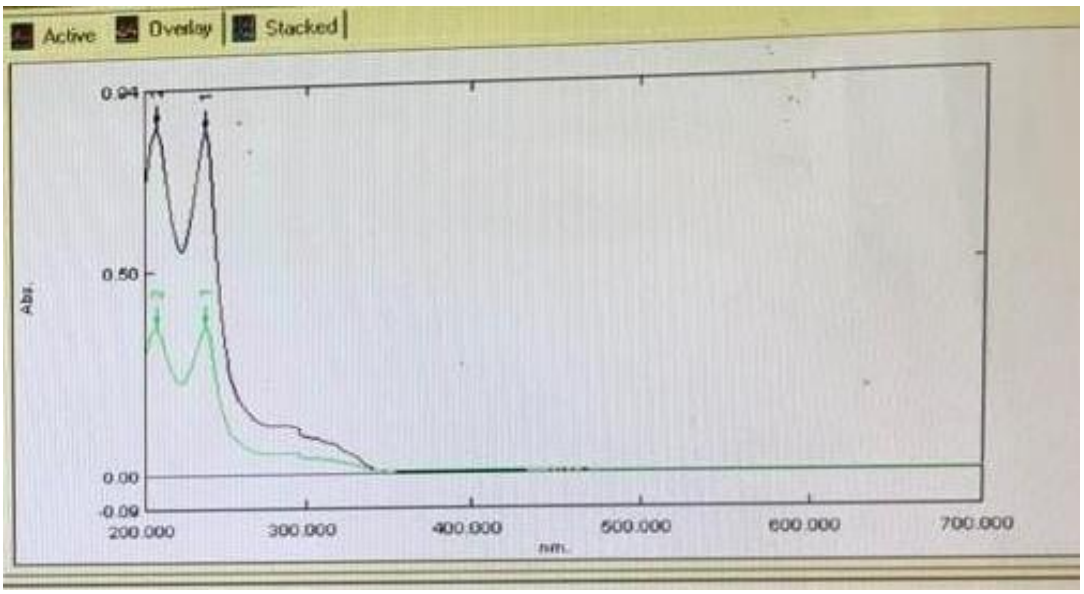

Fig-3: Absorbance Maxima of Darunavir Ethanolate

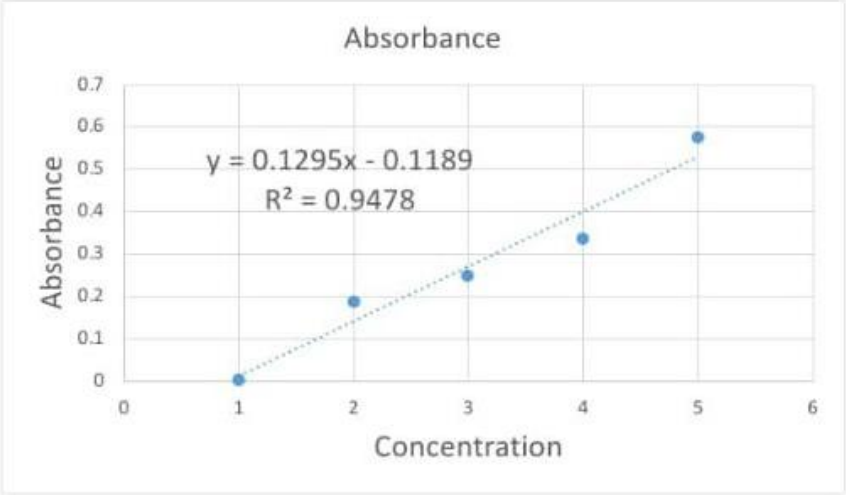

Fig-4: Standard Graph of Darunavir Ethanoate

Table-2: Linearity of Darunavir Ethanolate

Concentration	Absorbance
1ppm	0.002
2ppm	0.188
3ppm	0.247
4ppm	0.335
5ppm	0.576

FTIR STUDIES:

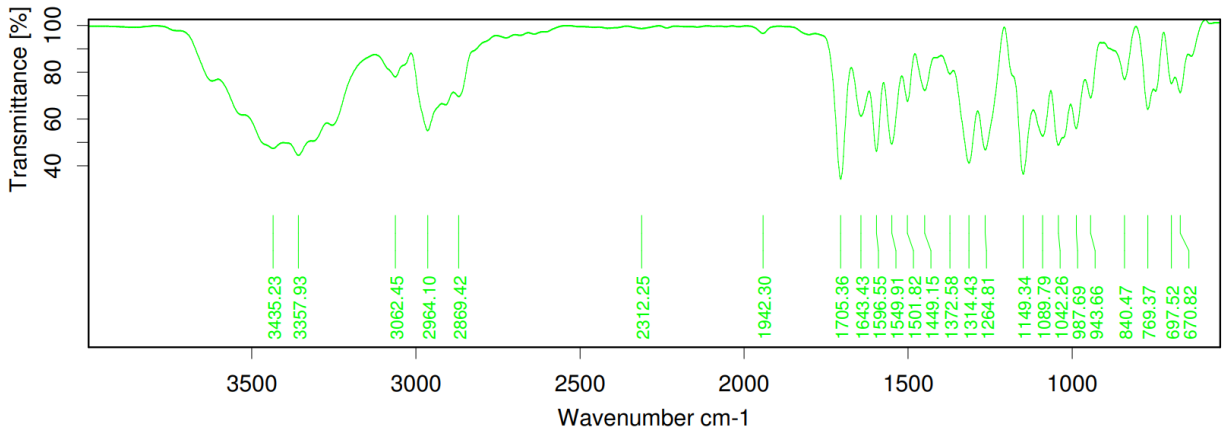

Fig-5: Darunavir Pure Drug FTIR

Table-3: FTIR of Darunavir pure drug

Wavenumber(cm-1)	Group	Compound class
3435	O-H stretching	Alcohol
3357	O-H stretching	Alcohol
3062	O-H stretching	Carboxylic acid
2964	N=H stretching	Amine salt
2312	O=C=O stretching	Carbon di oxide
1942	C=C=C	Allene
1705	C=O stretching	Aliphatic ketone
1264	C-O stretching	Aromatic ester

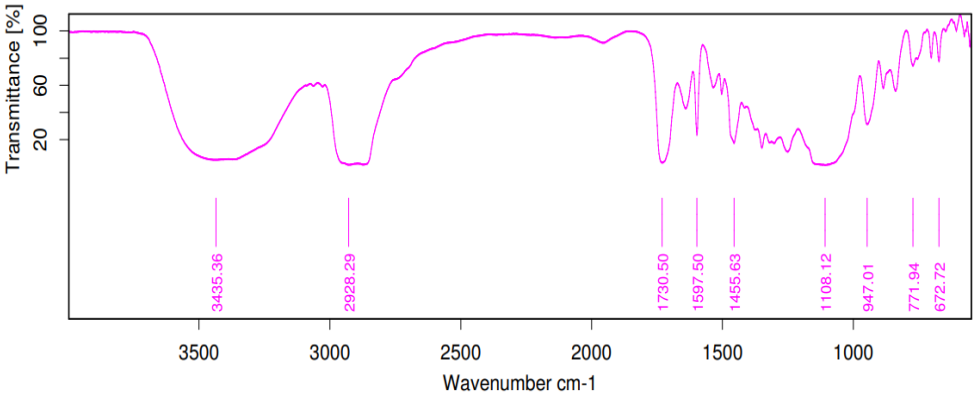

Fig-6: Darunavir SNEDDS Formulation FTIR

Table-4: FTIR of Darunavir SNEDDS formulation

Wavenumber(cm-1)	Group	Compound class
3435	O-H stretching	alcohol
2928	C-H stretching	Alkane
1730	C-O stretching	Alpha, beta unsaturated compound
1597	N-O stretching	Nitro compound
1458	C-H bending	Methyl group

SOLUBILITY STUDIES

To provide highest drug solubilization and avoid drug precipitation in gut lumen, the excipients utilised in the SEDDS should demonstrate maximum solubility for the drug. In the graph 1, 2, and 3, it is shown how well Darunavir dissolves in different lipid carriers, surfactants, and cosurfactants. Darunavir's maximum solubility in oils was discovered to be in Caproyl 90. In surfactants, Labrasol had the highest solubility, while in co-surfactants, Transcutol had the highest solubility.

Table-5: Solubility of Darunavir in various oils

Oils	Concentration (mg/ml)
Captex	30±0.34
Capmul MCM C8	230±0.57
Capmul MCM NF	270±0.73
Captex 355 EP/NF	30±0.38
Capryol 90	314±0.64
Masine	30±0.26
Labrafil	50±0.47
Labrafac Lipophile WL1349	80±0.61
Labrafac PG	20±0.18

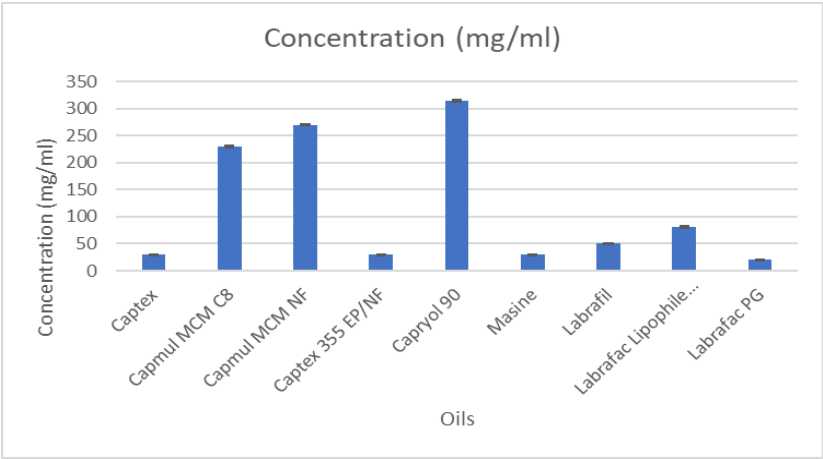

Fig-6: Solubility of Darunavir in various oils

Table-6: Solubility of Darunavir in various surfactants

Surfactants	Concentration (mg/ml)
Tween 80	150±0.23
Kolliphor RH 40	50±0.42
Cremphor EL	100±0.28
Labrasol	230±0.59

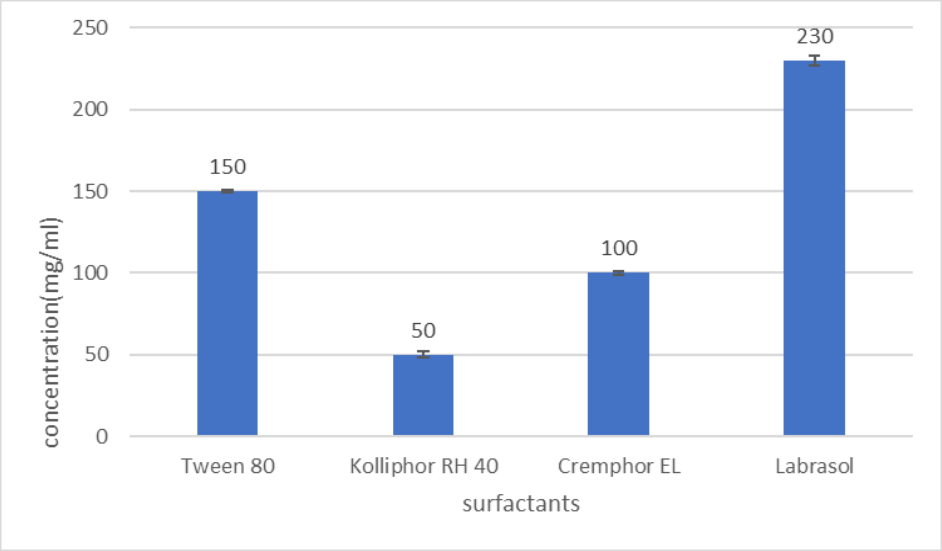

Fig-7: Solubility of Darunavir in various surfactants

Table-7: Solubility of Darunavir in various co-surfactants.

Co-surfactants	Concentration (mg/ml)
Lauroglycol FCC	60±0.32
Lauroglycol 90	10±0.18
PEG 400	160±0.69
Simusol	70±0.37
Transcutol	314±0.94
Gelusire-44	120±0.44

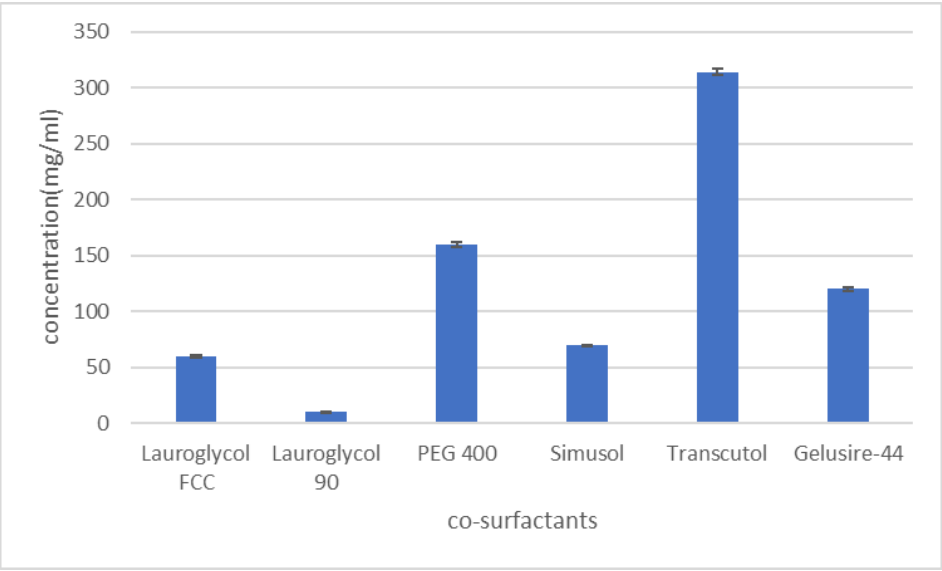

Fig-8: Solubility of Darunavir in various Co-Surfactant

Table-8: Aqueous titration of Capryol 90, Labrasol, Transcutol

Oil:Smix	Oil	Smix	Water	Total	%Oil	% Smix	%Water	Remarks
1:9	50	450	380	880	5.68	51.13	43.18	Stable
2:8	100	400	369	869	11.50	46.29	42.46	Stable
3:7	150	350	256	756	19.84	46.29	33.86	Unstable
4:6	200	300	350	850	23.52	35.29	41.17	Unstable
5:5	250	250	452	952	26.26	26.26	47.47	Unstable
6:4	300	200	379	879	34.12	22.75	43.11	Unstable
7:3	350	150	228	728	48.07	20.57	31.31	Unstable
8:2	400	100	252	752	53.19	13.29	33.54	Unstable
9:1	450	50	289	789	57.03	6.33	36.62	Unstable

Fig-9: Selected Caproyl 90 and Smix ratios of C90L3T1

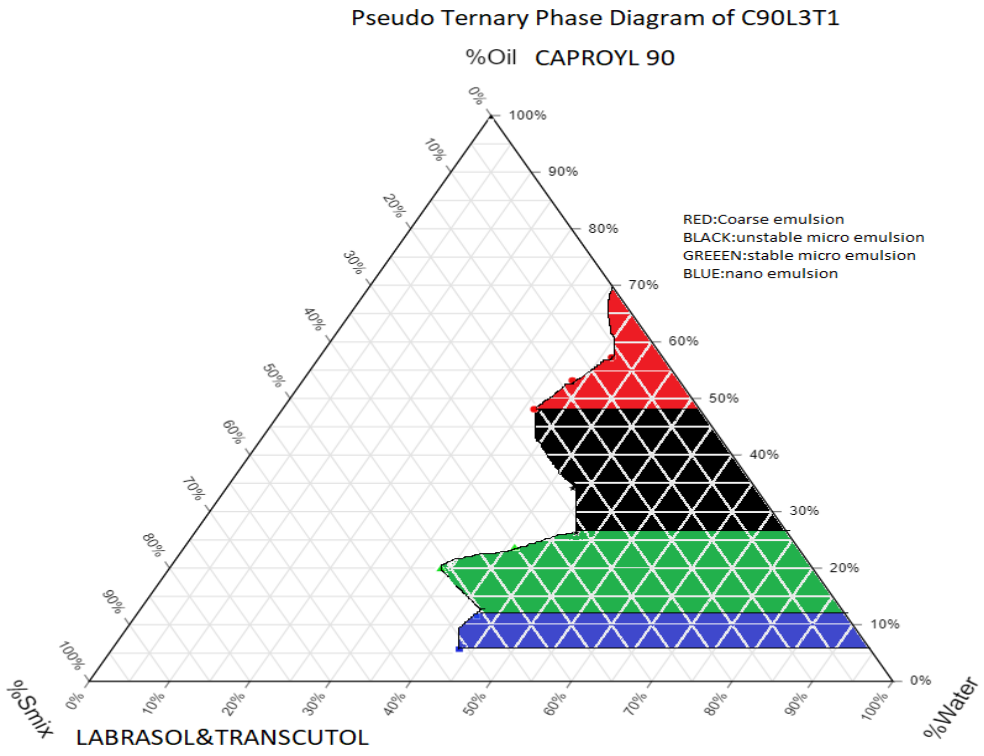

Fig-10: Pseudo Ternary Phase diagram of C90L3T1 formulation

Table-9: Aqueous titration of Capryol 90, Labrasol, Transcutol

Oil:Smix	Oil	Smix	Water	Total	%Oil	% Smix	% Water	Remarks
1:9	50	450	680	1180	4.23	38.13	57.62	Stable
2:8	100	400	650	1150	8.69	34.18	56.52	Stable
3:7	150	350	511	1011	14.83	34.61	50.54	Unstable
4:6	200	300	524	1024	19.53	29.29	51.17	Unstable
5:5	250	250	258	758	32.98	32.98	34.03	Unstable
6:4	300	200	257	757	39.63	26.42	33.94	Unstable
7:3	350	150	256	740	47.29	20.27	34.59	Unstable
8:2	400	100	282	782	51.15	12.78	36.06	Unstable
9:1	450	50	311	811	55.48	6.16	38.34	Unstable

Fig-11: Selected Caproyl 90 and Smix ratios of C90L3T1

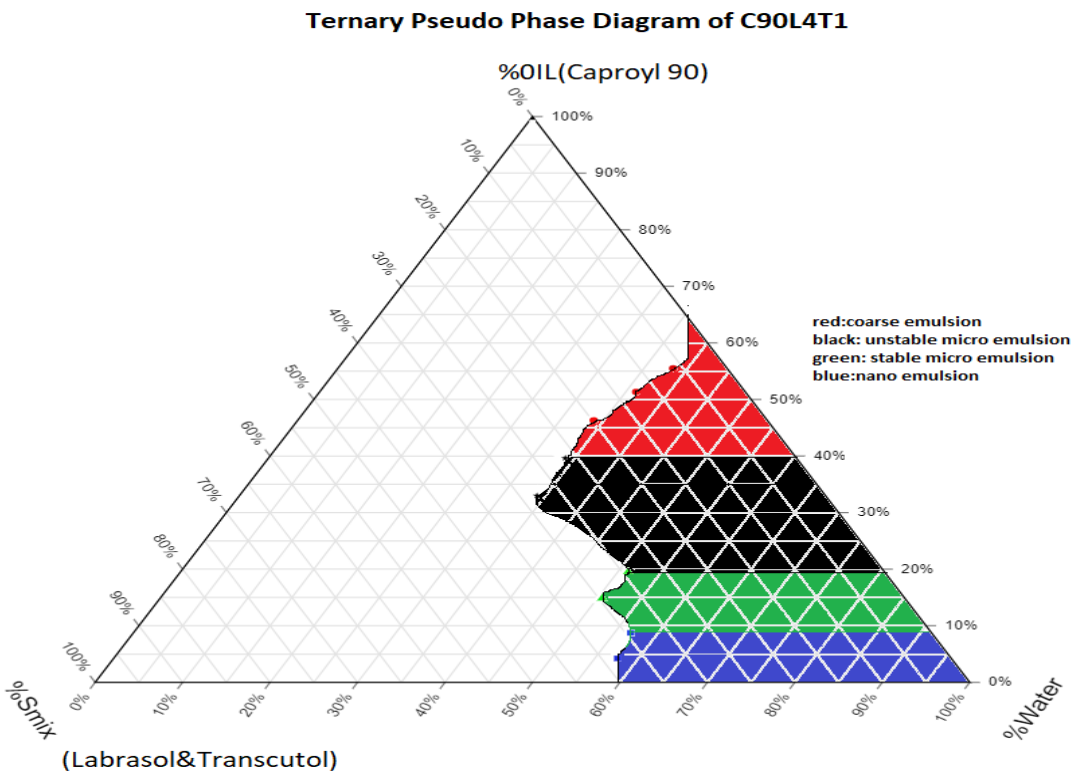

Fig-12: Pseudo Ternary Phase diagram of C90L3T1 formulation

Zeta Potential/PDI/Globule Size:

Results

			Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	77.97	Peak 1:	35.08	61.0	8.354
PdI:	0.243	Peak 2:	157.6	39.0	39.11
Intercept:	0.895	Peak 3:	0.000	0.0	0.000

Result quality : Refer to quality report

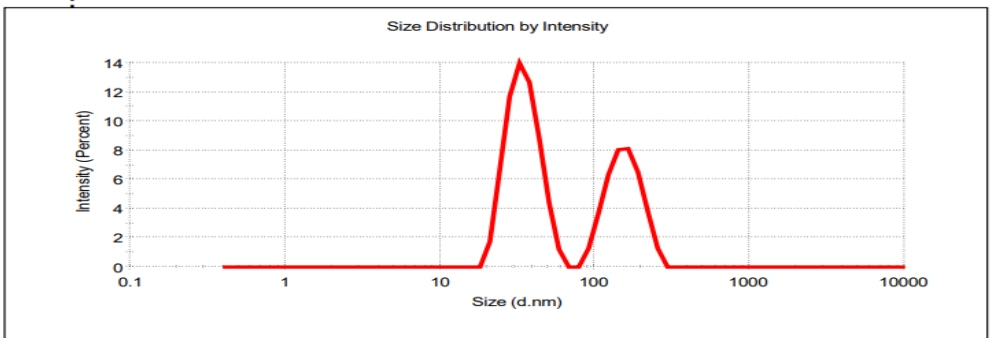

Fig-13: Globule size of C90L3T1

Results

			Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	60.39	Peak 1:	38.34	63.3	12.60
PdI:	0.366	Peak 2:	235.9	35.6	140.2
Intercept:	0.895	Peak 3:	4830	1.2	712.3

Result quality : Refer to quality report

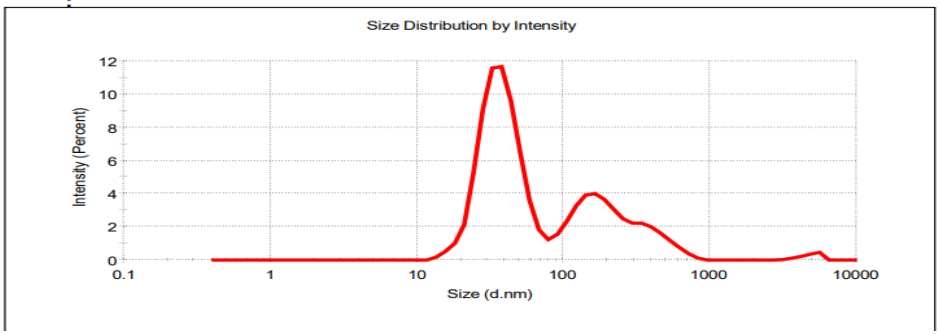

Fig-14: Globule size of C90L4T1

Results

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-30.0	Peak 1:	-30.0	100.0	3.59
Zeta Deviation (mV):	3.32	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.0585	Peak 3:	0.00	0.0	0.00

Result quality : Good

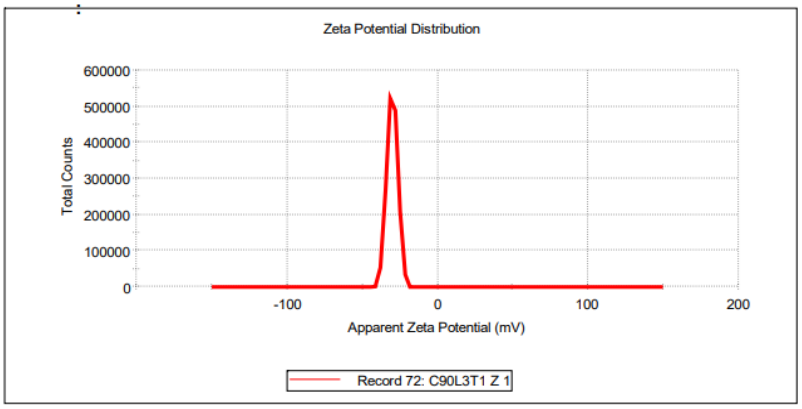

Fig-15: Zeta Potential of C90L3T1

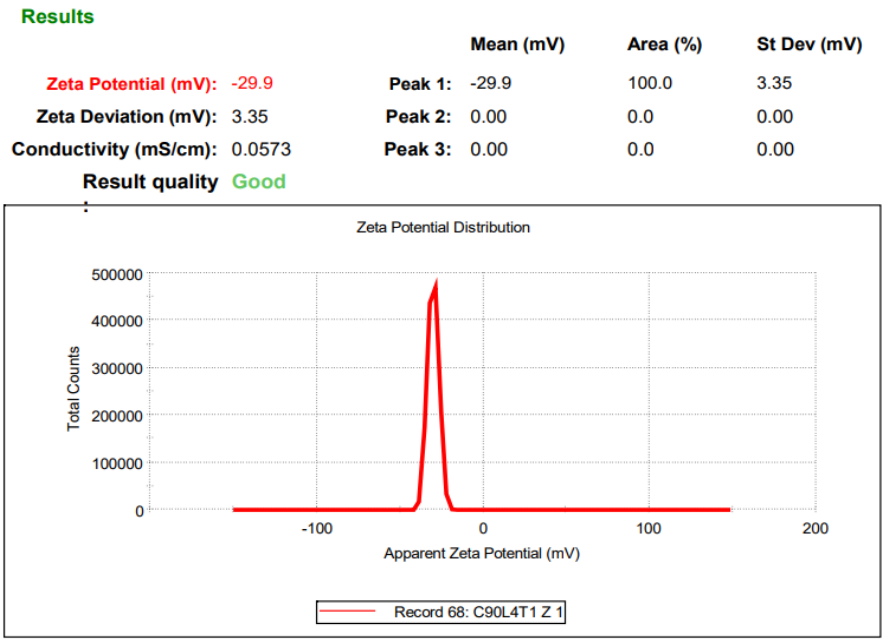

Fig-16: Zeta Potential of C90L4T1

Observation: From the above C90L3T1 & C90L4T1 formulation graphs, C90L3T1 shows good globule size and zeta potential, both formulations (C90L3T1 & C90L4T1) are in nano range. Hence SNEDDS are formed.

Composition of SNEDDS formulations:

Table-10: Composition of Darunavir SNEDDS formulations

S. No	Formulation	Observation	Result
1.	C90L3T1	No phase separation was observed after 24hrs	Stable
2.	C90L4T1	No phase separation was observed after 24hrs	Stable

Dispersibility Test: Visual observation showed that optimized SEDDS formulation (C90L3T1& C90L4T1) were found to be **Grade B & C.** The rapid self-emulsification of the investigated systems can be attributed to their low oil content.

Table-11: Dispersibility test results

SNO	FORMULATION	OBSERVATION	GRADE
1.	C90L3T1 (F1)	Rapidly forming slightly less clear emulsion with bluish appearance	B
2.	C90L4T1 (F2)	BRIGHT MILKY EMULSION	C

Self-Emulsifying efficiency test visual assessment test: All the formulations have shown self-emulsification within one minute and results were good.

Table-12: Self emulsification test results

S .NO	FORMUALTION	SELF EMULSIFICATION (sec)	result
1.	C90L3T1 (F1)	27	Good
2.	C90L4T1 (F2)	31	Good

PH Determination Test:
The formulation of Darunavir SNEDDS (C90L3T1) has shown pH 6.84.

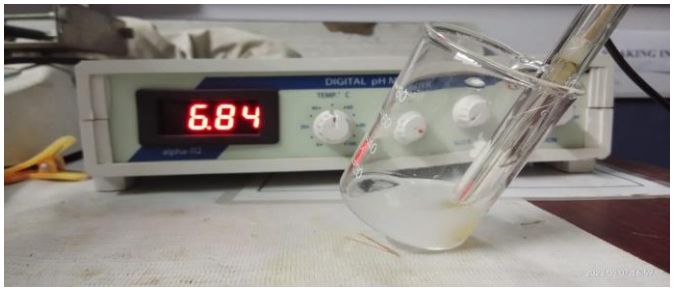

Fig-17: pH determination results

PHASE SEPARATION TEST: Phase separation or precipitation was not seen in any of the formulation of Darunavir and they are stable after 24hrs observation.

Table-13: Phase separation results

S. No	Formulation	Observation	Result
1.	C90L3T1	No phase separation was observed after 24hrs	Stable
2.	C90L4T1	No phase separation was observed after 24hrs	Stable

THERMODYNAMIC STABILITIY STUDIES:
Observation: No phase separation or precipitation observed for formulations C90L3T1 (1:9) & C90L4T1 (1:9) and it indicates stable formulations under effect of temperature.

Table-14: Freeze thaw, Heating -Cooling cycle & Centrifugation results

Formulation	Freeze thaw cycle (2 cycles NLT 48hrs)	(Heating & Cooling Cycle)	Centrifugation
C90L3T1 (1:9)	Passed	Passed	Passed
C90L4T1 (1:9)	Passed	Passed	Passed

Characterization of Solid SNEDDS:

Table-15: Micromeritic studies of Darunavir S-SNEDDS

Batch No	Angle of Repose^{o}	Bulk Density(g/ml)	Tapped Density(g/ml)	Hausner's Ratio (g/ml)
C90L3T1-CAP 1	24.93±0.05	0.631±0.03	0.671±0.04	1.12±0.03
C90L3T1-CAP 2	25.78±0.05	0.579±0.05	0.589±0.03	1.14±0.05
C90L3T1-CAP 3	26.91±0.05	0.611±0.03	0.607±0.05	1.15±0.03

Remarks: From the above micrometric studies, flow properties Solid SNEDDS are good. Justified by the standard ratios of Angle of repose and Hausner's ratio.

In-Vitro Dr ug Release Kinetics: For liquid SNEDDS formulations.

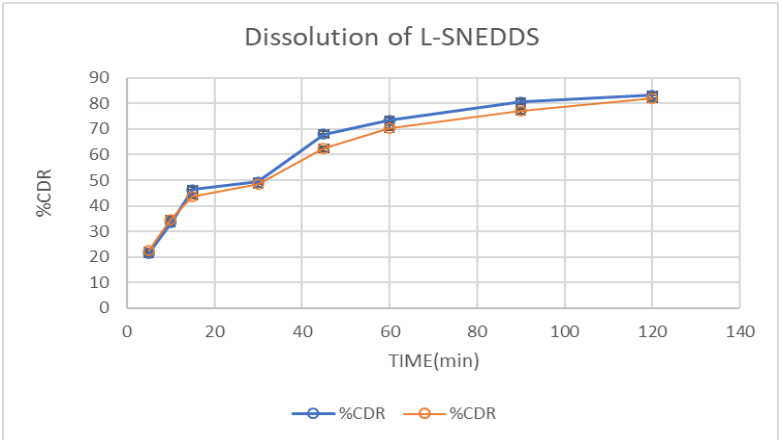

Fig-18: Dissolution of Liquid Darunavir SNEDDS

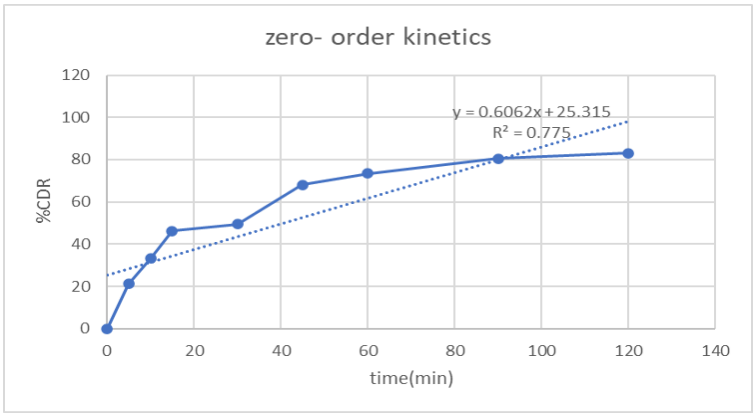

Fig-19: Zero order kinetics of liquid SNEDDS

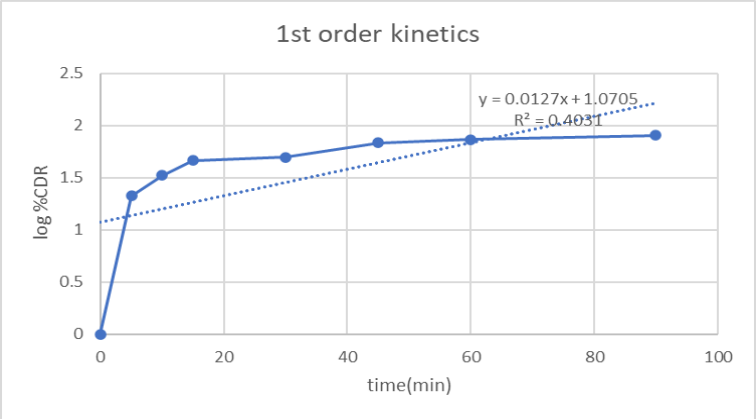

Fig-20: 1st order kinetics of Liquid Darunavir SNEDDS

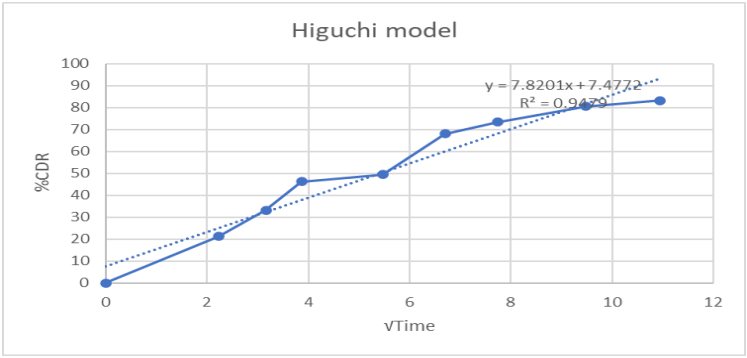

Fig-21: Higuchi model of liquid Darunavir SNEDDS

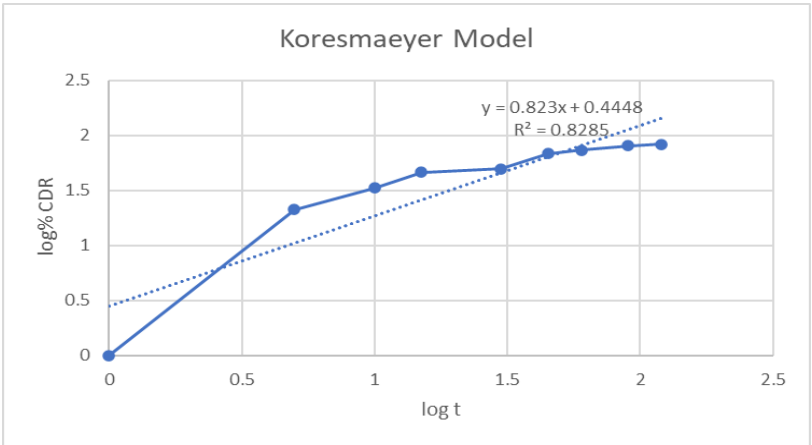

Fig-22: Korsmeyer model of liquid SNEDDS

Observation: From the above Graphical representations, it is clear that Liquid SNEDS formulations does not follow any drug release kinetics

For Darunavir Solid SNEDDS:

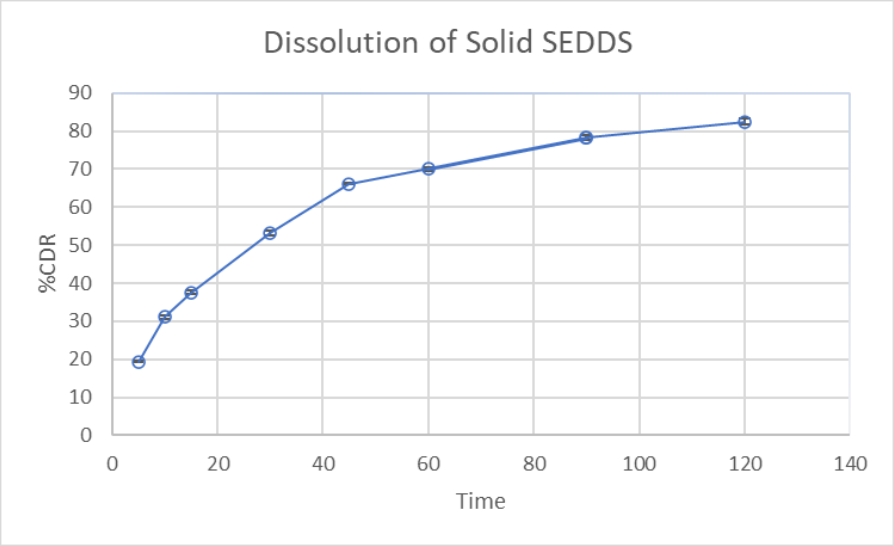

Fig-23: Dissolution of Darunavir S-SNEDDS

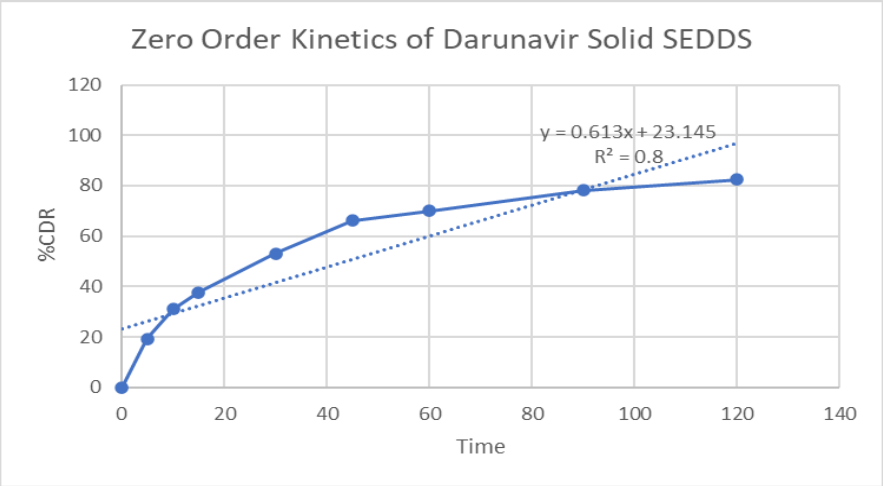

Fig-24: Zero order kinetics of Darunavir S-SNEDDS

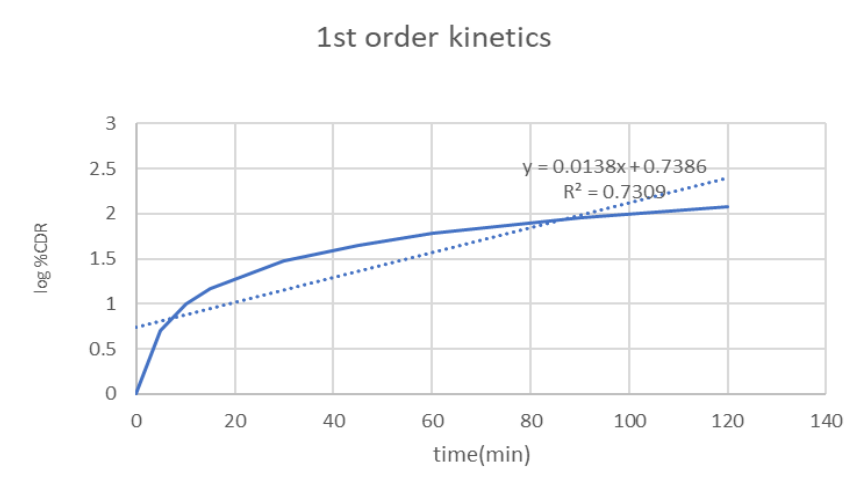

Fig-25: 1st order kinetics of Darunavir S-SNEDDS

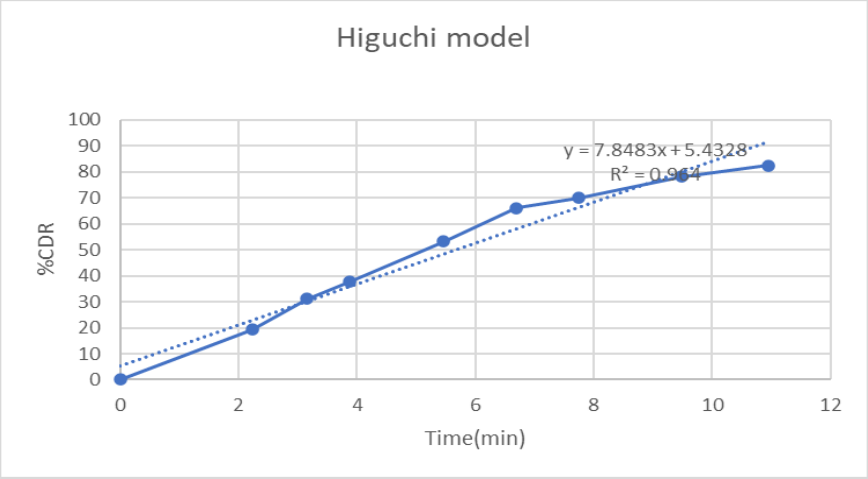

Fig-26: Higuchi kinetics of Darunavir S-SNEDDS

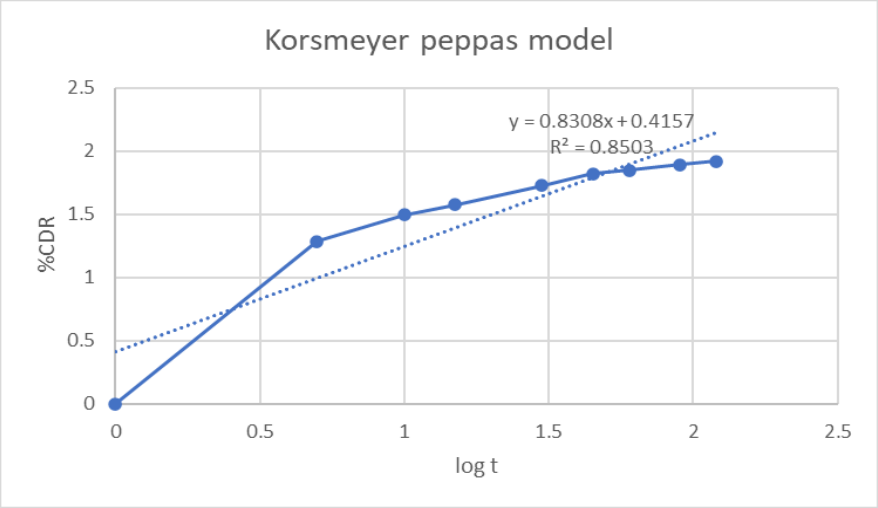

Fig-27: Korsmeyer model of Darunavir SNEDDS

Observation: From the above graphical representations, it is clear that Solid SNEDDS does not follow any drug release kinetics.

4. CONCLUSION

SEDDS are a feasible approach for lipophilic drug formulation and improving the bioavailability of drugs with low aqueous solubility. The present investigation established a successful and straightforward approach for generating Self nano emulsifying Darunavir, the generated SNEDDS showed noticeable increase in drug release activity. This promising technology has the potential to produce stable dosage forms that can be scaled up. More drug products appear to be developed as SEDDS in the near future, and these are the significant areas for future study into S-SNEDDS.

REFERENCE

1. Van Gyseghem, E., Baert, L., Van Remoortere, P., van't Klooster, G., Rouan, M. C., Voorspoels, J., ... & Van den Mooter, G. (2010). Co-administration of darunavir and a new pharmacokinetic booster: Formulation strategies and evaluation in dogs. *European journal of pharmaceutical sciences*, *41*(2), 193-200.
2. Kumar, A., Sharma, S., & Kamble, R. (2010). Self emulsifying drug delivery system (SEDDS): Future aspects. *Int J Pharm Pharm Sci*, *2*(4), 7-13.
3. Nasr, A., Gardouh, A., & Ghorab, M. (2016). Novel solid self-nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of olmesartan medoxomil: design, formulation, pharmacokinetic and bioavailability evaluation. *Pharmaceutics*, *8*(3), 20.
4. Saritha, D., Bose, P., & Nagaraju, R. (2014). Formulation and evaluation of self emulsifying drug delivery system (SEDDS) of Ibuprofen. *Int J Pharm Sci Res*, *5*(9), 3511-3519.
5. Chintalapudi, R., Murthy, T. E. G. K., Lakshmi, K. R., & Manohar, G. G. (2015). Formulation, optimization, and evaluation of self-emulsifying drug delivery systems of nevirapine. *International journal of pharmaceutical investigation*, *5*(4), 205.
6. Saggar, S., Upadayay, A., & Goswami, M. (2019). Formulation and evaluation of solid self-emulsifying drug delivery system of bambuterol

hydrochloride. *Indian Journal of Pharmaceutical Sciences*, *81*(4), 661-672.

7. CR, K., Kumbhar, S. A., & Patil, A. (2013). Formulation and Evaluation of Self-emulsifying Drug Delivery System of Carbamazepine. *Ind J Pharm Edu Res*, *47*(2), 172-177.
8. Karim, F. T., Kalam, A., Anwar, R., Miah, M. M., Rahman, M. S., & Islam, S. A. (2015). Preparation and evaluation of SEDDS of simvastatin by in vivo, in vitro and ex vivo technique. *Drug Development and Industrial Pharmacy*, *41*(8), 1338-1342. DOI:10.3109/03639045.2014.950271.
9. Shailendra, C., & Chauhan, L. S. (2021). Formulation and Evaluation of Self-Emulsifying Drug Delivery System of Poorly Soluble Drug using Varying Chain Surfactants, *International Journal of Pharmaceutical Sciences and Drug Research*, 130403.
10. Renuka, J. (2018). Formulation and Evaluation of Furosemide Solid Self-emulsifying Drug Delivery System. *Asian Journal of Pharmaceutics (AJP)*, *12*(02).
11. Rama, A., Kannan, S., & Naha, A. (2021). Formulation and Evaluation of Self Emulsifying Drug Delivery System (SEDDS) of a Novel Pharmacokinetic Enhancer Cobicistat. *Latin American Journal of Pharmacy*, *40*(11), 2682-2692.
12. Maheshwari Mittal, M., Prajapati Paresh, A. (2016). Formulation and Evaluation of Self-emulsifying Drug Delivery System containing Lipid Lowering Drugs, *Journal of Pharmaceutical Sciences and Bioscientific Research*, 6(2), 220-227.
13. Singh, B., & Sharma, M. (2022). 0Formulation and Evaluation of Self-Emulsifying Drug Delivery Systems for Candesartan Cilexetil. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *15*(2), 5844-5854.
14. Saifee, M., Zarekar, S., Rao, V. U., Zaheer, Z., Soni, R., & Burande, S. (2013). Formulation and in vitro evaluation of solid-self-emulsifying drug delivery system (SEDDS) of glibenclamide. *Am J Adv Drug Delivery*, *1*(3), 323-340.
15. Gupta, A. K, Mishra, D. K., & Mahajan, S. C. (2011). Preparation and In-Vitro Evaluation of antihypertensive Drug Valsartan, *International Journal of Pharmacy & Life Sciences*, 2(3), 0976-7126.
16. Bhandari, V., & Avachat, A. (2015). Formulation and characterization of self emulsifing pellets of carvedilol. *Brazilian Journal of Pharmaceutical Sciences*, *51(3)*, 663-671.
17. Karunakara Reddy, T., Sudhakar, Y., & Devanna, N. Development and Evaluation of Atazanavir Solid SEDDS: In vitro-in vivo Evaluation Studies. *International Journal of Pharmaceutical Sciences Review and Research*, 69, 380-387.
18. Jianxian, C., Saleem, K., Ijaz, M., Ur-Rehman, M., Murtaza, G., & Asim, M. H. (2020). Development and in vitro evaluation of gastro-protective aceclofenac-loaded self-emulsifying drug delivery system. *International journal of nanomedicine*, *15*, 5217.
19. Priyanka, S., Vidya, N., & Priyanka, M. Solid self-emulsifying drug delivery system: Formulation & evaluation of solid Self-emulsifying drug delivery BCS class II drug Mirtazipin.
20. Pehlivanov, I. (2020). Self-Emulsifying Drug Delivery Systems (SEDDS): Excipient Selection, Formula-Tion and Characterization. *Journal of IMAB–Annual Proceeding Scientific Papers*, *26*(3), 3226-3233.
21. Khoo, S. M., Humberstone, A. J., Porter, C. J., Edwards, G. A., & Charman, W. N. (1998). Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. *International journal of pharmaceutics*, *167*(1-2), 155-164.
22. Pouton, C. W. (2006). Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *European journal of pharmaceutical sciences*, *29*(3-4), 278-287.
23. Gursoy, R. N., & Benita, S. (2004). Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomedicine & pharmacotherapy*, *58*(3), 173-182.
24. Kumar, A., Sharma, S., & Kamble, R. (2010). Self emulsifying drug delivery system (SEDDS): Future aspects. *Int J Pharm Pharm Sci*, *2*(4), 7-13.
25. Garrigue, J. S., Lambert, G., & Benita, S. (2006). Self-emulsifying oral lipidbased formulations for improved delivery of lipophilic drugs. *Microencapsulation: Methods and Industrial Applications*, *2*, 429-480.
26. Kommuru, T., Gurley, B., Khan, M. A., & Reddy, I. K. (2001). Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. *International journal of pharmaceutics*, *212*(2), 233-246.