ORIGINAL ARTICLE

Design and Development of Docetaxel Solid Self-Microemulsifying Drug Delivery System Using Principal Component Analysis and D-Optimal Design

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Abstract

Aim: The aim of this research was to develop a solid self-emulsifying drug delivery system for BCS Class IV drug (Docetaxel) using Principal component analysis (PCA) and D-Optimal Design (cubic model). To convert liquid self-emulsifying drug delivery system in solid dosage form, the liquid-solid compact (LSC) technique was used and *in vitro* dissolution rate was increased up to 60 min. **Materials and Methods:** The Docetaxel liquid self-emulsifying drug delivery system was prepared by considering oleic acid as oil phase (42.37%), Tween-80 (43.39%) as a surfactant, and PEG-400 (14.21%) as cosurfactant. The pseudoternary phase diagram was plotted using Chemix School 7.0 software, and microemulsion region was spotted. Now, using PCA (Using The Unscrambler®X software) emulsification time and % cumulative drug release at 30 min were selected as two most important variables which were considered for preparing self-microemulsifying drug delivery system (SMEDDS) using D-Optimal Design (Design-Expert® V10). From the design output and desirability function, it was identified that among 16 batches DOXP-13 was coming out as a best-optimized batch. The optimized batch was further characterized by high-performance liquid chromatography (HPLC) method and its polydispersity index (PDI), zeta potential, and droplet size were determined. The optimized microemulsion was further converted into a 250 mg solid tablet using the LSC technique by considering HPMC K100LV (Methocel) as carrier and magnesium trisilicate as a coating agent. From differential scanning calorimetry and infrared studies, it was confirmed that no possible interaction was observed between liquid SMEDDS and carrier and coating materials of the LSC. The 250 mg final tablet (LSC-Tab) was kept for 1-month stability studies. **Results and Discussion:** From the solubility studies, it was confirmed that oleic acid with 413.66 mg/g has a higher Docetaxel solubility among all the oils. Same way, tween-80 (299.61 mg/g), PEG 400 (462.86 mg/g) has a maximum solubility with Docetaxel. The optimized DOXP-13 batch has shown 19.71 ± 0.08 seconds emulsification time and 95.21 ± 0.01% cumulative drug release at 30 min. From the HPLC studies, it was observed that Docetaxel SMEDDS has 103.23% w/v recovery and 9.180 min as retention time. The zeta potential of the DOXP-13 optimized batch was found to be 0.034mv with 0.218 PDI and 100.8nm zeta diameter. The mean droplet size of the SMEDDS was found to be 2.346µm. During conversion of liquid SMEDDS into solid, the optimum flowable liquid retention potential (Ø) at a 33° angle was found to be 0.80. The final 250 mg tablet (LSC-Tab) disintegration time was found to be 42 ± 0.20 min. LSC-Tab shows 100.39 ± 0.39% cumulative drug releases at 60 min. From the 1-month stability studies, it was confirmed that LSC-Tab has good stability with good dissolution profile. **Conclusion:** It can be concluded that Docetaxel loaded solid self-microemulsifying drug delivery system was successfully prepared, and solubility and dissolution of Docetaxel were improved.

Key words: Docetaxel, D-Optimal Design, optimization, principal component analysis, self-microemulsifying drug delivery system

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INTRODUCTION

Docetaxel is an antineoplastic agent. It belongs to second-generation Taxoid family. This chemotherapeutic agent sold under the brand name of Taxotere by Sanofi-Aventis.[1] This drug has versatile use in neck, stomach, prostate, and breast cancer treatment. However, Docetaxel is toxic for the fetus. After Docetaxel administration in patients, it propagates liver toxicity, numbness, shortness of breath, vomiting, muscle pain, alopecia, and low blood count. In the cellular level, it inhibits mitotic spindle assembly and so cells mitosis stops.[2] Docetaxel was proprietary in 1986, and its patent gets invalid in 2010. Docetaxel is highly soluble in Tween-80 and ethanol solvent system, but this system causes several side effects. At present Taxotere and Duopafei brands are available, but both are having side effects, and oral administration is restricted. The oral bioavailability of Docetaxel was reported very less (~5%) due to P-Glycoprotein mediated drug efflux, hepatic first-pass metabolism, low gastrointestinal tract (GIT) permeability, and high pre-absorption metabolism in the gut wall.[3]

Since Docetaxel is a BCS-IV drug; hence, improvement of bioavailability is a big challenge. A new approach called self-emulsifying drug delivery system (SEDDS) has potential ability to improve Docetaxel bioavailability. SEDDS could enhance bioavailability of any poorly water and lipid soluble drug by bypassing the first-pass metabolism, by facilitating intestinal lymphatic transport of drug, by inhibiting P-gp mediated drug efflux, and by preventing pre-absorption metabolism by gut membrane-bound cytochrome enzyme. However, SEDDS reported low drug loading, limited stability and difficulties in production hinders its pharmaceutical application and most importantly, increase the amount of surfactant can cause GIT irritation. To circumvent those associated problems an isotropic supersaturated solid self-emulsifying drug delivery approach was entertained. This approach could possibly decrease the toxicity of surfactant by converting SEDDS into solid dosage form.[4] However, very limited studies have been reported as far as solid supersaturated SEDDS formulations are concerned.[2] In this study, we formulated Docetaxel loaded solid supersaturated self-microemulsifying drug delivery system (DOX-sSSMDDS) by considering 42.37% oil (Oleic acid), 43.39% surfactant (Tween-80), and 14.21% Cosurfactant (PEG-400), and solid supersaturated SMEDDS was prepared using liquid-solid compact (LSC) technique by considering HPMC K-100 LV as solid carrier and magnesium trisilicate as coating material. The aim of this study was to design a Docetaxel Solid Supersaturated Self-Microemulsifying Drug Delivery System (DOX-sSSMEDDS), which could have to improve dissolution, solubility and stability profile. To influence cost cutting and to reduce number of trials principal component analysis (PCA).[5] PCA and D-optimal mixture design, a subtype of mixture design was implemented. PCA and D-Optimal Design minimize the number of variances associated with the evaluation parameters. In D-Optimal Design whole system of SMEDDS consider as 100%.

MATERIALS AND METHODS

Docetaxel was a gift sample from Naprod Life Sciences Pvt., Ltd. India. Reset of the chemicals were arranged from various sources, i.e., oleic acid (Loba Chemie Pvt., Ltd., Mumbai), Castor Oil (Loba Chemie Pvt., Ltd., Mumbai), Sunflower oil (Loba Chemie Pvt., Ltd., Mumbai), Olive oil (Loba Chemie Pvt., Ltd., Mumbai), Capmul MCM C8 EP (Abitec Corporation-JANESVILLE, USA), Capmul MCM EP (Abitec Corporation- JANESVILLE, USA), Captex-200P (Abitec Corporation-JANESVILLE, USA), Maisine 35-1(Gattefosse, France), Tween 80 (Loba Chemie Pvt., Ltd., Mumbai), Tween 20 (Loba Chemie Pvt., Ltd., Mumbai), Tween 60 (Loba Chemie Pvt., Ltd., Mumbai), Labrafil-M-2125 (Gattefosse, France), Labrafac PG (Gattefosse, France), Cremophor RH40 (BASF, Mumbai), Polyethylene glycol 200 (Astron chemicals-India Pvt., Ltd.), Polyethylene glycol 400(Astron chemicals-India Pvt., Ltd.), Polyethylene glycol 600 (Astron chemicals-India, Pvt., Ltd.), Magnesium trisilicate (Magxid Fine Chem-Gujarat), HPMC K100 LV(Colorcon Pvt., Ltd., India), Dibasic Calcium Phosphate (Vijaya Enterprise-Mumbai), Sodium Starch Glycolate (Alps pure Life sciences Pvt., Ltd., New Delhi), MCC (Akhil Healthcare Pvt., Ltd., Vadodara), and Magnesium stearate (Benzer Multitech India Pvt., Ltd., Pune).

Solubility studies

The solubility of Docetaxel was carried out in various oils; such as Campul MCM C8EP, Castor oil, Oleic acid, Olive oil, Maisine 35-1, Captex 200P, Sunflower oil than, and solubility study of Docetaxel was carried out in various surfactant such as; Tween 80, Tween 20, Tween 60, Cremophor RH40, Labrafac PG, and Labrafil M2125 followed by in various cosurfactant; such as PEG 200, Propylene Glycol, PEG 600, and PEG 400. The solubility of Docetaxel was determined by dissolving an excess quantity of drug in 2 ml of respective oils/surfactant/cosurfactant and then the mixture was then vortex for 72 h at 25°C. After attaining equilibrium stage, the sample mixture was subjected to centrifugation at 3000 rpm for 15 min, the supernatant was collected and filtered using Millipore membrane filter (0.45 µm), this filtrated was then diluted with methanol and drug in each oil/surfactant/cosurfactant was analyzed using ultraviolet (UV)-visible spectroscopy at 330 nm. The solubility of Docetaxel was calculated using $y = 0.0542x + 0.002$, standard curve formula. Each experiment was carried out in triplicate.

Construction of pseudoternary phase diagram and percentage transmittance

The pseudoternary phase diagram was constructed to analyze the oil, surfactant, and cosurfactant whole concentration range.[6] The presence of self-emulsification region within this diagram was observed. After solubility study, oleic acid considered as the oil phase, Tween 80 was considered as a surfactant and PEG-400 was considered as cosurfactant. A serious of SMEDDS formulation with the 20mg drug, oil (25–60 parts), surfactant (10–75 parts), and cosurfactant (0–30 parts) was prepared. In initial screening total, 24 batches were constructed. From these batches, a 0.3 ml isotopic mixture of SMEDDS was introduced into 0.01N HCl and % transmittance was recorded. In visual observation, those batches which had phase separation were omitted from this study. Further, based on solubility and % transmittance studies more nine batches (DOX-1 to DOX-9) were constructed considering 18–65% as oil, 35–55% as a surfactant, and 0–30% as cosurfactant, and pseudoternary phase diagram were constructed using Chemix School 7.0 software. Pseudoternary phase diagram helps to find out best optimal self-emulsifying region.

PCA

PCA is a mathematical algorithm that reduces the dimensionality of the data while retaining most of the variation in the data set; it allows the results to be simplified into latent variables (principal components) that explain the main variance in the data. PCA is used for getting an overview of data tables (their structure, similarities or dissimilarities, trends, and deviating observations). PCA incorporation also helps into reduce variables in formulation design. PCA was designed by the Unscrambler × 10.2 software.[7]

D-Optimal Design

The factors which have mixed number of levels of quantitative and qualitative factors can be explained by D-Optimal Design. D-Optimal Design can be used where we need minimum generalize variance of the estimated regression coefficients. In the equation, X always represents data matrix of independent variables. This design minimizes the overall variance of estimated regression coefficients by maximizing the determent of X'X. D-Optimal Design always reduces the number of runs and provide a reasonable choice.[8]

Preparation of SMEDDS

Preparation of optimized batch

About 20 mg of Docetaxel drug were taken into the 25ml beaker. Calculative amount of surfactant Tween-80 (43.39%) and cosurfactant-PEG-400 (14.21%) were added into the beaker and sonicate in 0.8L Stainless Steel Household Digital Ultrasonic (DK-Sonic) until and creamy pale yellowish white suspension formed. Now in 30ml Teflon-lined crew capped glass tube pour the suspension and to that add oil phase oleic acid (42.37%) and mix by gentle stirring until a semi-transparent solution formed. Whole SMEDDS was planned for 20 ml.

DOX-sSSMEDDS

Preparation of DOX-sSSMEDDS of the optimized batch using LSC technique

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculated required amount of powder excipients (carrier and coating materials), a mathematical approach is based on the flowable liquid retention (Ø-Value). The Ø value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of the slide.[9]

Ø value = (weight of non-volatile liquid vehicle)/(weight of carrier material)

Determination of angle of the slide and flowable retention potential for carrier and coating material

Determination of angle of slide

The required amount of carrier is weighted and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which the powder is about to slide. It was used to measure the flow property of powders. A value of 33°for the angle of slide gives an optimum flowability to the powders. Keeping the constant weight of carrier/coating material, increasing amount of solvent was incorporated and on each addition, the angle of the slide was determined. The flowable liquid retention potential (Ø-value) of each liquid/powder admixture was calculated using the following equation:

Ø value = (weight of non-volatile liquid vehicle)/(weight of carrier material)

The Ø value was plotted against the corresponding angle of repose for optimal flow property. Corresponding to 33° of a liquid/powder admixture represented the flowable liquid retention potential.

Determination of liquid load factor

The appropriate amount of carrier and coating material to produce an acceptable flowing and compatible powders was calculated using following equation:

Loading factor was calculated by the equation:

$Lf=Øca + Øco (1/R)$

Lf=W/Q
R=Q/q
Øca= Liquid retention potential for carrier material
ØCo= Liquid retention potential for carrier material
R= Ratio of carrier to coating material carrier: coating
Q= Amount of carrier material
q= Amount of coating material

The Docetaxel optimized batch was initially charged with HPMC K100 LV (Carrier), Magnesium trisilicate (coating agent) followed by admixing with Sodium Starch Glycolate (Super disintegrates), MCC (diluent), and Magnesium stearate (Lubricant). The liquid load factor and angle of the slide were recorded and resultant powder was punched with 10mm round shape Flat face bevel punch. Individual tablet weight was adjusted up to 250 mg.

Characterization of DOX- SMEDDS

Drug content of SMEDDS

Liquid SMEDDS equivalent to 20 mg of DOX was dissolved in 10 ml 0.01N HCl. Necessary dilutions were made with 0.01N HCl. The solution was filtered through filter papers (Whatman-35) and analyzed by UV-visible spectrophotometer (Model No: 1800 Shimadzu, Japan).

Phase separation study

Approximately 1 ml of DOX-SMEDDS was added to 5 ml of distilled water in a glass test tube at 25°C and vortex for 1 min. The mixture was stored at 25°C for a period of 2 h and observed visually for any phase separation.

Transmittance test

Stability of SMEDDS formulation on dilution was checked by measuring transmittance through UV-visible spectrophotometer (Model No: 1800 Shimadzu, Japan). The transmittance of the sample was measured at 230 nm and for each sample, three replicate measurements were performed.

Effect of dilution/robustness

Dilution study was done to access the effect of dilution on SMEDDS pre-concentrates, to mimic physiological dilution process after oral administration. The optimized batches of SMEDDS were subjected to various dilutions (50, 100, 500, and 1000 times) in 0.01N HCl. All the samples mixture of diluted SMEDDS were stored for 24 h and observed for any signs of phase separation or precipitation. Each experiment was carried out in triplicate.

Determination of self-emulsification time

The emulsification time of SMEDDS formulations was determined using United States Pharmacopeia (USP) Type II (Paddle type) dissolution apparatus (TDT-06-Electrolab, Mumbai). Each formulation of DOX-SMEDDS was added to 300 ml purified water at 37°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The time required to obtain clear dispersion was recorded at emulsification time. For each sample, three replicate measurements were performed.

Cloud point determination

The cloud point was an essential factor in the SMEDDS consisting of non-ionic surfactants, and it was responsible for the successful formation of a stable microemulsion, hence, the cloud point for SMEDDS should be above 37°C, which will avoid phase separation occurring in the GIT. DOX-SMEDDS was diluted with water in the ratio of 1:250, and the sample was placed in a water bath with the temperature increasing gradually, at 5°C intervals (or at 2°C intervals when approaching the cloud point), spectrophotometric analysis was carried out to measure the sample transmittance using an empty glass test tube as a blank.

Zeta potential determination

Each SMEDDS formulation was diluted to 250 ml with distilled water in a glass beaker with constant stirring. Zeta potential of the resulting microemulsions was determined using the Malvern Zetasizer (ZS90).

Globule size determination

Emulsion droplet size was considered a decisive factor in self-emulsification dispersion performance since it determines the rate and extent of drug release and absorption. 20 ml of each SMEDDS formulation was diluted with 250 ml distilled water in a glass beaker with constant stirring. Size of globules so formed and polydispersity index was determined the Malvern Zetasizer (ZS90).

In vitro drug release

In vitro release profiles of SMEDDS of Docetaxel was studied using USP Apparatus I at 37±0.5°C with a rotating speed of 100 rpm in 0.01N HCL as the dissolution media. During the study, 2 ml of aliquots were removed at predetermined time intervals (5, 10, 20, and 30 min) from the dissolution medium and replaced with fresh media. The amount of Docetaxel released in the dissolution medium was determined by UV-visible spectrophotometer (Model No: 1800 Shimadzu, Japan).

Stability study

The accelerated stability study was carried out of the optimized formulation. The sample of tablets was wrapped in the laminated aluminum foil and placed in the stability chamber at 40 ± 2°C/75 ± 5% relative humidity for a period of 1 month. Sampling was done at a predetermined time intervals of 0, 15, and 30 days. The tablets were evaluated for different physicochemical parameters.

RESULTS AND DISCUSSION

Solubility study

Solubility study was performed in various oils, surfactants, and cosurfactants. The results were enlisted in Tables 1-3 and Figures 1-3.

Docetaxel is significantly high soluble in oleic acid; hence, this oil was considered for further research.

Docetaxel is significantly high soluble in Tween-80; hence, this surfactant was considered for further research.

Based on solubility study PEG400 was considered as best cosurfactant.

% transmittance

Based on solubility study; oleic acid as oil, tween 80 as a surfactant, and propylene glycol-400 as cosurfactant were selected as a three-component system. For preparing DOTX-SEDDS, each (Drug [20 mg] + surfactant: cosurfactant: oil) formulation was introduced 100ml of 0.01N HCl in a glass beaker, and the content was mixed gently on a magnetic stirrer, and the % transmittance was checked in UV-spectroscopy [Table 4].

Robustness to dilution

The result of dilution showed no signs of precipitation, turbidity, or phase separation after 24 h.

Table 1: Solubility study of Docetaxel in various oils

Oil	B1	B2	B2	Mean±SD
Campul MCM C8EP	121.9	120.34	122.01	121.4166667±0.934041398
Castor oil	312.3	313.8	313.2	313.1±0.754983444
Oleic acid	412.4	413.8	414.8	413.6666667±1.205542755
Olive oil	147.9	148.8	147.1	147.9333333±0.850490055
Maisine 35-1	189.09	190.82	191.23	190.38±1.135825691
Captex 200P	190.02	190.22	191.39	190.5433333±0.740022522
Sunflower oil	289.01	290.22	289.19	289.4733333±0.652865479

SD: Standard deviation

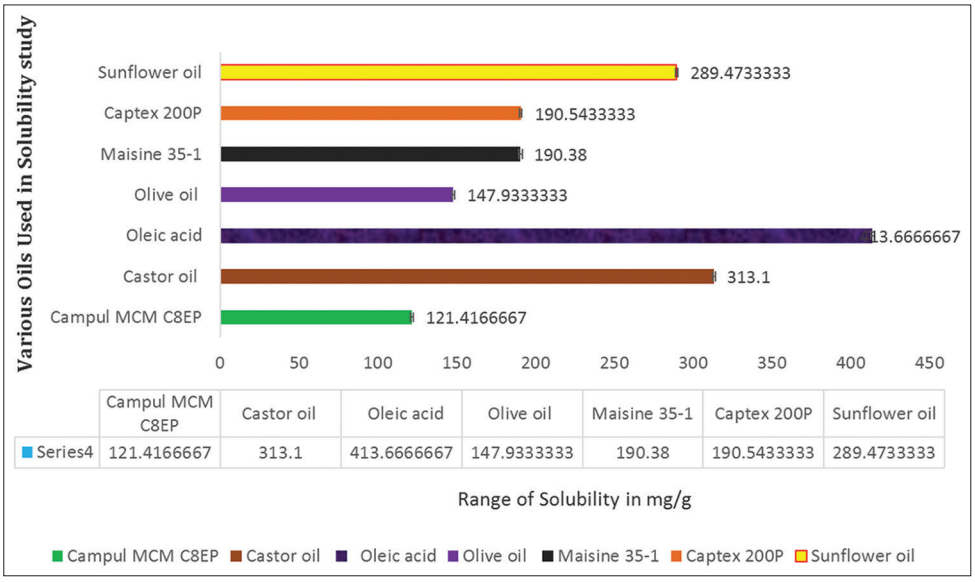

Figure 1: Solubility study of Docetaxel in various oils

Table 2: Solubility study of Docetaxel in various surfactants

Surfactant	B1	B2	B3	Mean±SD
Tween 80	298.75	299.97	300.12	299.6133333±0.751420876
Tween 60	245.98	246.12	245.12	245.74±0.541479455
Tween 20	213.83	214.27	213.11	213.7366667±0.5856051
Cremophor RH40	185.83	186.22	185.11	185.72±0.563116329
Labrafac PG	106.92	107.29	107.22	107.1433333±0.19655364
Labrafil M2125	93.27	94.28	93.18	93.57666667±0.610764548

SD: Standard deviation

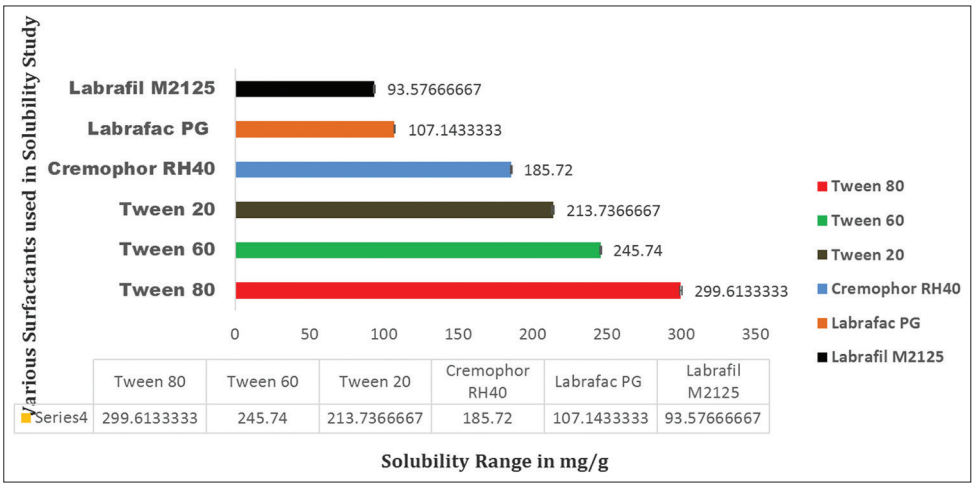

Figure 2: Solubility study of Docetaxel in various surfactants

Table 3: Solubility study of Docetaxel in various cosurfactants

Cosurfactant	B1	B2	B3	Mean±SD
PEG 200	326.23	326.12	327.29	326.5466667±0.646090809
Propylene Glycol	301.34	302.18	300.23	301.25±0.978110423
PEG 600	323.71	323.89	324.78	324.1266667±0.572916515
PEG400	462.45	463.81	462.33	462.8633333±0.822030008

SD: Standard deviation

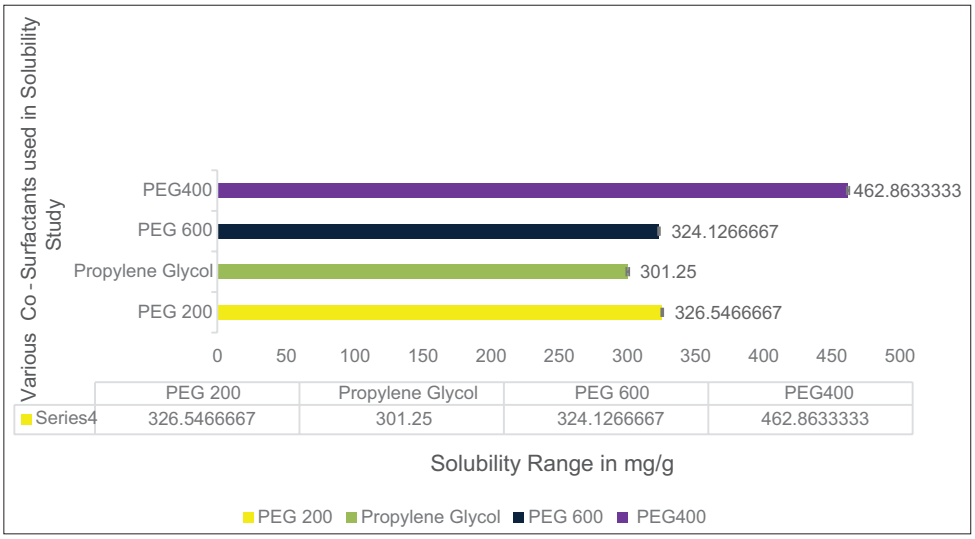

Figure 3: Solubility study of Docetaxel in various cosurfactants

Preliminary trial batches for selection of microemulsion region

A serious of SMEDDS formulation with varying concentration of oil (15–65 parts), surfactant (10–75 parts), and cosurfactant (0–30 parts) was prepared. Each formulation (0.5 ml) was introduced into 100 ml of 0.01N HCl and % transmittance was recorded. A total of 24 batches are selected, and individual batches % transmittance was recorded (97.28 ± 0.07 to 99.47 ± 0.01 %) [Table 4].

Outcomes from the preliminary trail batches

From the preliminary trail batch, it was concluded that oil part (18–65 parts), surfactant parts (35–55 parts), and cosurfactant (0–30 parts) need to be optimized.

Construction of pseudoternary phase diagram

To find best emulsification region, an isotropic mixture of oil, surfactant, and cosurfactant was formed. A total of 9 batches were reconstructed using outcomes of the preliminary batches (DOX-1 to DOX-9), and % transmittance (91.67 ± 0.01 to 100.6 ± 0.08%), emulsification time (15.59 ± 0.05 to 55.01 ± 0.02), cloud point (65.05 ± 0.06 to 70.26 ± 0.03°C), and drug content (95.510±0.01 to 101.507 ± 0.01%) were recorded [Figure 4].

In vitro drug release of Docetaxel SMEDDS

The prepared SMEDDS was kept in an infusion Dialysis Membrane-70 (HIMEDIA-LA-393-1MT) bag. While filling contents in a dialysis bag, the lower portion of that bag must be tied up with nylon robe. After filling the allocated amount of SMEDDS, the upper portion of Dialysis Membrane-70 was also tied up with nylon robe. This two side tied bag was then fixed with USP Type II paddle of TDT-06 dissolution apparatus (Electrolab, Mumbai) and submerged in 900 ml of 0.01N HCl maintaining a temperature around 37.5 ± 2°C. During the study, 100RPM was maintained for paddle speed, and 2 ml of aliquots was removed at predetermined time intervals (5, 10, 20, and 30 min) from the dissolution medium and replaced with fresh media. The amount of Docetaxel released in the dissolution medium was determined by

Table 4: Effect of oil, surfactant, and cosurfactant on percentage transmittance, emulsification time, cloud point, percentage drug content

Formulation Code	Oil (Oleic Acid)	Surfactant (Tween 80)	Cosurfactant (PEG-400)	% Transmittance	Emulsification Time	Cloud Point in degree Celsius	% Drug Content
DOX-1	35	65	0	94.10±4.10	15.59±0.05	65.23±0.05°C	96.903±0.01
DOX-2	37	53	10	91.67±0.01	18.25±0.04	67.13±0.09°C	95.887±0.01
DOX-3	40	40	20	99.45±0.03	20.57±0.019	68.23±0.03°C	95.510±0.01
DOX-4	42	28	30	94.21±0.05	25.34±0.08	65.91±0.07°C	100.377±0.01
DOX-5	45	55	0	93.51±0.06	31.58±0.06	70.26±0.03°C	98.477±0.02
DOX-6	47	43	10	97.24±0.07	35.02±0.03	67.29±0.012°C	99.930±0.09
DOX-7	50	30	20	100.6±0.08	41.18±0.018	68.31±0.08°C	101.507±0.01
DOX-8	52	18	30	96.33±0.06	50.27±0.05	69.24±0.04°C	97.463±0.02
DOX-9	55	45	0	93.79±0.03	55.01±0.02	65.05±0.06°C	99.834±0.02

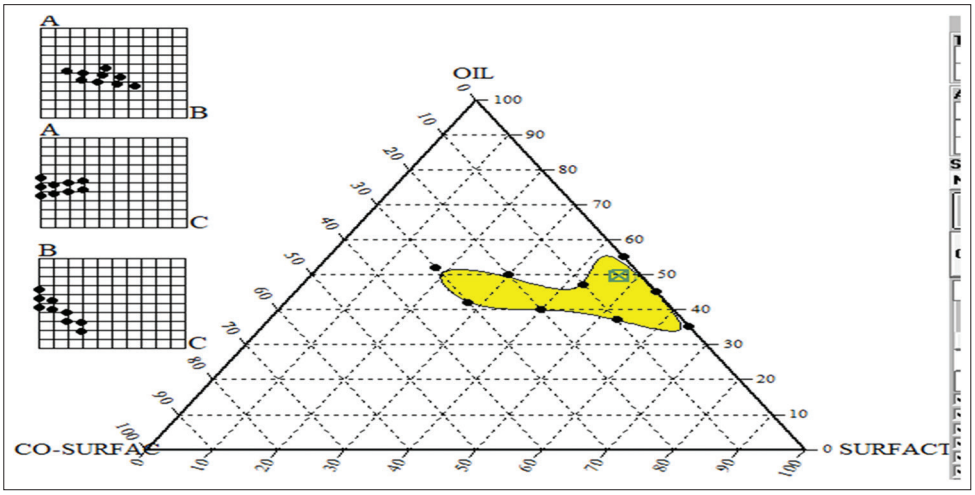

Figure 4: Construction of Pseudoternary Phase Diagram using Chemix School 7.0 software

UV-visible spectrophotometer (Model No: 1800 Shimadzu, Japan) [Table 4 and 5, Figure 5].

PCA

PCA can be used to reveal the hidden structure within large data sets. It provides a visual representation of the relationships between samples and variables (Y values) and provides insights into how measured variables cause some samples to be similar to, or how they differ from each other. This section provides the details of the PCA approach to the understanding data structure. When considering a data table, each row represents an object (or individual, or sample), and each column represents a descriptor (or measure, or variable).

Table 5: Cumulative drug release of Docetaxel SMEDDS

Time (min)						
Formulation Code	**5**	**10**	**15**	**20**	**25**	**30**
DOX-1	10.25±0.06	75.85±0.01	78.29±0.05	82.51±0.05	89.33±0.08	98.32±0.05
DOX-2	7.26±0.08	76.15±0.03	80.37±0.07	84.22±0.07	90.28±0.04	97.28±0.06
DOX-3	9.17±0.09	76.28±0.06	81.28±0.08	86.32±0.04	91.43±0.09	98.82±0.09
DOX-4	10.26±0.04	77.28±0.012	82.22±0.03	85.18±0.04	92.22±0.06	99.28±0.01
DOX-5	11.38±0.01	75.22±0.012	80.62±0.07	84.11±0.09	90.39±0.08	6.58±0.08
DOX-6	10.28±0.03	76.20±0.07	81.29±0.09	85.22±0.08	90.82±0.02	99.29±0.05
DOX-7	9.27±0.06	76.21±0.01	82.02±0.06	84.11±0.08	1.33±0.05	99.17±0.03
DOX-8	10.31±0.01	78.17±0.05	81.21±0.05	84.38±0.04	91.72±0.01	96.32±0.05
DOX-9	9.43±0.08	77.11±0.06	80.28±0.07	84.33±0.05	92.66±0.05	97.52±0.04

SMEDDS: Self-microemulsifying drug delivery system

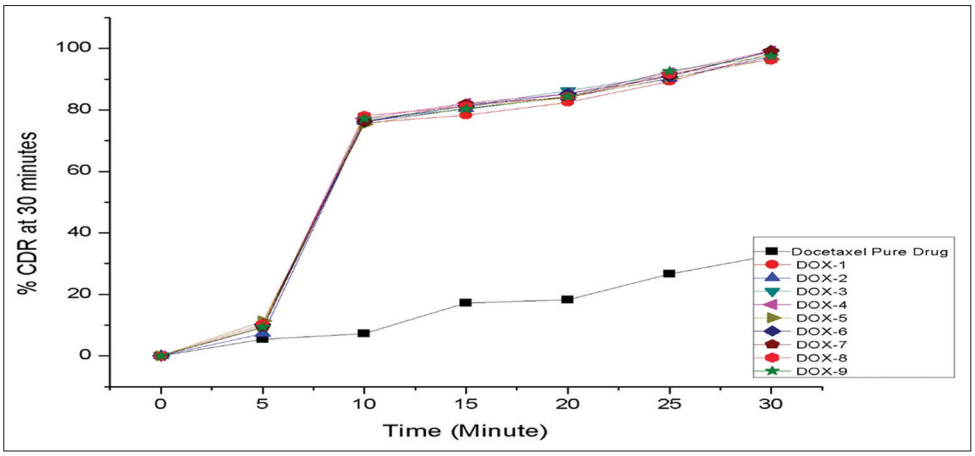

Figure 5: Percentage cumulative drug release of Docetaxel and DOX-1 to the DOX-9 formulation at 30 min

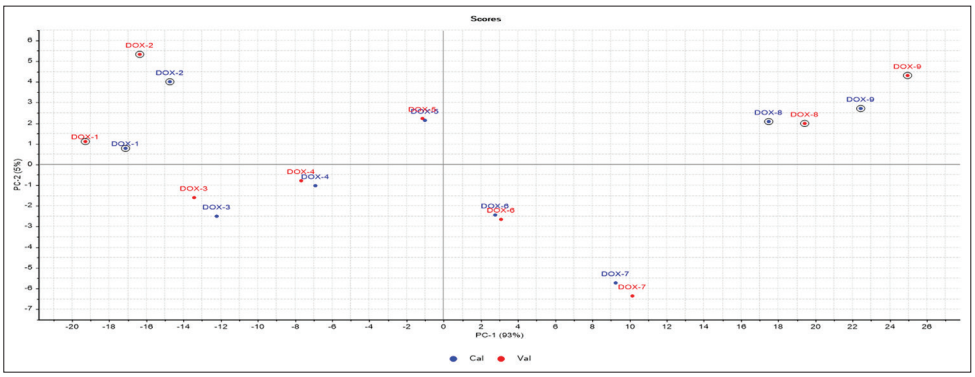

Figure 6: 2D-Scores plot of provided variables

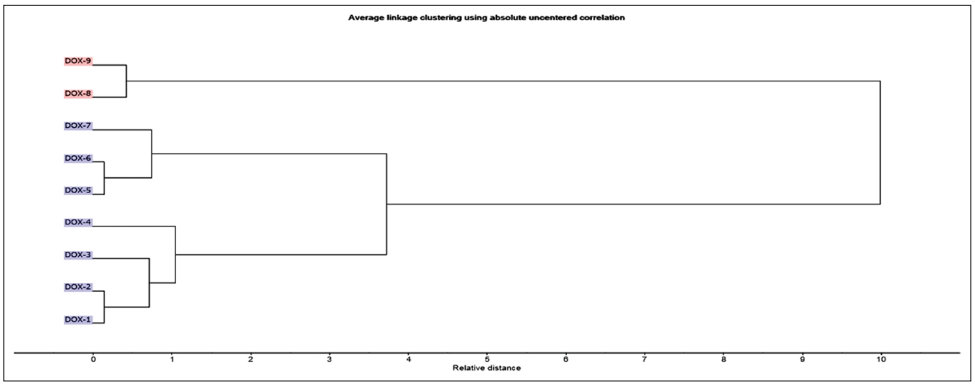

Figure 7: Dendrogram plot

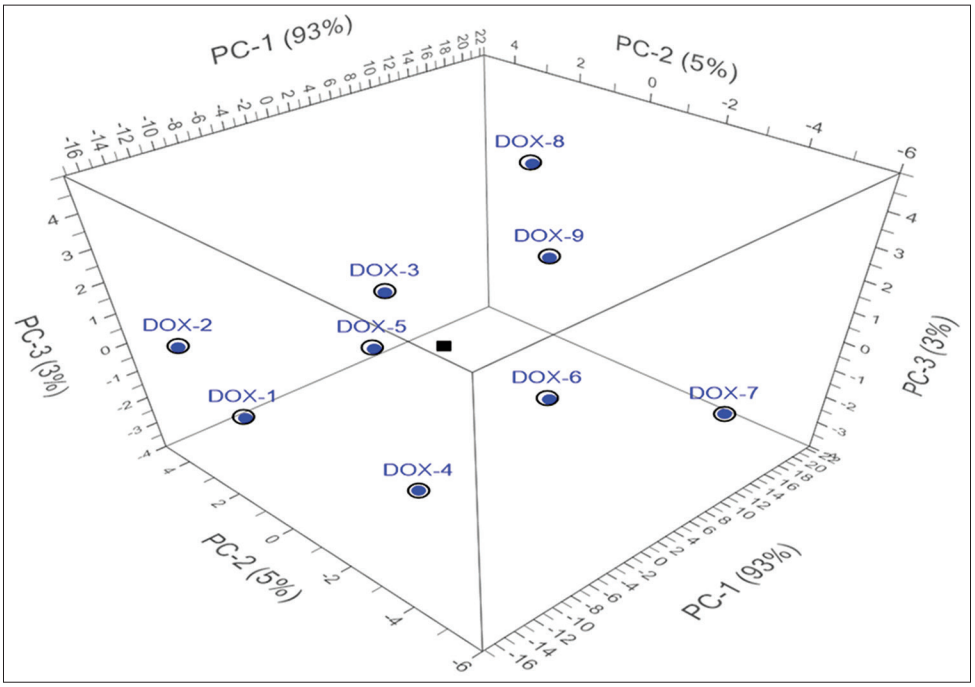

Figure 8: 3D score plot

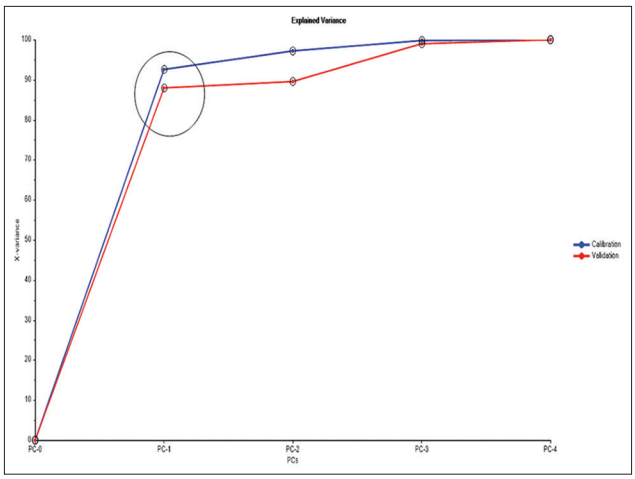

Figure 9: Explained variables

Throughout the rest of this section, rows will be referred to as samples, and the columns as variables. In this PCA analysis, we have taken DOX-1 to DOX-9 as sample batch and their evaluation variables as a descriptor [Table 4]. PCA analysis will help to understand the best variables for further design.

Interpretation of 2D score plot

PC-1 and PC-2 were explained 93% and 5% of total variables(y), respectively. From calculated and validated points, it is very clear that components are symmetrical. DOX-8 and DOX-9 come are almost similar and explain by PC-1. Both the batches are agonistic but antagonistic to DOX-1 and DOX-2 batches. Our target is to select positive and most explain variables; hence, DOX-8 and DOX-9 could be the best-fit batches [Figure 6].

Interpretation of dendrogram plot

From dendrogram plot, it was an analysis that DOX-9 and DOX-8 come under superior group and have higher

relative distance and figures were correlated with score plot [Figure 7].

Interpretation of 3D score plot

From the 3D score plot, it was confirmed that only PC-1 has a high influence on dosage form 93% and PC-2 has a minor influence on dosage form 5%; hence, PC-1 and PC-2 were considered for further analysis and PC-3 (3%) was omitted from further studies. The black spot within 3D group indicates above this points formulations are within the rage and bellow this points are outliners or trivial. Hence, DOX-8, DOX-9, DOX-3, and DOX-2 could be considered for further studies [Figure 8].

Interpretation of explained variables

There is a good correlation between calibrated and validated principal components. However, PC-1 was property correlated with validated variables [Figure 9].

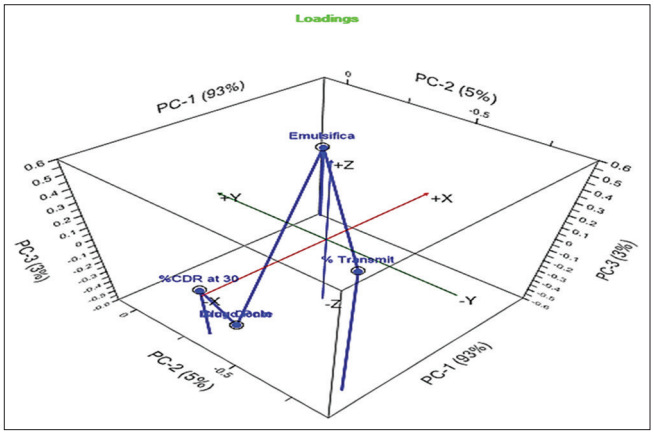

Figure 10: Correlation loading plot in 3D

Interpretation of correlation of loading plot

The outer ellipse is the unit circle, explains 100% of explained variables and inner circle explain 50% of explained variables. Most importantly, almost all the variables 100% explained by correlation loading plot. However, emulsification time has a strong positive influence on PC-1 and % CDR at 30 min has a negative influence on PC-1; hence, both are considered for optimization [Figure 10].

Interpretation of influence plot

From hoteling's influence plot one thing is clear that all the batches are within the limit (>21.1425). Nevertheless,

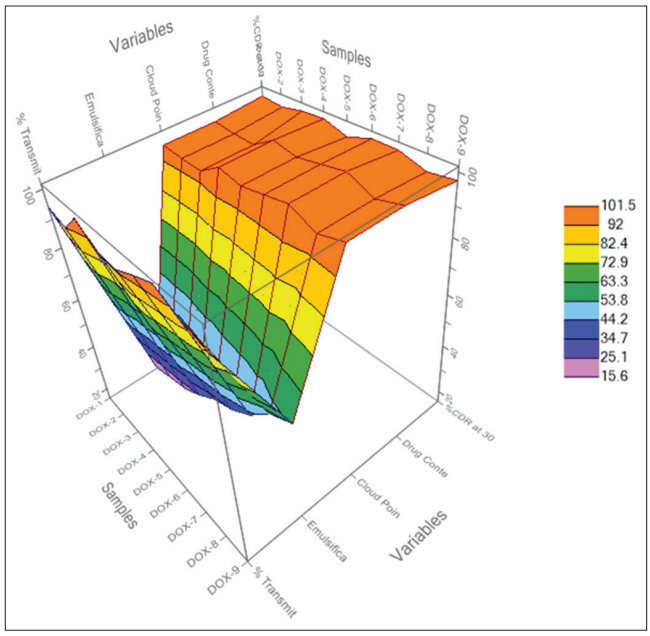

Figure 12: 3D matrix output for all the variables

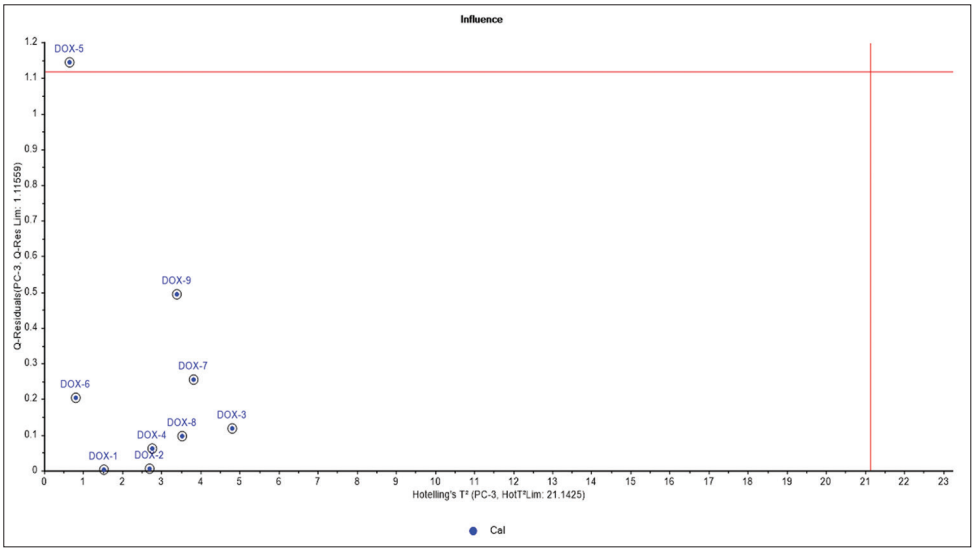

Figure 11: Influence Plot

DOX-5 is outliner (because the residual limit is 1.119 - it is above the limit); hence, it cannot be considered best-fit consider dangerous among all the batches. DOX-9 has good residual and average hoteling's value. Hence, DOX-9 could be considered for further studies [Figure 11].

3D matrix of all the variables

From 3D matrix plot of all the variables, one can conclude that emulsification time has a higher influence on all the variables [Figure 12].

Eigenvalue and PCA output

For the loan applicant data, it can be concluded that the first three principal components, accounts for best variability in data (given by the eigenvalue). The remaining principal components account for a very small proportion of the variability (close to zero) and are probably less important. The percentage coefficient of variance was nearly 100% for PC-3 to PC-5; hence, they easily removed from further analysis. On the other hand, for PC-1, 54.54% CV, and eigenvalue 2.674 were recorded. Hence, PC-1 was considered as best principal component [Figure 13a and b and Table 6].

The conclusion from the PCA

It was concluded that emulsification time and % cumulative drug release at 30 min were two most important variables which should be taking into account in the preparation of SMEDDS. Now, optimization was carried out using simplex centroid D-Optimal Design.

Table 6: Eigenvalue and percentage coefficient of variation for four different principal components

Principal Component	Eigenvalue	% coefficient of variation (%CV)
PC-1	2.674	53.54350259
PC-2	1.413	81.83705875
PC-3	0.78773	97.61036589
PC-4	0.10613	99.73548629

Statistical analysis of Docetaxel self-microemulsifying drug delivery system using the D-optimal mixture design

The D-optimal mixture design was used to optimize the SMEDDS formulation, Oleic Acid as a Lipid Phase (X1), Tween 80 as a surfactant (X2), and PEG-400 as Cosurfactant an (X3) were chosen as the independent variables. The mean emulsification time (Y1) and mean percentage of drug released in 30 min (Y2) were chosen as response variables because they were considered as critical factors for self-microemulsification to improve oral absorption of the poorly water-soluble drug. Lower emulsification time allows drugs to release controlled manner. Dissolution is a rate-limiting step for oral absorption of poorly water-soluble drugs, especially the drugs belongs to Class IV of BCS classification. Table 7 explained the independent variables (X values) and response variables (Y values). Where else Table 8 explained the D-Optimal Design and effect of X on Y variables.

Statistical design of emulsification time (Y1)

The Model F-value (885.79) of D-optimal model implies it is significant. Values of "Prob > F" <0.0500 indicate model terms are significant. In this case, X1, X3, X1X3, and X1X3(X1-X3) are significant model terms. Values >0.1000 indicate the model terms are not significant [Table 9].

Statistical design of percentage cumulative drug release at 30 min (Y2)

The D-optimal Model F-value of 421.317 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. Values of "Prob > F" l<0.0500 indicate model terms are significant [Table 10].

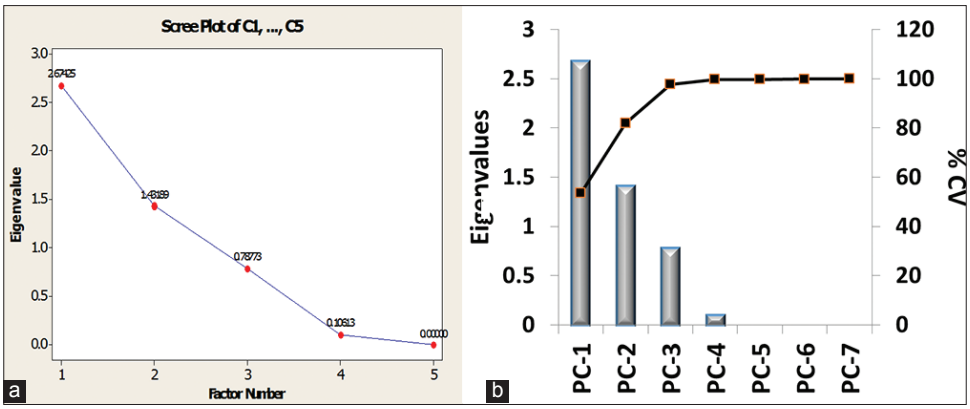

Figure 13: Eigenvalue analysis (a) eigenvalue versus factor number (b) relationship of eigenvalue with % coefficient of variance

Summary of statistical responses

From the statistical design, it was concluded that for Y1 and Y2 cubic model is suggested, because in both the cases adjusted R^2 value is nearby one, Predicted Residual Error Sum of Squares value is lowest [Table 11].

Influence of independent variables on emulsification time (Y1)

Following polynomial equation was constructed based on analysis of variance results, which signify the relationship between independent variables with emulsification Time (Y1)

$$\text{Emulsification Time (Y1)} = +22.75\ X_1 - 79.45\ X_2 + 42.094 X_3 + 148.98 X_1X_2 - 46.38 X_1X_3 + 127.30 X_2X_3 - 102.54 X_1X_2X_3 - 57.26\ X_1X_2(X_1-X_2) + 17.60\ X_1X_3(X_1-X_3) + 69.98\ X2X3(X_2-X_3) \quad (1)$$

From this equation, one can easily predict that oleic acid (X_1) has an agonistic effect on emulsification time, but X_1 coefficient was less + 22.75; hence, the oleic acid will have week agonistic effect on emulsification time. Where else X_2 (Tween-80)-Surfactant has a higher antagonistic effect on emulsification time because of its negative coefficient (−79.45). On the other hand, PEG-400 (Cosurfactant) would have a strong agonistic effect on emulsification time.

From this equation (1), it is also reviled that oil and surfactant combined concentration (X_1X_2) would have a strong agonistic effect on emulsification time. The oil and cosurfactant combined concentration (X_1X_3) causes decrease effect on emulsification time. However, the combined effect of only surfactant and cosurfactant causes an agonistic effect on emulsification time.

However, altogether oil-surfactant and cosurfactant combination cause a strong antagonistic effect on emulsification time ($X_1X_2X_3$). The D-optimal batch coefficient $X_1X_3(X_1-X_3)$ has shown significant $P = 0.0025$ and strong agonistic effect on emulsification time.

Interpretation of two-component mixture plot

From Figure 14a showing two-component oil and surfactant effect on emulsification time. Increase concentration of oil

Table 7: Variable used in D-optimal design

(Independent variables)	Unit	Component	Standard deviation	Upper limit	Lower limit
Oil (X1)	Parts	Oleic Acid	0	15	65
Surfactant (X2)	Parts	Tween-80	0	35	55
Cosurfactant (X3)	Parts	PEG-400	0	0	30
(Response variables)	Unit	Type	Standard deviation	Upper limit	Lower limit
Emulsification time (Y1)	Seconds	Response	0.119425	14.16	22.89
Cumulative drug release at 30 min (Y2)	%	Response	0.115392	92.82	99.56

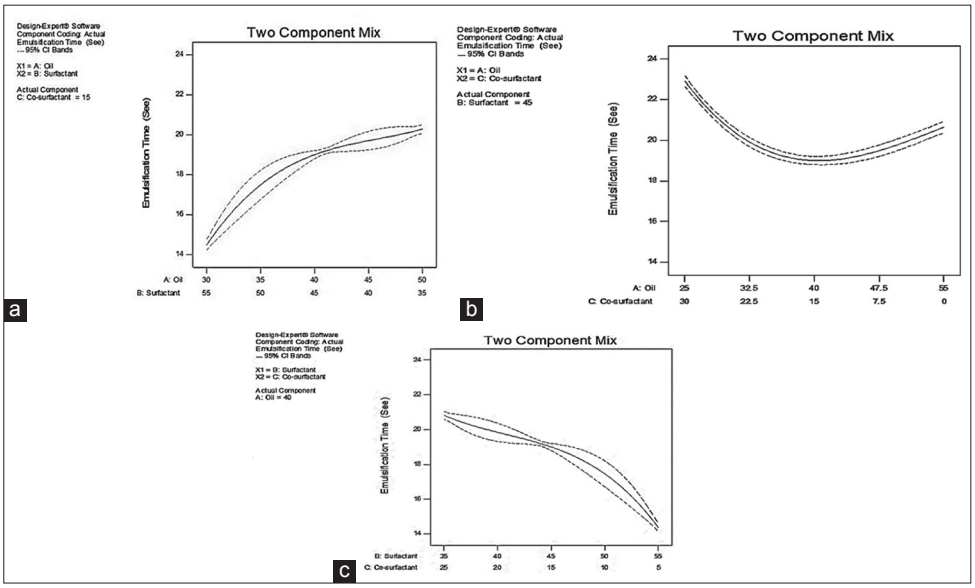

Figure 14: (a-c) Two-component mixture plot for the effect of varying ratio of two components with a prefixed amount of the other component. X1-Oil, X2-Surfactant, X3-cosurfactant; Y1, emulsification time

Table 8: The influence of D-optimal design output (16 batches) independent variables (X1 to X3) and independence variables (Y1andY2)

Batch	Oil (Oleic acid) (X1)	Surfactant (Tween 80) (X2)	Cosurfactant (PEG-400) (X3)	Emulsification time in second (Y1)	Percentage cumulative drug release at 30 min (Y2)
DOXP-1	65	35	0	22.75±0.05	92.82±0.03
DOXP-2	20.3451	55	24.6549	17.32±0.04	97.23±0.09
DOXP-3	32.78	45.436	21.784	19.71±0.08	95.21±0.01
DOXP-4	34.7027	55	10.2973	14.16±0.02	99.56±0.08
DOXP-5	23.5435	46.4565	30	22.89±0.08	93.68±0.04
DOXP-6	35	35	30	22.39±0.09	93.17±0.07
DOXP-7	45	55	0	14.88±0.03	99.23±0.06
DOXP-8	42.3813	43.3995	14.2193	19.06±0.05	95.55±0.05
DOXP-9	20.3451	55	24.6549	17.39±0.01	97.45±0.02
DOXP-10	42.3813	43.3995	14.2193	19.41±0.06	95.55±0.05
DOXP-11	65	35	0	22.75±0.05	92.82±0.03
DOXP-12	53.9782	35	11.0218	17.32±0.04	97.23±0.09
DOXP-13	42.3813	43.3995	14.2193	19.71±0.08	95.21±0.01
DOXP-14	23.5435	46.4565	30	14.16±0.02	99.56±0.08
DOXP-15	54.7492	45.2508	0	22.89±0.08	93.68±0.04
DOXP-16	43.2954	35	21.7046	22.39±0.09	93.17±0.07

Table 9: ANOVA analysis report on emulsification time (Y1) of D-optimal design

Source	Sum of squares	df	Mean square	F value	*P*-value Prob>F	Result
Model	113.7017	9	12.6333	885.7938	<0.0001	significant
Linear Mixture	74.1531	2	37.0765	2599.6074	<0.0001	significant
X_1X_2	0.0634	1	0.0634	4.4510	0.0794	Non- significant
X_1X_3	1.6433	1	1.6433	115.2199	<0.0001	significant
X_2X_3	0.0450	1	0.0450	3.1582	0.1259	Non- significant
$X_1X_2X_3$	0.0246	1	0.0246	1.7258	0.2369	Non- significant
$X_1X_2(X_1-X_2)$	0.0315	1	0.0315	2.2121	0.1875	Non- significant
$X_1X_3(X_1-X_3)$	0.3520	1	0.3520	24.683	0.0025	significant
$X_2X_3(X_2-X_3)$	0.0412	1	0.0412	2.8913	0.1400	Non- significant

Table 10: ANOVA analysis report on cumulative drug release at 30 min (Y2) of D-optimal design

Source	Sum of squares	df	Mean square	F Value	*P*-value Prob>F	Result
Model	64.888	9	7.209	421.317	<0.0001	Significant
Linear Mixture	49.756	2	24.878	1453.811	<0.0001	Significant
X_1X_2	0.017	1	0.017	1.0430	0.3465	-
X_1X_3	0.187	1	0.187	10.956	0.0162	-
X_2X_3	0.017	1	0.017	1.011	0.3534	-
$X_1X_2X_3$	0.009	1	0.009	0.544	0.4883	-
$X_1X_2(X_1-X_2)$	0.007	1	0.007	0.412	0.5446	-
$X_1X_3(X_1-X_3)$	0.001	1	0.001	0.103	0.7586	-
$X_2X_3(X_2-X_3)$	0.006	1	0.006	0.390	0.5552	-

and decrease surfactant concentration causes an increase of emulsification time. From Figure 14b, bit was also reviled that, the optimal concentration of oil (40 parts) and cosurfactant (15 parts) decrease emulsification time, but increase the concentration of oil and decrease the concentration of cosurfactant (0 parts) could increase emulsification time. From Figure 14c, it is clearly understood that decrease in cosurfactant concentration (5 parts) and an increase of surfactant concentration (55 parts) could cause a decrease in emulsification time. Besides, it is also confirmed that oil content had a significant effect on emulsification time.

2D counter plot for Y1

2D plot indicating that oil (35–65%) would have a huge impact on emulsification time. However, a lower concentration (35%) and higher oil concentration (65%), both would have negative impacts on emulsification time. Nevertheless, moderate oil concentration, i.e.,, 42-45% would have a good impact on lowering the emulsification time. As per the D-Optimal Design, the predicted emulsification time was found to be 18.559 seconds [Figure 15a]. Further, from real D-optimal mixture design, it is clearly indicating that the higher concentration of surfactant and moderate concentration of oil could influence emulsification time [Figure 15b].

Predicted versus actual design and 3D surface plot

This graph is talks about observed responses versus predicted responses the data points were mostly linear with 45◦ line, indicating best-fit model [Figure 16a]. From this 3D surface plot, one can predict that optimal emulsification time would be 118.599 seconds [Figure 16b].

From residual versus predicted plot, it can be assumed that one formulation (Run-12) is an outliner, rest of the runs are satisfies cubic model [Figure 17].

Influence of independent variables on cumulative drug release at 30 min (Y2)

Following polynomial equation was constructed based on analysis of variance results, which signify the relationship between independent variables with Cumulative Drug Release (Y2)

Cumulative Drug release (Y2) = +92.99X1+152.71X2+ 87.08X3-78.99X1X2+15.66X1X3 -78.91X2X3+ 63.10X1X2X3+27.07 X1X2(X1-X2) +1.24 X1X3(X1-X3)- 28.15X2X3(X2-X3)--- (2)

From equation (2), it has been observed that all the independent variables would have agonistic effect with cumulative drug release at 30 min, but the higher coefficient of surfactant concentration (X2)+152.71, indicates an increase of surfactant concentration could lead to increase in drug release. However, a combination of oil and surfactant concentration would have an antagonistic effect on cumulative drug release at 30 min (−87.99X1X2), moreover, oil and the cosurfactant combination could improve drug release (+15.66X1X3), where else a combination of surfactant and

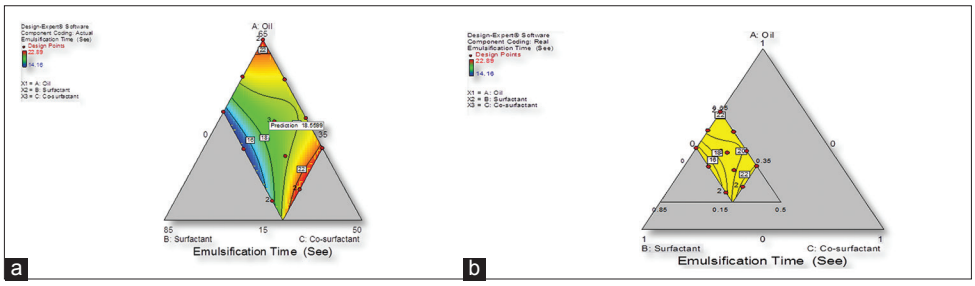

Figure 15: (a) 2D contour plot of emulsification time with oil, surfactant, and cosurfactant. (b). D-optimal mixture design for emulsification time (Y1)

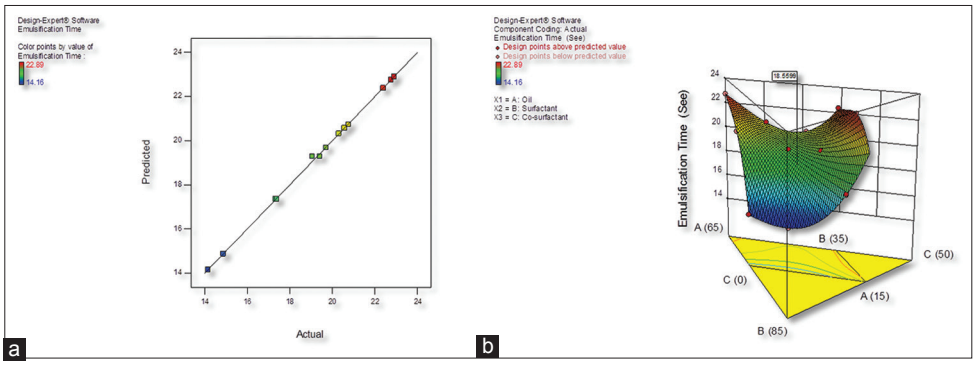

Figure 16: (a and b) Predicted versus actual graph and 3D surface plot against emulsification time

cosurfactant could decrease drug release (−78.91X2X3). However, altogether oil, surfactant and cosurfactant combination cause a strong agonistic effect on Percentage Cumulative Drug Release at 30 min (+63.10X1X2X3). From D-Optimal Design, it was concluded that X1X3 (X1-X3) could have a higher influence in percentage Cumulative Drug Release at 30 min.

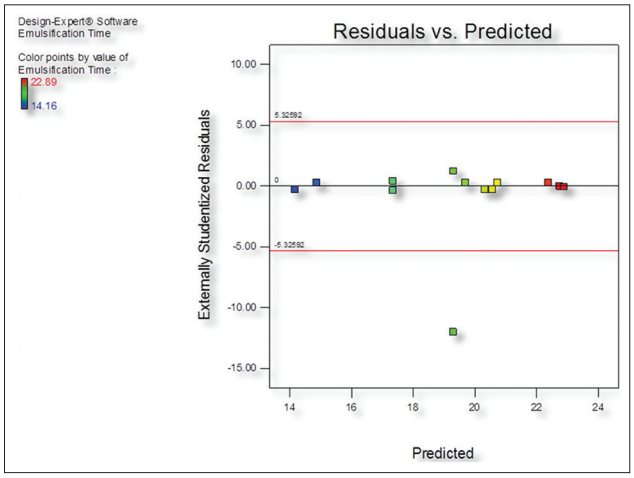

Figure 17: The serpent model of Residual versus Predicted model against externally standardized residual.

Two-component mixture plot on percentage cumulative drug release at 30 min

From Figure 18a, it is simply understood that increasing concentration oil and decrease the concentration of surfactant could lead to decrease in percentage cumulative drug release at 30 min. However, the concentration of oil above 40 and concentration surfactant above 45 could produce optimum drug release at 30 min. Figure 18b explained 40 parts of oil, 45 parts of surfactant, and 15 part of cosurfactant could produce optimal drug release at 30 min. From Figure 18c, one can easily predict that increasing concentration of surfactant and cosurfactant could lead to higher percentage of drug release, which is aisle [Figure 18].

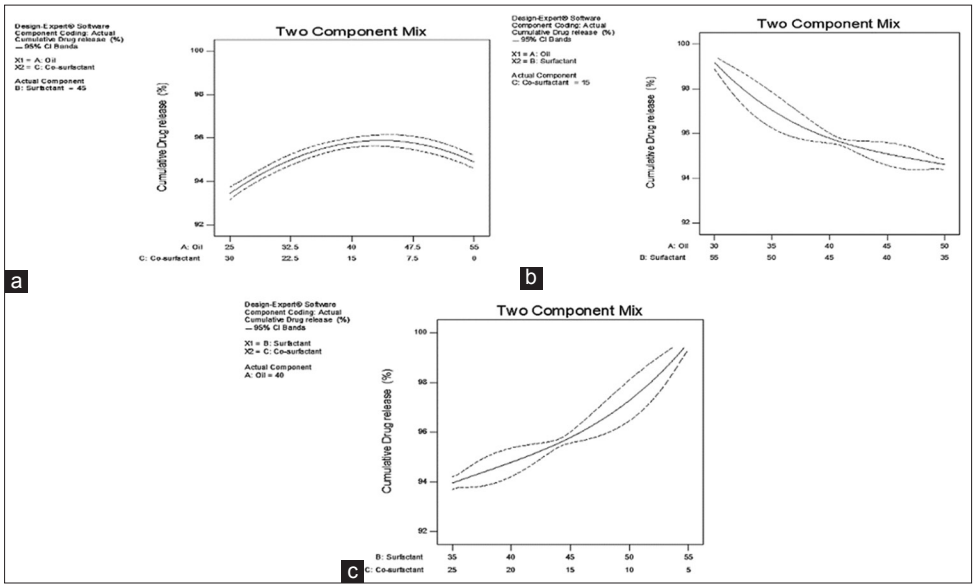

Figure 18: (a-c) Two-component mixture plot for the effect of varying ratio of two components with a prefixed amount of the other component. X1-Oil, X2-Surfactant, X3-Cosurfactant on Y2-% Cumulative Drug Released in 30 min

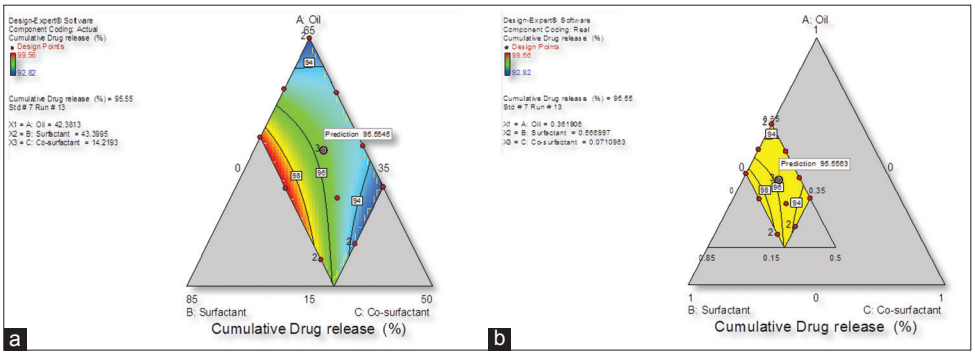

Figure 19: (a) 2D counterplot of cumulative drug release at 30 min (b) D-optimal mixture design for cumulative drug release (Y2)

Table 11: Summary of statistical response and model equation from the measurement

Models	Sequential the	Lack of Fit the	SD	R^2	Adjusted R^2 value	Adequate precision	PRESS Value	Remarks
Emulsification time (Y1)								
Linear	0.0011	<0.0001	1.75	0.6517	0.5981	-	61.96	
Quadratic	<0.0001	0.0292	0.25	0.9944	0.9915	-	1.42	
Special Cubic	0.3142	0.0262	0.25	0.9950	0.9917	-	1.75	
Cubic	0.0070	0.7803	0.12	0.9992	0.9981	92.429	0.69	Suggested
Cumulative drug release at 30 min (Y2)								
Linear	< 0.0001	< 0.0001	1.08	0.7656	0.7295		24.14	
Quadratic	0.9062	0.6533	0.13	0.9984	0.9961		1.91	
Special cubic	0.2237	0.9422	0.11	0.9983	0.9971		0.41	
Cubic	<0.0001	0.8593	0.12	0.9980	0.9969	92.868	0.39	Suggested

SD: Standard deviation, PRESS: Predicted residual error sum of squares

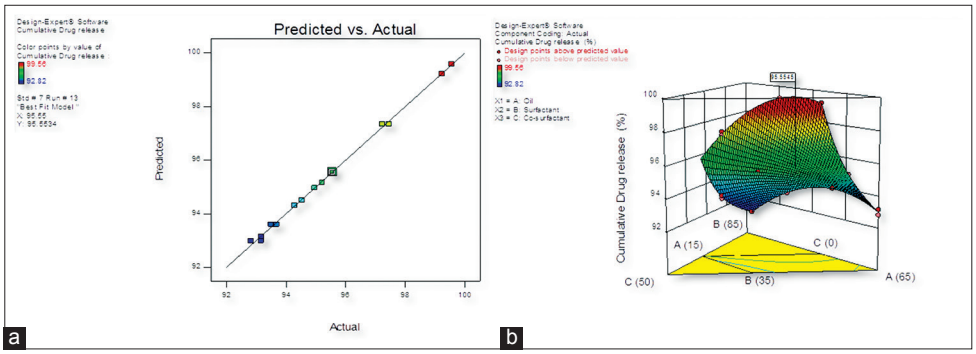

Figure 20: (a) Predicted versus actual (b) 3D Surface plot on percentage cumulative drug release at 30 min

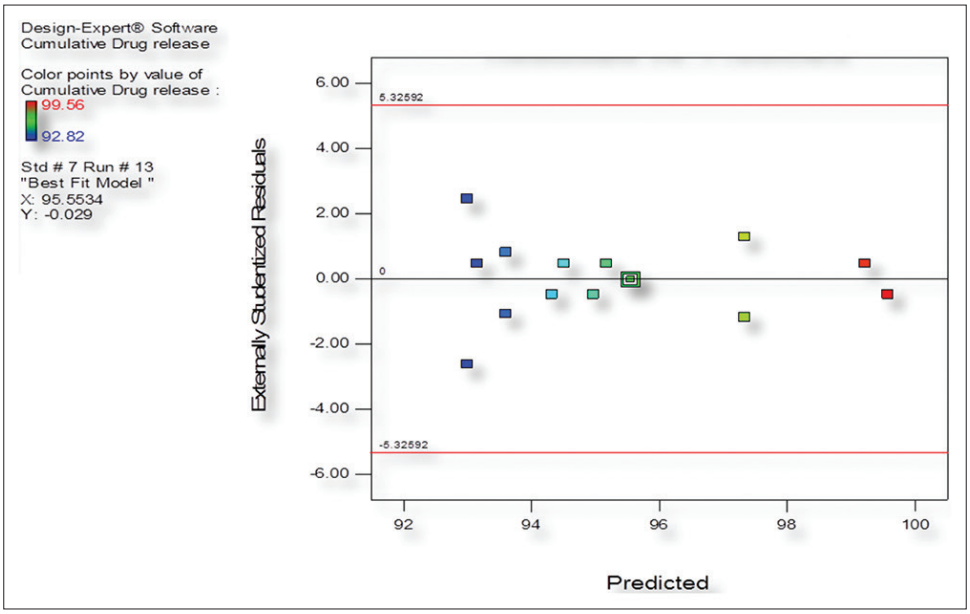

Figure 21: Residual versus predicted model

2D contour plot of cumulative drug release

This 2D counter plot indicating that oil (35–65%) would have a huge impact on cumulative drug release at 30 min. However, a lower concentration (red color shade - 35%) and higher oil concentration (in blue color shade - 65%), both would have negative impacts on cumulative drug release at 30 min. As per the design expert 10.0X software,

Table 12: Overall desirability study of DOXP-1 to DOXP-16 formulations

Batch	Oil (Oleic Acid) (X1)	Surfactant (Tween 80) (X2)	Cosurfactant (PEG-400) (X3)	Emulsification Time in second (Y1)	d1 (Using equation on 4)	Percentage cumulative drug release at 30 min (Y2)	d2 (Using equation on 5)	D (Overall Desirability)
DOXP-1	65	35	0	22.75	1.970	92.82	2	1.08873773
DOXP-2	20.3451	55	24.6549	17.32	1.274	97.23	1.414	1.037212066
DOXP-3	32.78	45.436	21.784	19.71	0.692	95.21	0.675	0.953988012
DOXP-4	34.7027	55	10.2973	14.16	−0.197	99.56	−0.108	0.788090389
DOXP-5	23.5435	46.4565	30	22.89	−7.0922	93.68	−2.921	1.206760072
DOXP-6	35	35	30	22.39	4.424	93.17	3.396	1.182964785
DOXP-7	45	55	0	14.88	5.089	99.23	5.75	1.232864407
DOXP-8	42.3813	43.3995	14.2193	19.06	0.872	95.55	0.788	0.977088178
DOXP-9	20.3451	55	24.6549	17.39	1.506	97.45	1.759	1.062295077
DOXP-10	42.3813	43.3995	14.2193	19.41	0	95.55	0	0
DOXP-11	65	35	0	22.75	0.032	93.16	−0.126	0.08621486
DOXP-12	53.9782	35	11.0218	20.75	−0.087	94.53	−0.349	0.805747716
DOXP-13	42.3813	43.3995	14.2193	19.41	0.5	95.55	0.664	0.994002206
DOXP-14	23.5435	46.4565	30	22.89	1.235	93.5	0.972	1.01144102
DOXP-15	54.7492	45.2508	0	20.57	1.110	94.96	0.987	1.005727334
DOXP-16	43.2954	35	21.7046	20.30	1.096	94.28	0.980	1.004456126

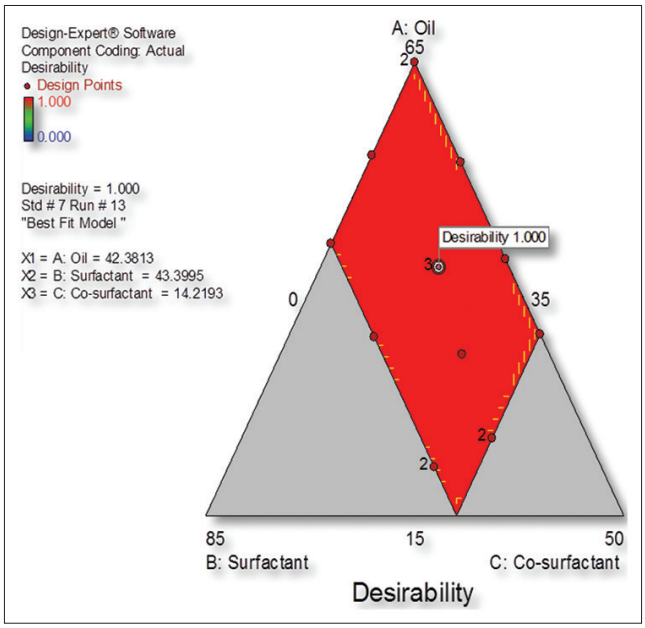

Figure 22: Desirability output

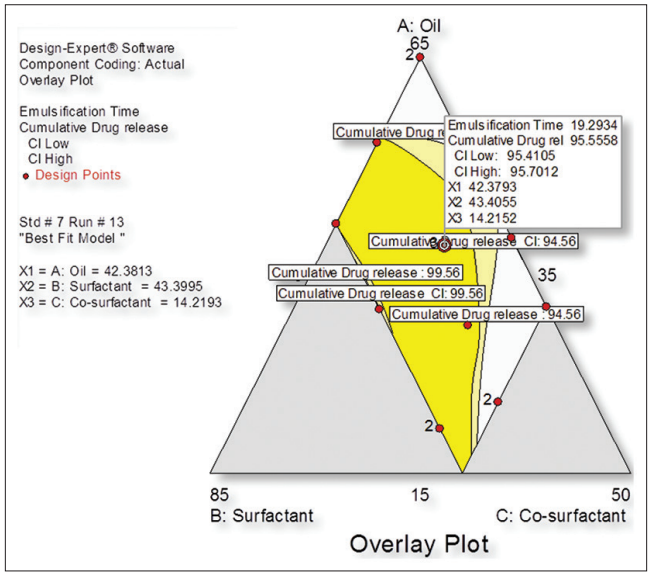

Figure 23: Overlay plot of experimental design batch

predicted Cumulative Drug Release with optimum oil concentration (42.38%) was found to be 95.55% at a 13th run [Figure 19a]. From real D-optimal mixture design, it is clearly indicating that the higher concentration of surfactant (0.566 Normalized Point) and moderate concentrations of oil (0.361 Normalized Point) could produce legitimate drug release [Figure 19b].

Predicted versus actual design and 3D surface plot

The predicted versus actual graph is talking about linearity observed responses with software predicted responses. The data points were mostly linear with 45° line, indicating best-fit model and as per software output, it was considered for a 13th run [Figure 20a]. From this plot, one can easily predict that optimum cumulative drug release at 30 min, as predicted 95.55% could be the best [Figure 20b].

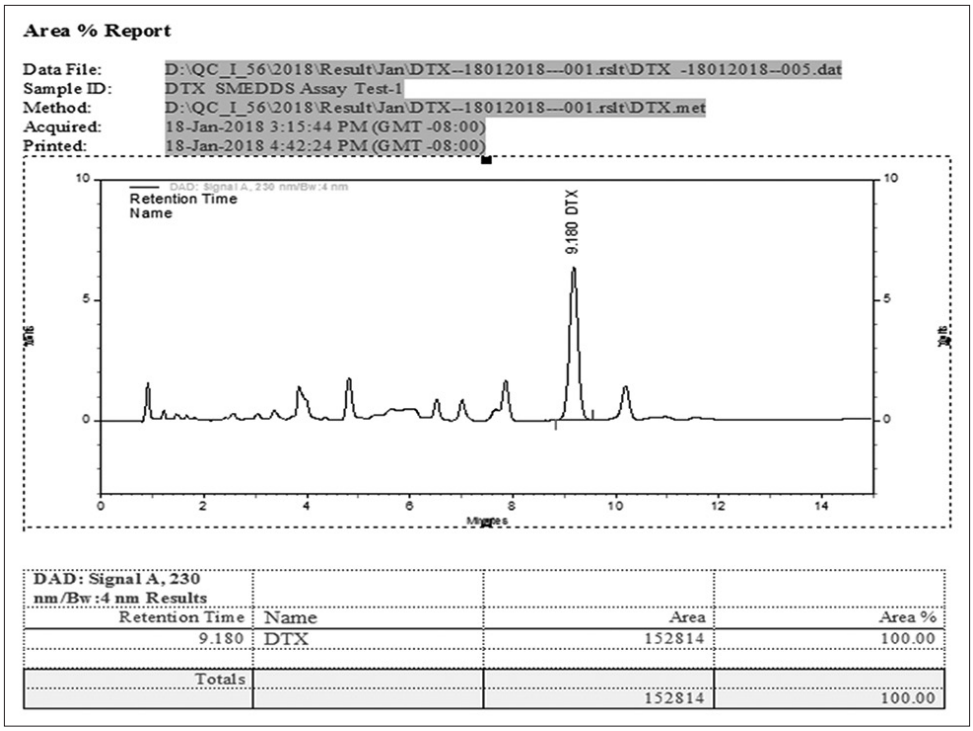

Figure 24: High-performance liquid chromatography assay of optimized formulation batch

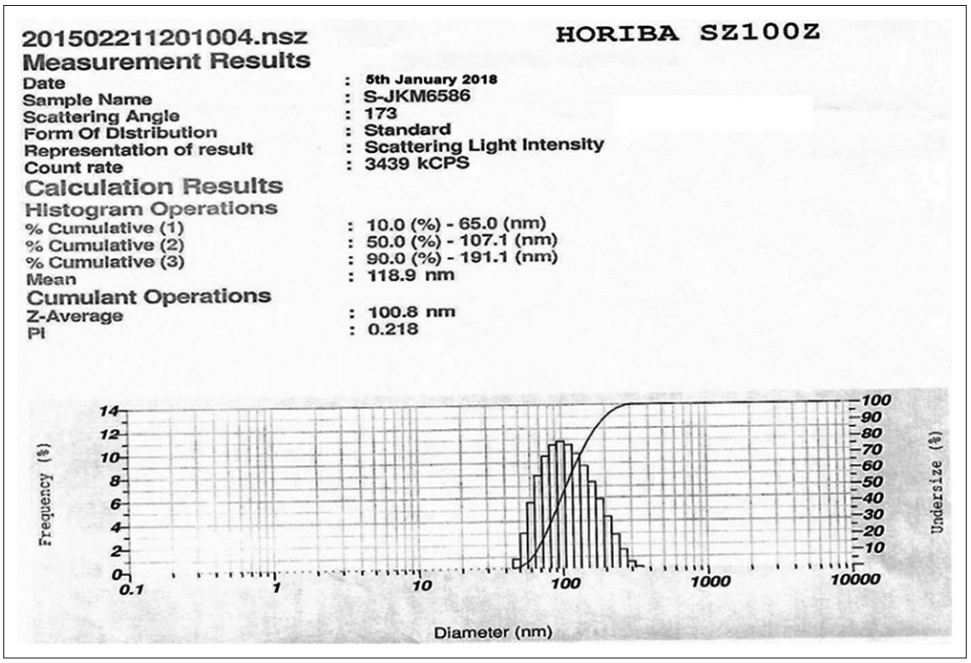

Figure 25: PDI and Z-average diameter of optimized batch of self-microemulsifying drug delivery system

Residual versus predicted plot

From the residual versus predicted plot one can easily conclude that run 13 is within the line, and consider as a best-fit model [Figure 21].

Optimization of SMEDDS formulation using desirability function

Desirability function used for optimizing independent variables. Independent variables such as Y_1 (emulsification time, need to be minimized), where else % cumulative drug release (Y2) at 30 min need to be maximized. After obtaining the desire polynomial equation (1 and 2), the optimization was carried out. The optimize concentration was found to be 42.38% oil, 43.39% surfactant, and 14.219% cosurfactant, respectively.

The desirability value d_i will be within the range of 0 (Less desirable) to 1 (most desirable). The value of d_i will either be

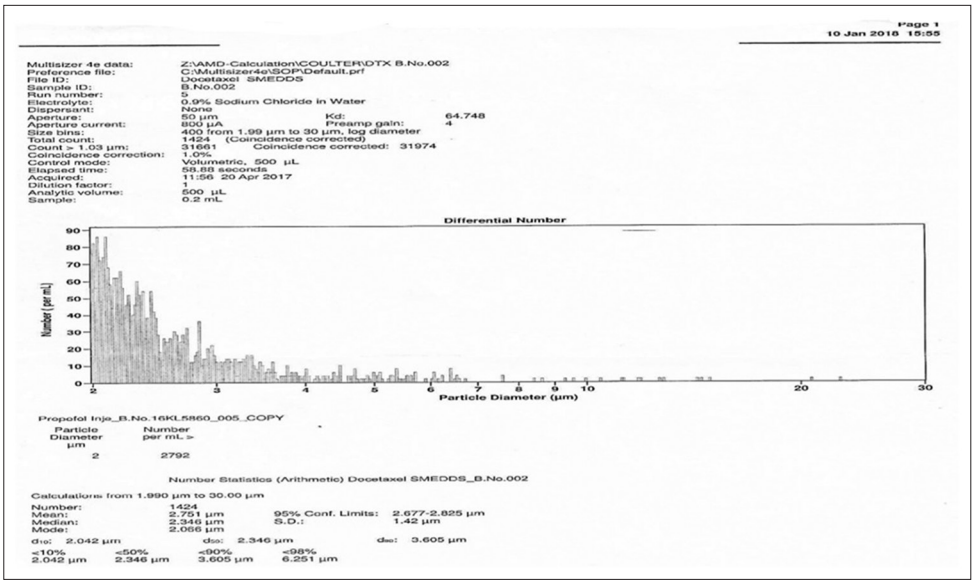

Figure 26: Measurement of Docetaxel SEMDDS optimized batch Droplet size using light scattering nicomp DLS system

Table 13: Comparative profile of independent variables of predicted and actual

Responses	Experimental value	Predicted value	Percentage prediction error (%)
Emulsification time (see)	20.74±0.156	19.29±0.52	6.99
% cumulative drug release	98.21±0.11	95.55±0.42	2.70

A calculated using the formula ([experimental value - predicted value]/experimental value) ×100 (%); values are presented as the mean±standard deviation (*n*=3)

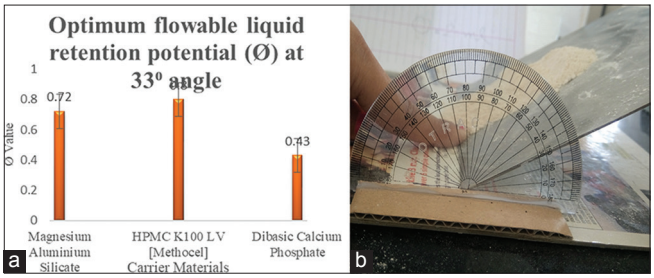

Figure 27: (a) Optimum flowable liquid retention potential study (b). The angle of slide determination

one direction or in two directions. Here is the list of equations:

$$di=\frac{Y_{max}-Yi}{Y_{max}-Y_{min}} \quad (3)$$

$$di=\frac{Yi-Y_{min}}{Ci-Y_{min}} \quad (4)\ (y\leq yi<ci)\ [\text{When we need minimum Y value}]$$

$$di=\frac{Yi-Y_{max}}{Ci-Y_{max}} \quad (5)\ (Ci<Yi\leq Y_{max})\ [\text{When we need maximum Y value}]$$

In this three equation, Y_{max} considered being as maximum desired value for the responses. Y_{min} is the minimum desired value of the responses obtained. Yi indicating batch wise experimental results. Ci indicates mean of upper and lower limit for the two side responses. The cumulative desirability defines as the geometrical mean of the entire di, which is calculated as:

$$D=\sqrt[n]{d1\times d2\times d3\ldots\ldots dn} \quad (6)$$

Where, n is the number of batches (*n* = 16)

Emulsification time for all DOXP1-16 was in the range of 14.16 to 22.89 second. Hence, Ci= 18.52. % Cumulative drug release at 30 min: All DOXP1-16 was in the range of 92.82 to 99.56%, hence, Ci=96.19. The optimum desirability of DOXP-13 was found to be 0.994002206 (Almost one), which is almost 1; hence, DOXP-13 is considered to be as an optimized batch [Table 12 and Figure 22].

Overlay Plot

After optimization, the validity of product response was measured by overlay plot. Busied on predicted responses from the DOXP-13 batch, one more trial batch was constructed, and results were compared with predicted responses [Table 13 and Figure 23]. As per the regulation, percentage prediction error must not be above 9%.

High-performance liquid chromatography (HPLC) studies of the optimized batch

HPLC studies were carried out to find the assay of prepared optimized SMEDDS. In this experiment, Agilent 1200 series HPLC with UV detector was used. Acetonitrile and water ratio of 60:40 were used as a mobile phase. C-18 (4.6 × 250 mm,

Table 14: Acceptable flowable retention potential of different carriers

Carrier	Weight of volume (ml)	Weight of solid (g)	Ø value	Angle of slide (°)	Optimum flowable liquid retention potential (Ø) at 33° angle
Magnesium aluminum silicate	0	1	0	20	0.72
	0.1	1	0.1	22	
	0.2	1	0.2	26	
	0.3	1	0.3	32	
	0.4	1	0.4	34	
	0.5	1	0.5	37	
HPMC K100 LV (Methocel)	0	1	0	23	0.80
	0.1	1	0.1	28	
	0.2	1	0.2	32	
	0.3	1	0.3	35	
	0.4	1	0.4	36	
	0.5	1	0.5	38	
Dibasic calcium phosphate	0	1	0	31	0.43
	0.1	1	0.1	36	
	0.2	1	0.2	37	
	0.3	1	0.3	42	
	0.4	1	0.4	45	
	0.5	1	0.5	48	

5µ pentafluorophenyl) was used as a column. The flow rate was maintained around 1.0 ml/min. The injection volume was considered up to 10µl, and operating temperature was maintained around 40°C. Docetaxel SMEDDS formulation assay results had shown 103.23% w/v recovery. The retention time was found to be 9.180 min [Figure 24].

Zeta potential and polydispersity index (PDI) studies on an optimized batch of SMEDDS

The PDI and zeta potential were measured using Malvern Zetasizer. The PDI indicates the sample width of a particle size distribution and zeta potential indicates a measurement of particle surface potential. Zeta potential near to isoelectric point could cause particle aggregation. In this experiment, zeta potential was found to be 0.034 mV, indicating positive zeta potential and lower then isoelectric point; hence, no chance of particle agglomeration was observed. The average zeta diameter was found to be 100.8nm and PDI was found to be 0.218 [Figure 25].

Droplet size determination using light diffraction method

The mean size of the SEMDDS droplet size measured using diffraction or dynamic light scattering Nicomp DLS method. Before initiate experiment, the performance of the system was verified with the pre-validated standard at 100, 250, and 400 nm. The coefficient of variance value was maintained <10% of the reference value. The sample was then diluted with 0.9% sodium chloride solution and measured at 90°. The Chi-square error calculation was checked. The intensity mean droplet size diameter was recorded [Figure 26], and it was found to be 2.346 µm (Limit is <500 µm).

Evaluation of the angle of the slide and flowable liquid retention potential for carrier selection

The prepared self-microemulsifying drug delivery system was shaped to LSC. The angle of slide measurement [Figure 27b] was performed of three carriers as Magnesium Aluminum Silicate, HPMC K100 LV (Methocel), and Dibasic Calcium Phosphate. Based on Ø value, HPMC K100 LV (Methocel) was selected as carrier material [Table 14]. The best optimum flowable liquid retention potential (Ø) was found to be 0.80 for HPMC K100 LV [Figure 27a]. The Ø Value of magnesium trisilicate [Coating material] was reported to be 0.54. After suitable calculation, the liquid load factor was found to be 0.8168, the number of carrier materials (Q) was found to be 122.735mg, amount of coating materials (q) used in LSC was found to be 3.835mg, respectively.

Formulation of Docetaxel loaded solid SMEDDS

Based on LSC studies, carrier and coating materials were calculated, pre-formulation and flow characteristics were studied [Table 15], and 250 mg tablets were prepared [Table 16].

Post-compression parameters

All the post-compression parameters were found to be within expectable limits [Table 17].

Compatibility study of Docetaxel loaded solid SMEDDS

Differential scanning calorimetry (DSC)

Figure 28a and b represents the thermal behavior of the pure docetaxel drug and thermal behavior of the solid-SMEDDS of docetaxel. Pure docetaxel shows less instance high width endothermic peak at 140.08°C, which interpreted as the pure drug is dehydrated. Now DSC Spectra of docetaxel solid SMEDDS shown no peak at 140.08°C, besides a hump peak was observed at 117.24°C, indicating that drug is partially converted into an amorphous form or present in the solubilized form. Near 300°C, there are some irregular humps in docetaxel solid SMEDDS spectra, which signify that liquid droplets were solidified. The partial disappearance of characteristic peak in solid-liquid compact batch, indicating drug gets completely dissolve in liquid-solid powder system. The drug gets molecularly disappear within liquid-solid system.

Table 15: Flow characteristic of solid SMEDDS

Characteristics	Results
Angle of repose(°)	32.50±0.07
Bulk density (g/ml)	0.35±0.03
Tapped density (g/ml)	0.4±0.05
Carr's Index	12.5±0.07
Hausner's Ratio	1.14±0.12

SMEDDS: Self-microemulsifying drug delivery system

Table 16: Formula for Docetaxel loaded solid SMEDDS

Ingredient	Use	Quantity
Docetaxel Optimized SMEDDS	Liquid Medicament	100.25
HPMC K100 LV	Carrier	122.735
Magnesium Tri Silicate	Coating agent	3.835
Sodium Starch Glycolate	Superdisintegrant	7.5
MCC (Avicel FD-100)	Diluent	10.68
Magnesium stearate	Lubricant	5
	Total	250 mg

SMEDDS: Self-microemulsifying drug delivery system

Fourier-transform infrared (FTIR) study of Docetaxel loaded solid SMEDDS

As per the FTIR spectra of Pure Docetaxel [Figure 29a], N-H stretch was observed in 3378 cm^{-1}, O-H stretch due to carboxylic acid was observed at 2981 cm^{-1}, -C=O anhydrous ketone stretch was observed at 1737 cm^{-1} and 1712 cm^{-1}, and the aromatic stretch C=C stretch was observed at 1497cm^{-1}. This spectra confirmed that Docetaxel is stable and in anhydrous form. From Figure 29b (Docetaxel solid SMEDDS), it was confirmed that no characteristic shift was observed in final formulation against of Docetaxel pure drug; hence, the drug has no compatibility issue with final formulation.

In vitro dissolution studies of final Docetaxel solid SMEDDS formulation

An *in vitro* dissolution study was performed for LSC tablet and the profile was compared with Docetaxel pure drug and optimized SMEDDS formulations [DOXP13] dissolution profile. For dissolution, 0.01N HCl was used as dissolution

Table 17: Post-compression parameters of solid-solid SMEDDS

Parameters	Value
Weight variation (mg)	Pass
Hardness (kg/cm^2)	7±0.03 kg/cm^2
Thickness (mm)	8±0.06 mm
Disintegration time (min)	42±0.20
Drug content (%)	98.13
Friability (%)	0.7

SMEDDS: Self-microemulsifying drug delivery system

Table 18: % cumulative drug release profile of pure drug, DOXP13, and LSC-Tab

% Cumulative drug release			
Time (min)	Pure drug	DOXP13	LSC-Tab
5	0.15±0.02	9.43±0.03	34.75±0.03
10	1.16±0.28	77.11±0.38	65.88±0.09
15	10.25±0.02	80.28±0.38	82.78±0.38
20	12.35±0.39	84.33±0.19	95.26±0.38
25	20.87±0.27	92.66±0.93	95.98±0.11
30	23.59±0.03	95.55±0.33	96.62±0.36
35	25.48±0.61	97.18±0.18	97.02±0.83
40	27.28±0.82	98.76±0.39	97.87±1.38
45	30.21±0.03	100.10±0.53	98.24±0.38
50	31.62±0.92	-	98.93±0.83
55	33.38±0.02	-	99.81±0.19
60	35.51±0.04	-	100.39±0.39

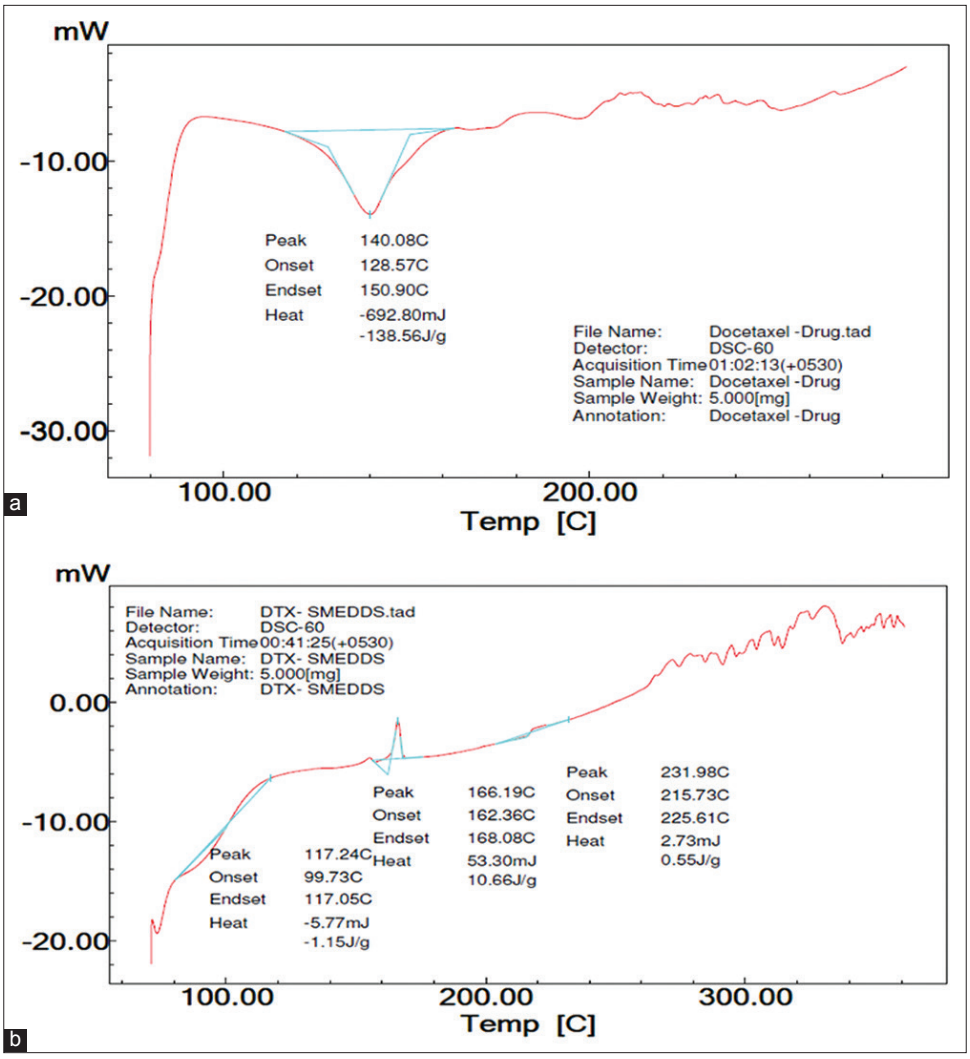

Figure 28: (a) Differential scanning calorimetry (DSC) spectra of Docetaxel (b) DSC Spectra of Docetaxel solid self-microemulsifying drug delivery system

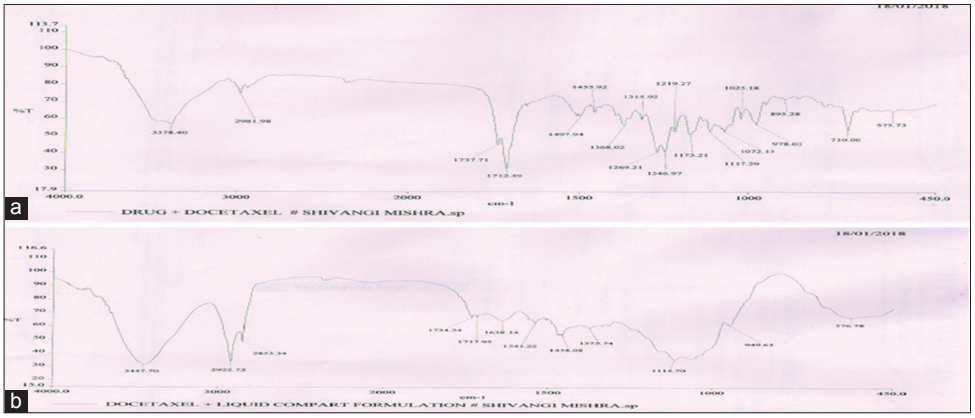

Figure 29: (a) Infrared (IR) spectra of Docetaxel pure drug (b) IR spectra of Docetaxel solid self-microemulsifying drug delivery system formulation

medium. In USP Type II dissolution apparatus 50-RPM speed and the 37±0.5°C temperature was maintained during this study. The study was planned for 60 min, and every 5 min 5 ml sample was withdrawn, and 5ml of fresh buffer was reintroduced in the system. The withdrawn 5 ml sample was filtered with Whatman filter paper and after suitable dilution; absorbance was taken at 230 nm in UV-Visible spectrophotometer. The amount of drug present in the

Table 19: Evaluation parameters during accelerated stability study for LSC-Tab

Evaluation parameters	Initial	After 15 days	After 30 days
Hardness (Kg/cm^2)	7±0.03	7.2±0.12	8.2±0.13
Drug content (%)	98.13±0.19	96.18±0.11	95.11±0.39
Disintegration time (min)	42±0.20	45.18±0.22	48.11±0.12
% Cumulative drug release at 60 min	100.39±0.39	102.93±0.13	103.19±0.13

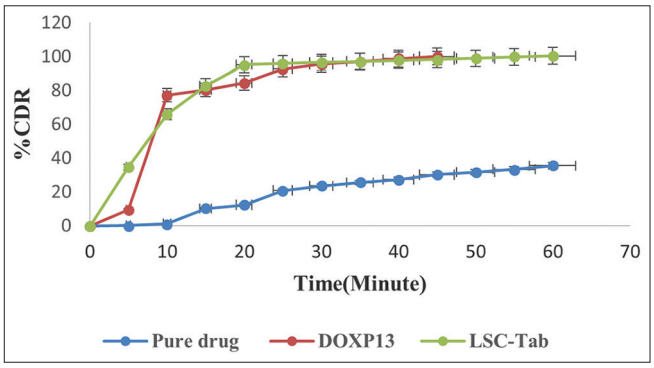

Figure 30: *In vitro* dissolution profile of Docetaxel pure drug, DOX13 and liquid-solid compact -tab accelerated stability study

filtrate then calculated from the calibration curve equation and cumulative percent of drug release was calculated. The result reviled that dissolution enhanced for LSC tablet as compare with pure drug and DOXP13 formulation; this might be due to solubilization of the drug in the non-volatile solvent. Cumulative drug release of pure drug after 60 min of the study was found to be 35.51 ± 0.04%, where else DOX13; the optimized batch shown 100.10 ± 0.53% drug release at 45 min. Nevertheless, LSC-Tablet shown improve dissolution profile and shown 100.39 ± 0.39% drug release after 60 min. Hence, it can be concluded that liquid-solid compact formulation/solid SEMDDS (LSC-Tab) would have extensive dissolution profile [Table 18 and Figure 30].

The accelerated stability study was planned for 1 month for LSC-Tab. The stability condition was maintained around 40 ± 2°C/75 ± 5% RH, respectively, at room temperature. Time to time hardness, drug content, disintegration time, and % cumulative drug release were measured and reported [Table 19].

CONCLUSION

Solid self-emulsifying drug delivery system of Docetaxel was prepared by LSC technique. Using pseudoternary plot diagram best possible SMEDDS formulations were screened. Furthermore, by PCA and D-Optimal Design provides best possible SMEDDS formulations. This liquid formulation was then converted into 250 mg tablets. With this approach enhancement of *in vitro* dissolution profile was increased for Docetaxel. Thus, solid SMEDDS formulation (LSC-Tab) can be considered as a novel and commercially feasible approach for increasing dissolution and solubility of Docetaxel.

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