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Development of Darunavir Loaded Solid Self Micro Emulsifying Drug Delivery System for Enhanced Solubility and Dissolution using Box-Behnken Designs

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Abstract
The purpose of the current work was to develop S-SMEDDS of Darunavir (DRV), which falls under BCS Class II, by using Box-Behnken designs for improved solubility and dissolution. In the solubility investigation of DRV, oleic acid, Tween 80, and Transcutol P were selected as oils, surfactants, and co-surfactants, respectively, and the impact of their concentrations on globule size, zeta potential, and liquid SMEDDS was investigated using a box-Behnken design. Liquid SMEDDS were developed and evaluated in twelve separate batches (DRVL1 to DRVL12). As a solid carrier, Neusilin US2 is used in an adsorption method; four successful batches (DRVS1 to DRVS4) of liquid SMEDDS were then transformed into solid form. In-vitro drug release study DRVS4 of batch S-SMEDDS released 85.792 percent of DRV in 60 min, as compared to 22.532 percent of plain DRV. The study's findings suggest that a potential method for improving the solubility, dissolution, and simultaneous bioavailability of DRV is S-SMEDDS.

1. Introduction

Darunavir (DRV), a protease inhibitor (PI), is very efficient against wild-type HIV.[1] In contrast to early-generation PIs, DRV exhibits low cytotoxicity, great potency against HIV isolates that have been resistant to multiple drugs, and a strong genetic barrier to resistance. [2, 3]

DRV falls under Class II of the biopharmaceutical classification system. DRV has a very poor solubility in water and is a lipophilic drug. This poor solubility may cause poor dissolution and unpredicted bioavailability. Enzymes of the CYP family, particularly CYP3A, significantly metabolize it, during hepatic metabolism. It has low permeability because, for an ABC transporter such as P-gp, it serves as a substrate, which leads to increased enzymatic degradation and decreased bioavailability. As a result, relatively high doses are needed to produce the desired therapeutic effect. [4-7]

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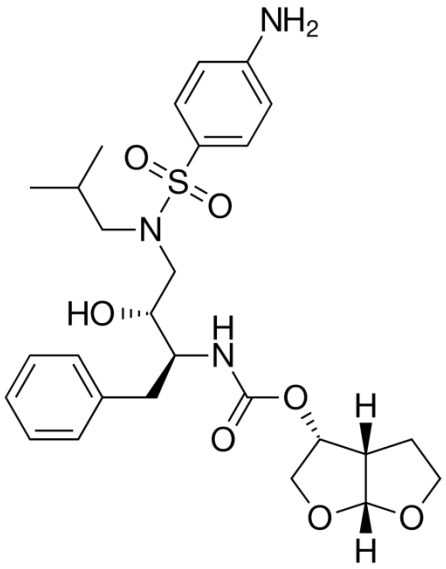

Figure 1: Chemical structure of DRV

The solubility of drugs that are poorly water-soluble can be improved in several ways; lipid-based isotropic systems have recently undergone substantial research for delivering BCS class II drugs orally. One of these, the self-microemulsifying drug delivery system (SMEDDS), has proven to be a successful delivery method. "SMEDDS is a thermodynamically stable isotropic mixture of oil, surfactant, co-surfactant, and drug that forms a spontaneous o/w microemulsion when introduced into an aqueous medium under gentle agitation."[8] The drug stays in solution form, which eliminates the need for dissolving and increases bioavailability due to the reduced free energy need and increased surface area associated with micro globules.[9] SMEDDS are commonly fabricated in liquid form or enclosed in capsules (soft gelatine), each of which has drawbacks, particularly during manufacturing operations, which raises the cost of production. SMEDDS could be difficult to utilize and have compatibility issues with the usual soft gelatine. The problems of liquid formulations mentioned above may be overcome by incorporating a liquid SMEDDS to solid dosage form, which would combine the benefits of SMEDDS and solid dosage forms. [10, 11] The aim of this investigation was to solubilize and dissolve the poorly water-soluble antiretroviral drug DRV using solid SMEDDS.

2. Materials And Methods

Materials

From Cipla Ltd. in Mumbai, India, we received a free sample of darunavir (DRV). The provider of oleic acid Tween 80 was Loba Chemie Pvt. Ltd., Mumbai. The Mumbai-based Gattefosse India Pvt. Ltd. donated Transcutol P. A free sample of neusilin was received from Gangwal Chemicals Pvt. Ltd., Mumbai. All additional compounds were of the analytical variety.

Methods

Solubility study of DRV

In this study, small vials holding 2.00 mL of various oils, surfactants, and co-surfactants were taken individually, and excess drug was added to each vial. The shake flask technique was used to shake the vials for 72 hours at 25 °C. By centrifuging oils, surfactants, and co-surfactants at 10,000 rpm for 10 minutes, undissolved DRV was separated. Then the sample was taken. After diluting the sample with methanol, the sample's solubility was assessed using UV spectroscopy (Shimadzu 1800) at 266 nm. [12]

Construction of pseudo ternary phase diagram

Based on solubility tests and screening of oil, surfactants and co-surfactants, Transcutol P, Tween 80, and oleic acid were selected as the co-

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surfactant, surfactant, and oil respectively. By constructing a pseudo ternary phase diagram with various surfactant ratios, the micro emulsion area was identified. Co-surfactant i. e., S/Co (Km value of 1:1, 2:1, 3:1, 1:2 and 1:3), oil and water, be required for the formation of stable SMEDDS. The following ratios of Smix and oil were blended in a pre-weighed test container: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. To determine the end point, following equilibrium, add gradually double distilled water to the resultant mixtures till the first indication of turbidity. The water addition was then continued if the system became clear. Once perfect equilibrium had been achieved, the mixtures were visually inspected for flow and distinct phases. Using CHEMIX School 10.0, the pseudo ternary phase diagram was created. [13, 14]

Formulation of Liquid SMEDDS of DRV using Box–Behnken designs

From the created phase diagrams, the Km value required to create a high microemulsion area was chosen for additional research. This microemulsion region's three points were chosen, and they were utilized to conclude the composition of the oil, surfactant, and co-surfactant. To check effect of concentration of Oleic acid, Tween 80 and Transcutol Pon Particle size, Zeta potential and % Transmittance Box–Behnken designs was used. Factorial design was performed with Design Expert software version 13. By using the following process, 12 batches of liquid SMEDDS (DRVL1 to DRVL13) of DRV were prepared. By gently stirring and vortex mixing at 37 °C, DRV, oleic acid, Tween 80, and Transcutol P were combined until DRV was fully dissolved. The combination was then placed in a glass vial, sealed, and kept at room temp till needed. [15, 16] Table 1 displays the SMEDDS liquid's chemical composition.

Table 1: Composition of liquid SMEDDS of DRV

		Factor 1	**Factor 2**	**Factor 3**
Batches	**Run**	**A:Conc. of Oleic acid**	**B:Conc. of Tween 80**	**C:Conc. of Transcutol P**
		%	**%**	**%**
DRVL1	1	60	26.25	10
DRVL2	2	60	26.25	7.5
DRVL3	3	50	22.5	10
DRVL4	4	40	26.25	10
DRVL5	5	60	30	8.75
DRVL6	6	40	30	8.75
DRVL7	7	40	26.25	7.5
DRVL8	8	50	30	7.5
DRVL9	9	60	22.5	8.75
DRVL10	10	50	22.5	7.5
DRVL11	11	40	22.5	8.75
DRVL12	12	50	30	10

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Evaluation of Liquid SMEDDS of DRV

Thermodynamic stability studies

Heating cooling cycle

In the refrigerator, there were six cycles between 4 and 45 degrees Celsius, with storage lasting at least 48 hours at each temperature. A centrifuge test was conducted if SMEDDS demonstrates stability at this temperature. [17, 18]

Centrifugation test

SMEDDS that passed were centrifuged for 30 minutes in a digital centrifuge (Remi Motors Ltd.) at 3500 rpm. If no phase separation occurred, SMEDDS was processed for freeze-thaw cycles. [17, 18]

Freeze thaw cycle

For SMEDDS, three freeze-thaw cycles were carried out between -21°C and +25°C for at least 48 hours at each temperature. [17, 18]

Robustness to dilution

Liquid SMEDDS was diluted 50, 100, and 1000 times with water and buffer pH 1.2 to investigate robustness to dilution. For 12 hours, the diluted SMEDDS was stored to check for any signs of drug precipitation or phase separation. [18]

Assessment of Efficiency of self-emulsification

The efficiency of self-emulsification was assessed using a Veego VDA-8DR USP-type-II dissolving test apparatus. Add 1 ml of liquid SMEDDS, drop by drop, to 0.1 N HCl (200 ml) at 37 °C. A typical stainless steel dissolving paddle was then used to agitate it at 60 revolutions per minute. SMEDDS are assessed visually based on the final emulsion appearance and emulsification rate. By visual inspection, in vitro performance is evaluated using the grading method. [19-21]

% Transmittance

In 100 ml distilled water, add 1 ml liquid SMEDDS and check for turbidity. Shimadzu-1800, Japan, UV-Vis spectrophotometer was used to determine the percentage of transmittance at 650 nm using pure water as a reference. [20, 21]

Zeta potential, PDI, and globule size

Using the Malvern Zetasizer (Nano ZS90), the zeta potential, PDI, and globule size of the liquid SMEDDS were estimated; it investigates changes in light scattering dependent on the particle's Brownian motion. [22, 23]

Viscosity

A Brookfield LVDV II + PRO viscometer and spindle S18 at 20 rpm at room temperature without dilution were used to measure the formulation's (0.5 g) viscosity. [24]

Dye solubilisation test

By dusting eosin (a water-soluble dye) on the microemulsion surface and monitoring the spontaneous dispersion, the oil-in-water nature of SMEDDS was confirmed. [25]

Measurement of a cloud point

Distilled water was used to dilute the SMEDDS liquid by a factor of 1:250, and after that, it was gradually heated in a water bath. Visually examine the appearance of sudden cloudiness and calculate the cloud point as a function of temperature. [26]

Formulation of S-SMEDDS

A 1:1 mixture of liquid SMEDDS containing DRV and Neusilin US2 was used to produce S-SMEDDS of DRV. SMEDDS liquid was quickly added drop by drop over an adsorbent carrier placed in a large porcelain dish. Glass rod was used to homogenize the mixture after each addition to ensure that the formulation was distributed evenly. [27, 28]

Characterization of S-SMEDDS

The micromeritic characteristics of prepared batches of S-SMEDDS, such as angle of repose, bulk density, compressibility index, Hausner ratio, etc., were assessed. [20, 29]

Drug Content

DRV was extracted from S-SMEDDS to estimate the drug content. In 10 mg of S-SMEDDS, they were

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dissolved in enough methanol. The DRV was extracted from the solution using sonication for 10 to 15 minutes, followed by filtering. On a UV-visible spectrophotometer (Shimadzu 1800, Japan), the filtrate's absorbance was measured at 266 nm. [30]

Solubility study of DRV and S-SNEDDS in Water

The saturation solubility study of DRV and the S-SNEDDS formulation of DRV (DRVS1 to DRVS4) were assessed in water at room temperature to check for enhancement of the drug's aqueous solubility. [31]

In-vitro dissolution studies of S-SMEDDS of DRV

Using USP-type-II dissolving test equipment, an in-vitro dissolution study of plain DRV and S-SMEDDS of DRV was conducted. S-SMEDDS (equal to 75 mg of Darunavir) and hard gelatin capsules of size "0" containing plain darunavir were put into separate 900 mL containers of phosphate buffer, which had a pH of 6.8, at a speed of roation 75 rpm, at 37°C.

At regular intervals of 5, 10, 15, 20, 30, and 60 minutes, 5 mL samples were taken and filtered using a 0.45 m filter. The volume was maintained by adding an equal amount of the dissolving media. The sample's drug content was examined with a UV spectrophotometer at 266 nm. [31]

Solid state characterization of DRV loaded S-SMEDDS

FTIR study

To determine whether DRV and Neusilin US2 possibly interact, FTIR tests were conducted. Infrared spectra of plain drugs, physical mixtures of drugs, and carriers were captured in the 4000 to 400 cm-1 wavelength range. The compatibility of the components in the formulations was determined through the spectrum analysis. [32]

Powder X-ray diffraction (PXRD)

The PXRD investigation was performed to validate the physical condition of DRV in its pure state and the changes in crystallinity in S-SMEDDS using an X-ray diffractometer (D8 Advanced, Bruker AXS). Using an X-ray diffractometer, PXRD of plain DRV, Neusilin US2, and selected S-SMEDDS were performed. [33]

Differential scanning calorimetry (DSC)

The physical state of DRV in S-SNEDDS was determined using a differential scanning calorimeter. The DRV, Neusilin US2, and S-SNEDDS thermograms were obtained using a differential scanning calorimeter (TA Instruments SDT-2960, USA). [32, 34]

3. Result and Discussion

Solubility study of DRV

The solubility study's purpose was to locate oils and surfactants with effective DRV solubilizing properties. Figures 2, 3, and 4 show how DRV dissolves in various oils, surfactants, and co-surfactants. According to the findings, DRV is highly soluble in oleic acid, Tween 80, and Transcutol P.

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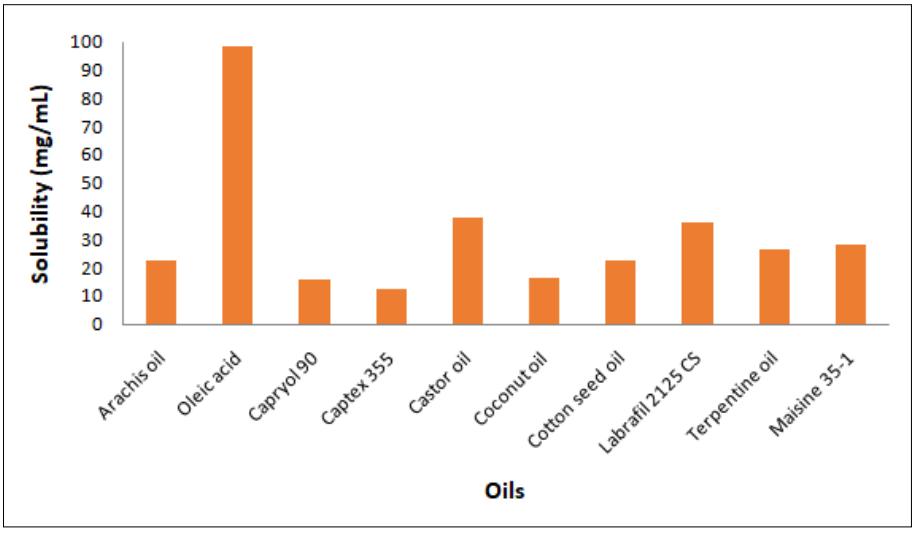

Figure 2: Solubility of DRV in different oils

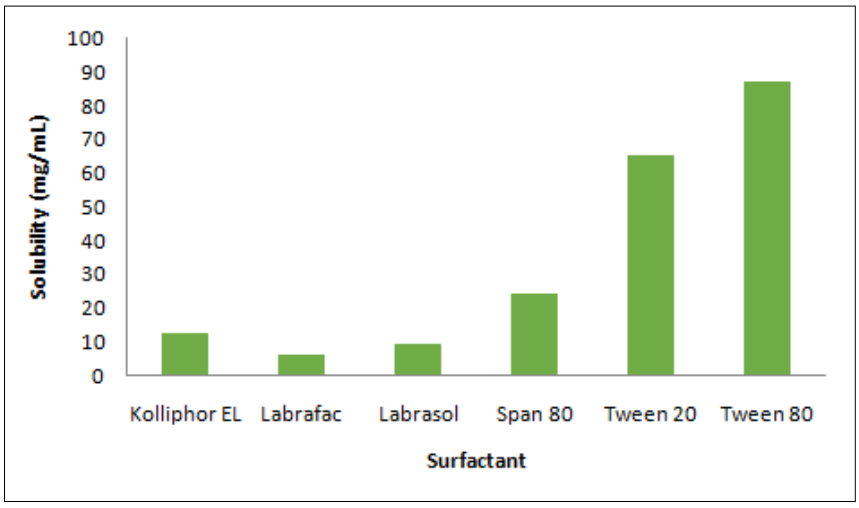

Figure 3: Solubility of DRV in different surfactants

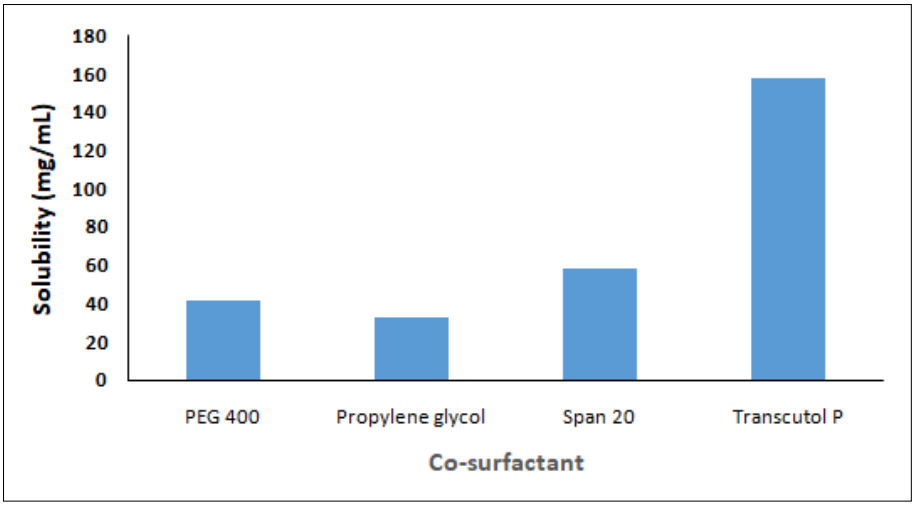

Figure 4: Solubility of DRV in different co-surfactant

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Construction of pseudo ternary phase diagram

Based on findings from studies on solubility, the oil, surfactant, and co-surfactant for the microemulsion formulation were chosen to be oleic acid, Tween 80, and Transcutol P. For the phase diagram analysis of DRV-loaded SMEDDS, nine distinct possible surfactant mixtures in oil at various Km values (Km values 1:1, 2:1, and 3:1) were used. Each phase diagram revealed the o/w microemulsion's boundary layer. A microemulsion zone is shown on the phase diagram in the shaded area. [35] Figure 5 displays pseudo ternary phase diagrams for the corresponding Km values. The microemulsion area increases as surfactant and co-surfactant concentrations increase. The ratio of 3:1 was intended to be the maximum self-micro-emulsifying region. As a result, the ideal ratio of surfactant to co-surfactant for the formulation of DRV-loaded SMEDDS was chosen to be 3:1.

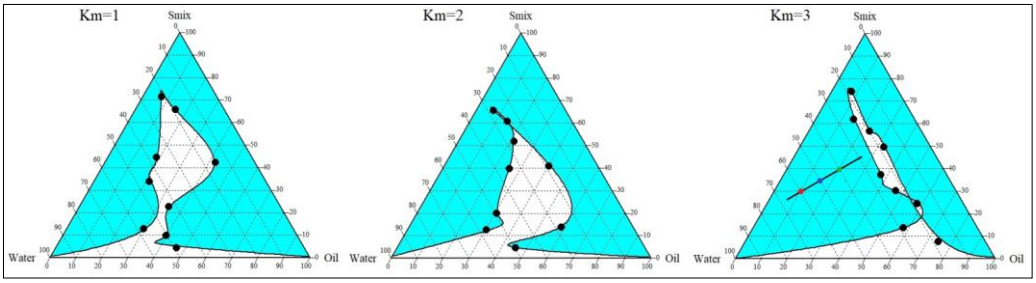

Figure 5: Pseudo ternary phase diagram of Oleic acid, Tween 80, Transcutol P and water at Km=1, 2 and 3

Formulation of DRV loaded Liquid SMEDDS using Box–Behnken designs

Twelve liquid SMEDDS batches with DRV were successfully developed and used for further investigation.

Evaluation of DRV loaded Liquid SMEDDS

Table 2 provides a summary of the findings of studies on thermodynamic stability, robustness to dilution, and self-emulsification efficiency. The heating-cooling cycle test was observed to have passed, and the formulation was then subjected to a centrifugation test. SMEDDS was used for the freeze-thaw stress test because the centrifugation test revealed no phase separation. It was discovered that SMEDDS demonstrated good stability with no phase separation, creaming, or cracking after the freeze-thaw stress test. It was determined from the robustness of the dilution testing data that no evidence of phase separation or drug precipitation existed.

According to the findings of the evaluation of the efficiency of the self-emulsification study, formulations DRVL5, DRVL6, DRVL8, and DRVL12 rapidly formed microemulsion within 1 min that was clear and had a faintly bluish appearance as per grade A, while formulations DRVL1, DRVL2, DRVL4, and DRVL7 rapidly formed an emulsion that was slightly less clear and had a bluish appearance Also, DRVL3, DRVL9, DRVL10, and DRVL11 displayed a bright white emulsion that formed in less than 2 minutes. According to the findings, all liquid SMEDDS of DRV formulations passed the preliminary thermodynamic stability studies and the robustness to dilution test. However, batches DRVL5, DRVL6, DRVL8, and DRVL12 were discovered to be superior than other batches based on the evaluation of the efficiency of self-emulsification test.

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Table 2: Thermodynamic stability studies, robust to dilution and dispersibility tests

Formulation	Observations					Inference
	H/C	Cent.	Friz. Thaw	Robust	Dispers.	
DRVL1	✓	✓	✓	✓	Grade B	Passes
DRVL2	✓	✓	✓	✓	Grade B	Passes
DRVL3	✓	✓	✓	✓	Grade C	Passes
DRVL4	✓	✓	✓	✓	Grade B	Passes
DRVL5	✓	✓	✓	✓	Grade A	Passes
DRVL6	✓	✓	✓	✓	Grade A	Passes
DRVL7	✓	✓	✓	✓	Grade B	Passes
DRVL8	✓	✓	✓	✓	Grade A	Passes
DRVL9	✓	✓	✓	✓	Grade C	Passes
DRVL10	✓	✓	✓	✓	Grade C	Passes
DRVL11	✓	✓	✓	✓	Grade C	Passes
DRVL12	✓	✓	✓	✓	Grade A	Passes

H/C: Heating cooling cycle, Cent.: Centrifugation, Friz. Thaw: Freeze thaw cycle,

Robust.: Robustness to dilution Disperse, Dispers.: Efficiency of self-emulsification

% Transmittance, globule size, zeta potential and viscosity

Table 3 summarizes the results of % transmittance, globule size, zeta potential, and viscosity. All liquid SMEDDS formulations with DRV were found to have a transmittance of between 72.30 and 94.82 percent. This means that produced liquid SMEDDS are clear and have no turbidity. The zeta potential and globule size of all formulations were found to be between -8.0 mV and -75.0 mV and 218.3 nm and 676.5 nm, respectively. The formulations' globule size increased in tandem with the increase in oil concentration. However, the globule size of formulations differs only slightly. All formulations were found to have viscosities that fell between 12.78 to 24.36 cP. The zeta potential and globule size of batches DRVL5, DRVL6, DRVL8, and DRVL12 are showed in respectively Figures 7 and 6.

Table 3: Results of globule size, zeta potential, % transmittance and viscosity

Formulation	Globule size (µm)	Zeta potential (mV)	% Transmittance	Viscosity (cP)
L-DRV 1	290.3	-24.2	87.39	19.76
L-DRV 2	335.2	22.7	84.28	22.39

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L-DRV 3	422.1	-9	81.92	23.58
L-DRV 4	323.9	-13.3	85.58	21.85
L-DRV 5	**243.9**	**-40.6**	**92.63**	**13.92**
L-DRV 6	**250.9**	**-32.5**	**90.74**	**16.74**
L-DRV 7	336.1	-8	84.71	23.72
L-DRV 8	**253.9**	**-30.3**	**89.68**	**17.68**
L-DRV 9	506.1	75	78.82	24.36
L-DRV 10	676.5	60.8	72.30	23.44
L-DRV 11	510.2	60.7	76.33	22.69
L-DRV 12	**218.3**	**-43.5**	**94.82**	**12.78**

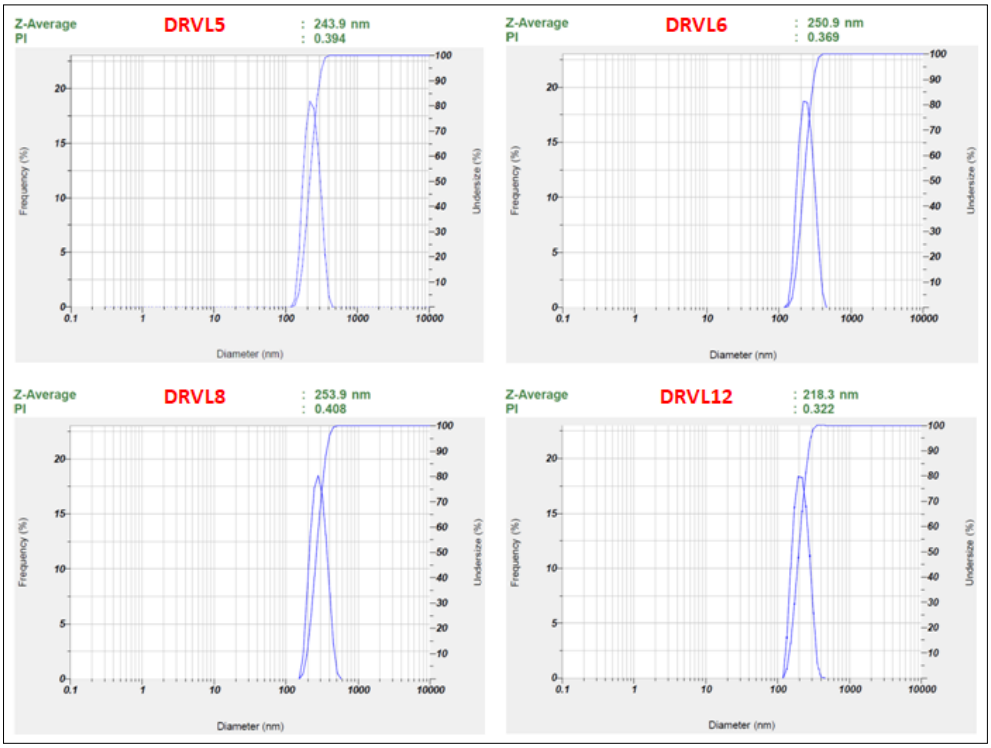

Figure 6: Globule size of Liquid SMEDDS of batch DRVL5, DRVL6, DRVL8 and DRVL12

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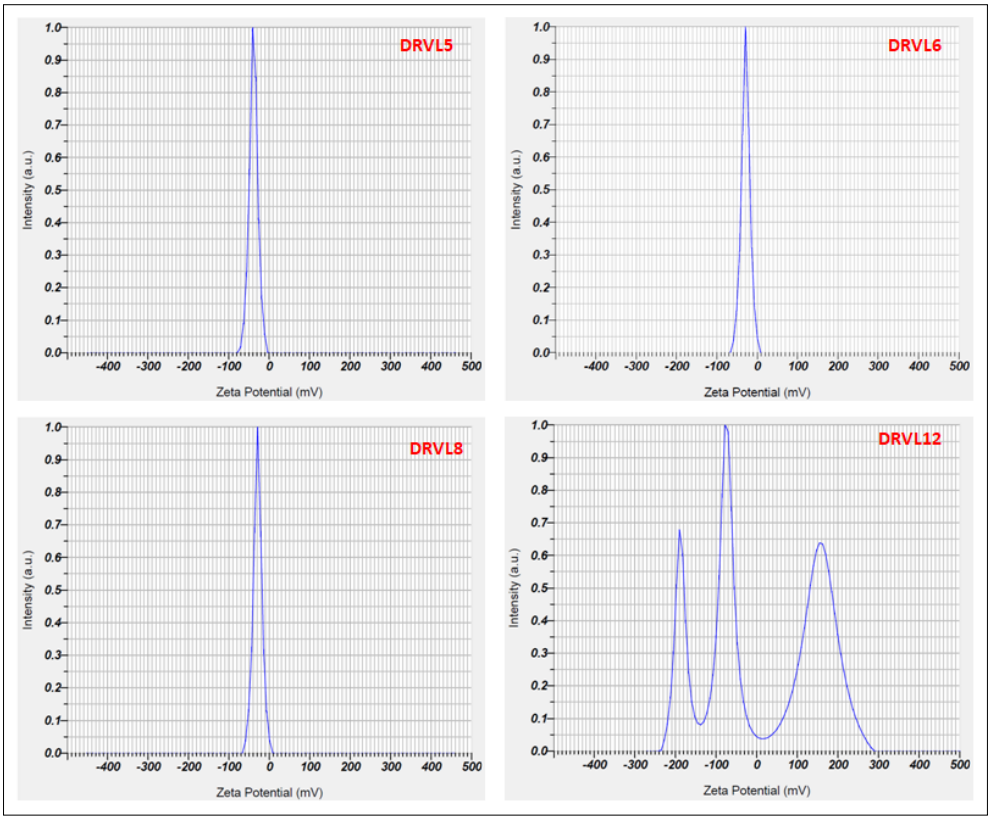

Figure 7: Zeta potential of Liquid SMEDDS of batch DRVL5, DRVL6, DRVL8 and DRVL12

Optimization of DRV Loaded SMEDDS by Box–Behnken designs

Response 1: Particle size

Oleic acid, tween 80, and transcutol p concentrations have an impact on the globule size of liquid SMEDDS, as shown by three-dimensional response surface plots and counter plots. The complete mathematical formula is as follows:

Particle size = +363.95 -5.70A -143.49B -43.39C

The equation in terms of coded factors allows for the prediction of the responses to particular levels of each factor. The high values of the factors are by default recorded as +1 and the low levels as -1. The coded equation can be used to determine the relevance of the elements by comparing the factor coefficients. The model's F-value of 15.10 suggests that it may be significant. Only 0.12% of the time may noise be the cause of an F-value this high. When the P-value is less 0.0500, model terms are deemed significant. The adjusted R^2 of 0.7937 and the expected R^2 of 0.6624 are reasonably in agreement, therefore there is a variance of less than 0.2. According to the study, globule size increases as oil concentrations increase and decreases when surfactant and co-surfactant concentration increases. Figure 8 displays a Counter and Response surface plot illustrating the influence of factors on globule size.

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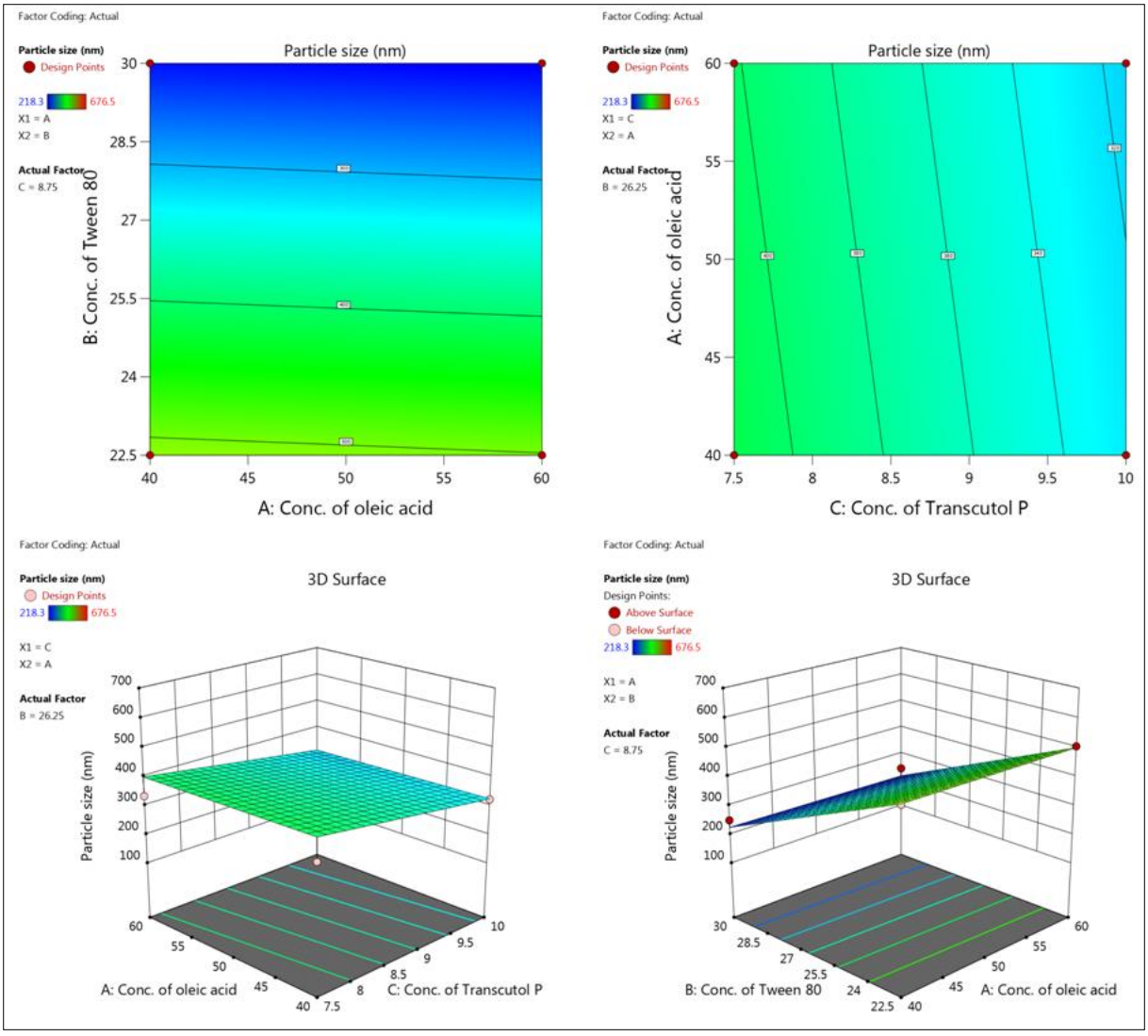

Figure 8: Counter and Response surface plot showing effect of variables on globule size

Response 2: Zeta potential

The stability of colloidal particles is shown by the zeta potential. By measuring the droplets' electrophoretic mobility, it is determined. High zeta potentials (40 mV) result in repulsive electrostatic forces that decrease the probability of particle aggregation. [36] The higher concentration of oleic acid, which contains esters and fatty acids, was the cause of the negative charge on SMEDDS in some liquid SMEDDS formulations. SMEDDS stability was proven by the formulations' negative zeta potential values. The Model F-value of 12.21 suggests that the model is significant. An F-value this large may result from noise only 0.24% of the time. The discrepancy is less than 0.2 because the Adjusted R^2 of 0.7535 and the Predicted R^2 of 0.5967 are reasonably in agreement. Zeta potential = +1.48 +3.25 A -41.80B -16.90C.

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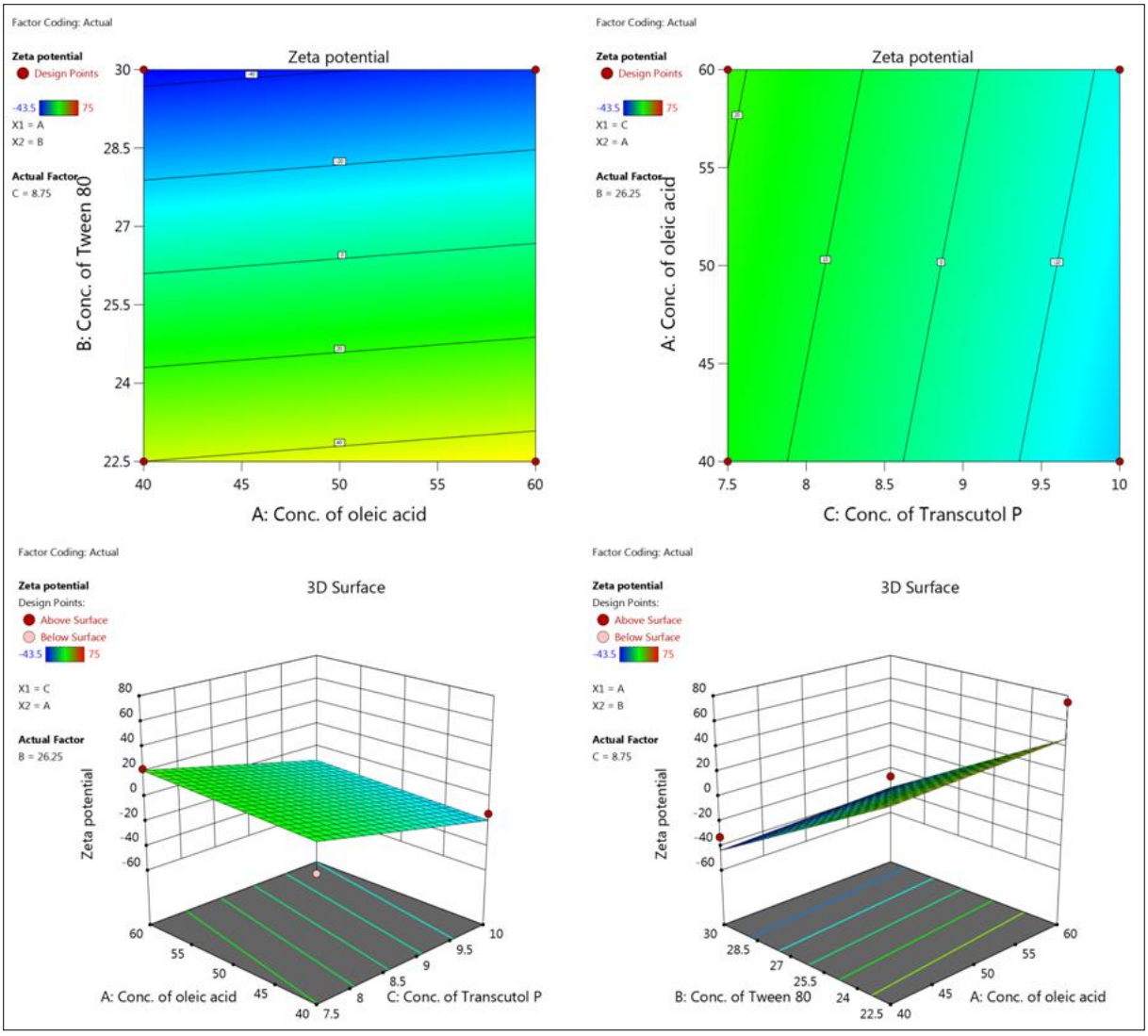

Figure 9: Counter and Response surface plot showing effect of variables on zeta potential

Response 3: % Transmittance

Positive results were seen when oleic acid concentration was combined with Tween 80 and Transcutol P. Surfactant and co-surfactant concentrations are directly related to the percent of transmission. Transmittance increases when surfactant and co-surfactant concentrations rise. The model's F-value of 51.99 suggests that it may be significant. Only 0.01% of the time may noise be the cause of an F-value this high. When the P-value is less 0.0500, model terms are deemed significant. The variation is less than 0.2 because the Predicted R2 of 0.8902 and the Adjusted R2 of 0.9329 are reasonably in agreement.

% Transmittance = +84.93 +0.7200A +7.31B +2.34C

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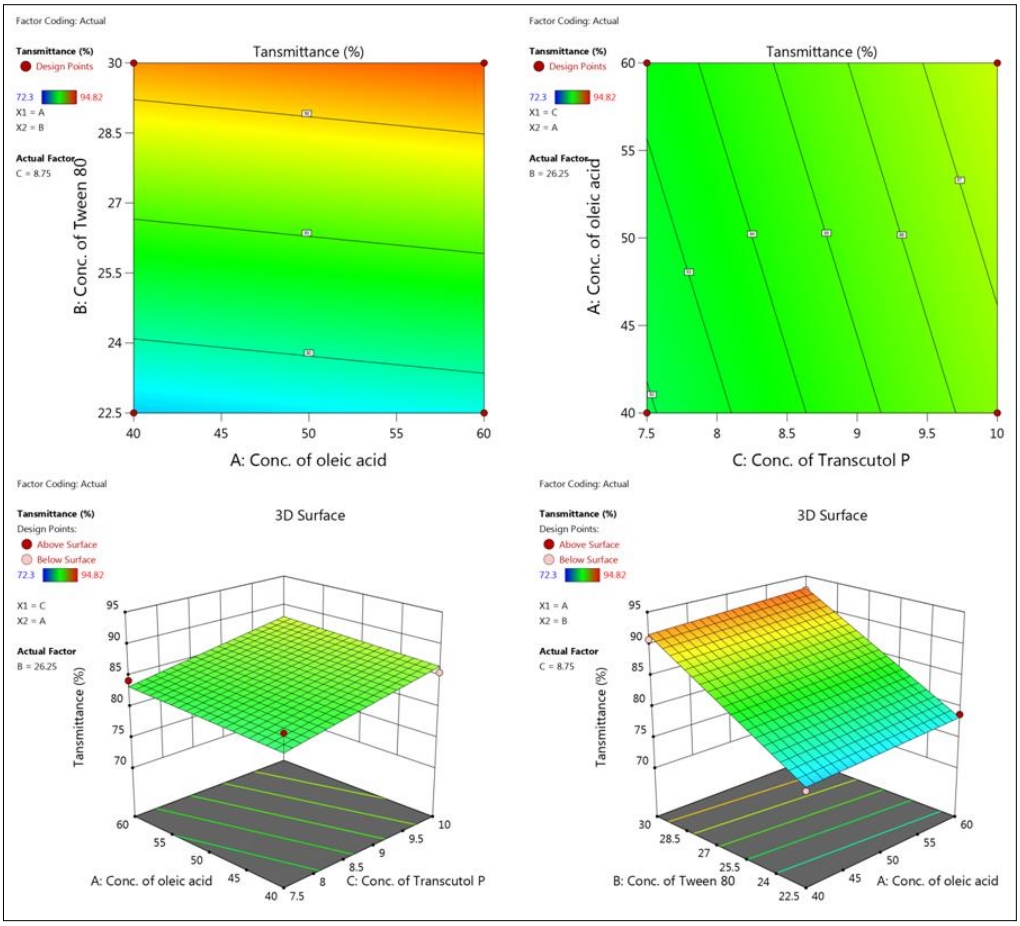

Figure 10: Counter and Response surface plot showing effect of variables on % Transmittance

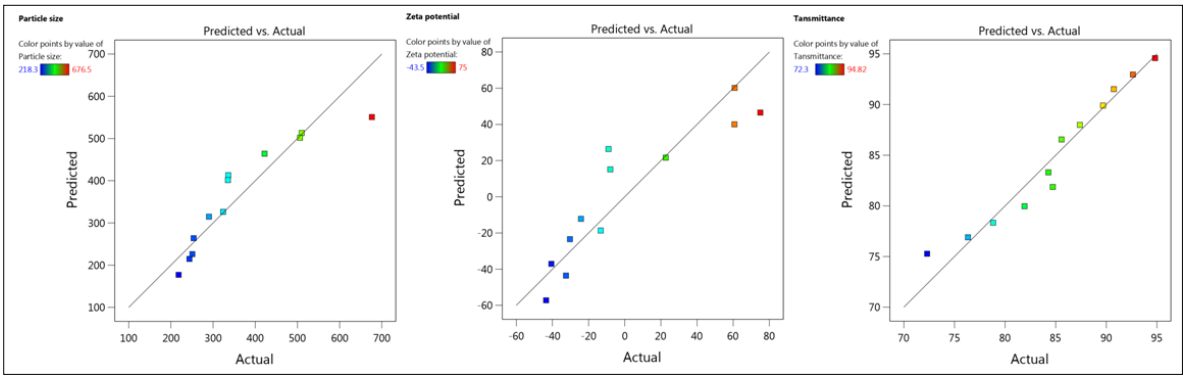

Figure 11: Predicted Vs Actual plot of Globule size, Zeta potential and % Transmittance

Dye solubilization test and Cloud point measurement

A dye solubilization test was used to confirm the emulsion type. The water-soluble dye (eosin) was rapidly incorporated into the system, indicating that water was the continuous phase and an o/w microemulsion had formed. All liquid SMEDDS were found to have cloud points that were greater than 85ºC, indicating that at physiological temperatures, micoemulsions won't phase separate, making them stable.

Formulation of Solid SMEDDS (S-SMEDDS) of DRV

By using Neusilin US2, four satisfactory formulations of liquid SMEDDS of DRV such as

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DRVL5, DRVL6, DRVL8, and DRVL12 were successfully converted to S-SMEDDS (DRVS1 to DRVS4).

Evaluation of S-SMEDDS of DRV

Table 4 lists the findings for angle of repose, bulk and tapped density, compressibility index, Hausner ratio, and drug content. It was reported that all S-SMEDDS formulations exhibited excellent drug content and good flow properties.

Table 4: Micromeritic properties and drug content of DRV loaded S-SMEDDS

Formulation	Angle of repose	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner's ratio	Drug content (%)
DRVS1	21.87±2.87	0.573±0.05	0.682±0.04	15.98±1.63	1.19±0.04	97.84±1.62
DRVS2	22.73±2.51	0.538±0.03	0.784±0.06	31.38±2.44	1.46±0.03	96.59±2.81
DRVS3	23.48±2.77	0.559±0.06	0.729±0.02	23.32±1.89	1.30±0.06	96.39±2.75
DRVS4	19.52±2.69	0.578±0.02	0.681±0.02	15.12±1.23	1.18±0.02	98.57±1.36

All value represents Mean ± SD (n=3)

Saturation solubility

Figure 12 displays the solubility of several batches of S-SMEDDS of DRV in water. Results indicated that after the formulation of S-SMEDDS, the DRV's water solubility had significantly increased.

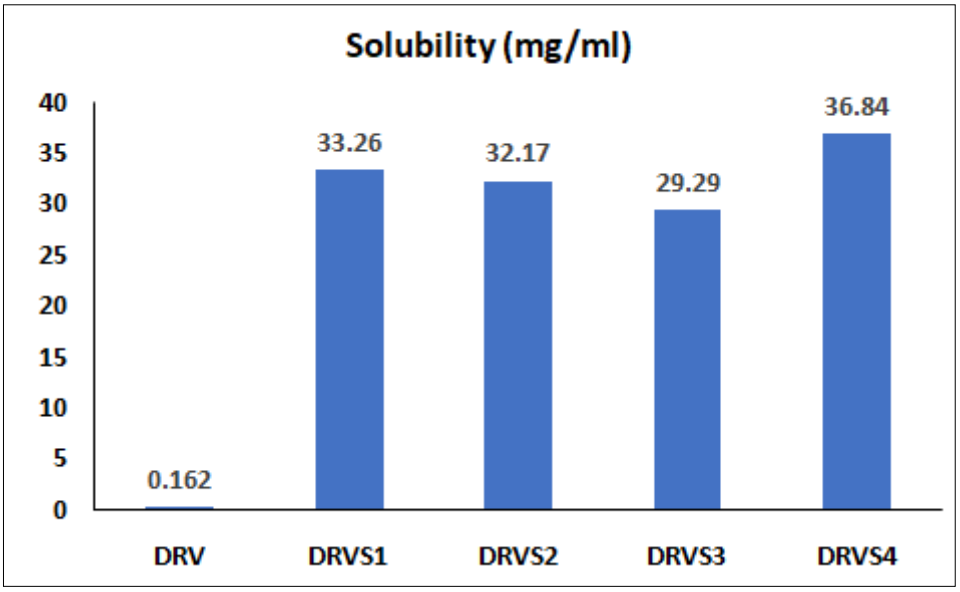

Figure 12: Solubility of DRV and DRV loaded S-SMEDDS in Water

In-vitro dissolution studies of DRV loaded S-SMEDDS:

Figure 13 displays the cumulative percent drug release from Plain DRV and S-SMEDDS. Results showed that, S-SMEDDS of batch DRVS4 released 85.79±2.08 % of DRV in 60 min as compared to that of 22.53±2.97 % from plain DRV. Hence amount of DRV release from S-SMEDDS batches was significantly increased as compared to plain DRV.

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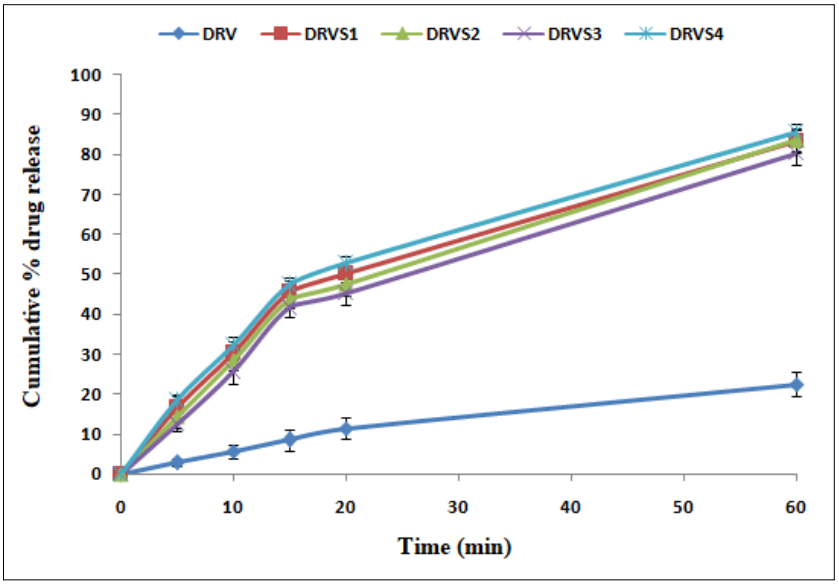

Figure 13: Cumulative % drug release of DRV from S-SMEDDS and Plain DRV

Solid state characterization of DRV loaded S- SMEDDS

FTIR study

FTIR spectra of plain DRV and DRVS4 showed all characteristic peaks of DRV. Hence it was found that, there is not any interaction between DRV and Neusilin US2 and found to be compatible.

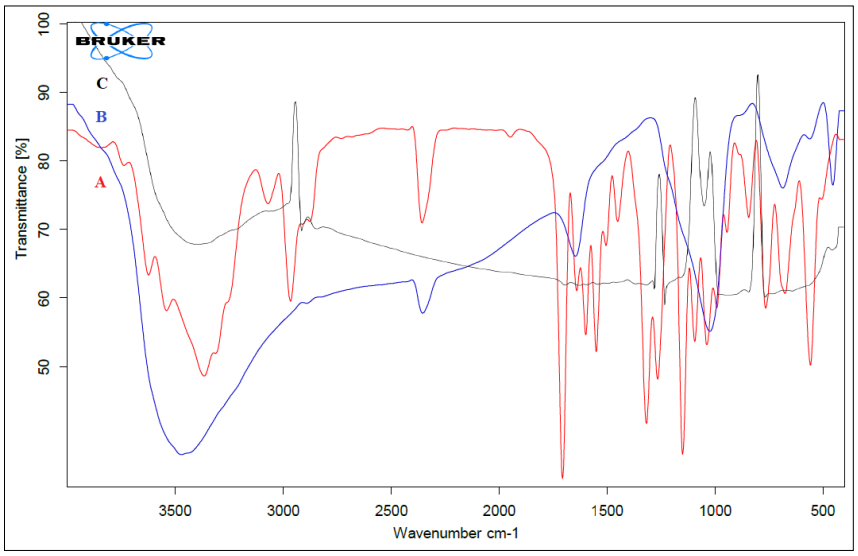

Figure 14: FTIR Spectra of A) DRV, B) Neusilin US 2 and C) S-SMEDDS of batch DRVS4

Powder X-ray diffraction (PXRD)

XRD spectra of DRV exhibited multiple peaks attributed to its crystalline nature, but it is observed Figure 15 C) that the peaks were absent from the diffractogram of the S-SNEDDS indicatedcomplete amorphization of DRV in S-SNEDDS**.**

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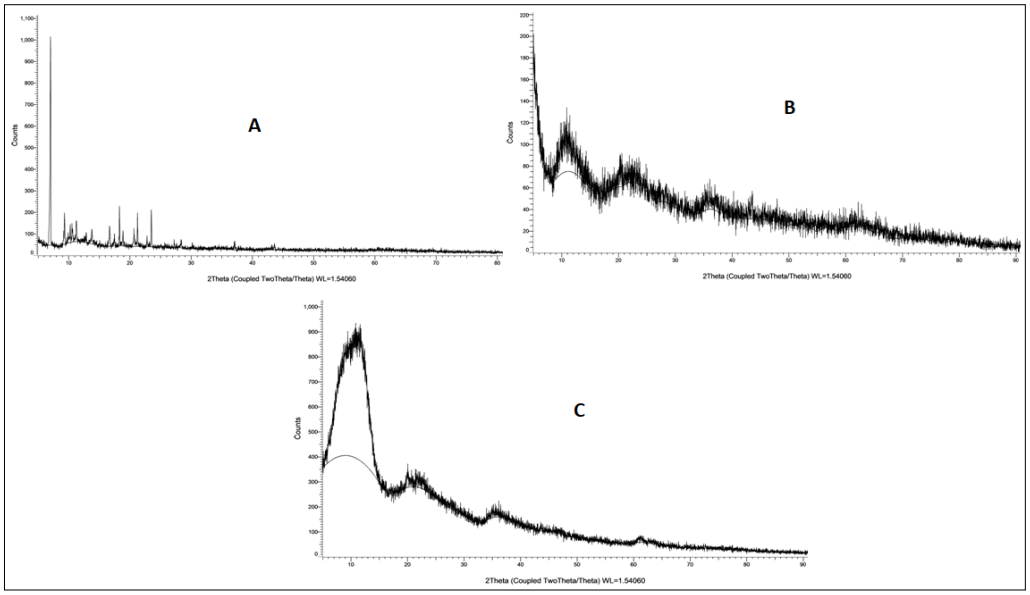

Figure 15: XRD Spectra of A) DRV, B) Neusilin US 2 and C) S-SMEDDS of batch DRVS4

Differential scanning calorimetry (DSC)

Figure 15 displays a DSC thermogram for batch DRVS4 that includes the DRV, Neusilin US2, and S-SMEDDS. The outcomes demonstrated that the S-SMEDDS of batch DRVS4 significantly reduced the sharp endothermic peak of the plain DRV at 391.55ºC. The transition of the drug's physical state (from crystalline to amorphous), which was further validated from powder X-ray diffraction tests, is unraveled by the absence of a recognizable drug peak in the S-SMEDDS formulation over the melting range of DRV.

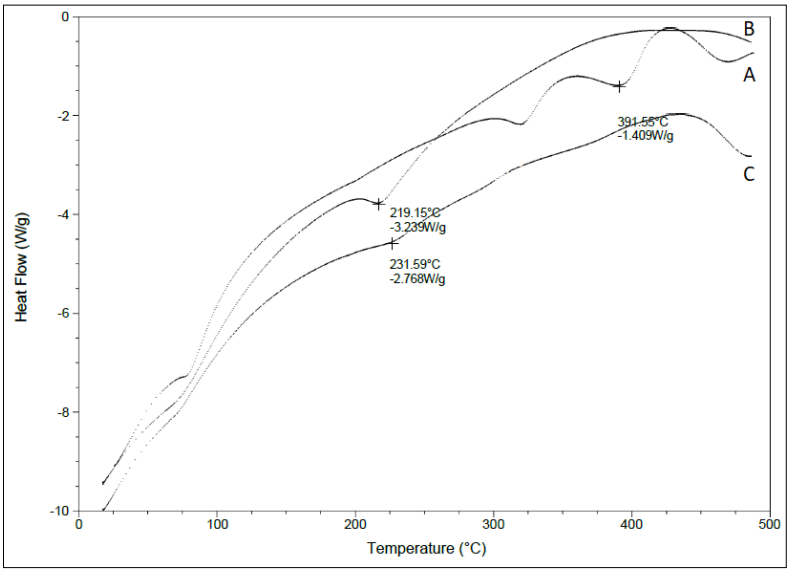

Figure 15: DSC thermogram of A) DRV, B) Neusilin US 2 and C) S-SMEDDS of batch DRVS4

4. Conclusion

The aim of the current work was to create S-SMEDDS of Darunavir using Box-Behnken designs to improve solubility and dissolution. Oleic acid, Tween 80, and Transcutol P were chosen as the oil, surfactant, and co-surfactant for the preparation of liquid SMEDDS, respectively, after researching DRV's solubility in various solvents. It was demonstrated using a box-behnken factorial design

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that the concentration of oil, surfactant, and co-surfactant has an impact on the particle size, zeta potential, and percent transmittance of liquid SMEDDS. The study found that the size of the microemulsion globules reduces as Tween 80 and Transcutol P concentrations increase. Furthermore, it was discovered that globule size reduces with an increase in oleic acid concentration. Using an adsorption approach and Neusilin US2, four optimized batches of liquid SMEDDS were transformed into solids. According to the findings of the S-SMEDDS evaluation, batch DRVS4 was good in terms of drug content, solubility enhancement, and in-vitro drug release. Results indicate that SMEDDS is a promising method for improving the solubility, dissolution, and concurrent bioavailability of drugs like DRV that are poorly water-soluble.

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Conflict Of Interest

Mahesh Biradar and Parul Mehta declare that they have no conflict of interest.

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