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Design, development and optimization of self-nanoemulsified drug delivery system for poorly water-soluble drug by QbD approach

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ABSTRACT

The objective of the present study was to develop SNEDDS containing a poorly water-soluble drug by application of QbD principles. Two statistical designs were used to systematically understand the effect of various formulation variables in the development of SNEDDS. Initially, PB design was used as a screening design to identify the significant effect of six independent variables on the characteristics (globule size (nm), self-emulsification time (sec) and percent dissolution efficiency at 15min) of SNEDDS. Statistical results suggested oleic acid as a type of oil, Cremophor EL as a surfactant and Trancutol HP as co-surfactant but their respective amount in the isotropic mixture was found to in wider range. This allowed us to utility CCD to identify the optimal design space between the amount of oleic acid (X_1), surfactant (X_2) and co-surfactant (X_3). The dependent variables studied were globule size (Y_1) and self-emulsification time (Y_2) and were fitted to the second-order quadratic model. A numerical optimization technique by desirability function was used to identify the optimal design space. The results demonstrate the feasibility of the model in the development of SNEDDS and the same can be extrapolated to other poorly water-soluble drugs.

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INTRODUCTION

The BCS (Biopharmaceutical Classification System) is a scientific framework for the classification of drug substances based on their aqueous solubility and intestine permeability (Amidon *et al.,* 1995). A large number of drugs in the market and even those in the pipeline (new NCE/API) are poorly water-soluble and may belong to either class II or IV of BCS. These drugs are hydrophobic and exhibit poor aqueous solubility, dissolution and bioavailability when administered orally through conventional dosage forms. Since the rate limiting step for poorly soluble drugs is dissolution rate and any alteration in dissolution rate result in a large effect on bioavailability (Hauss, 2007; Fahr and Liu, 2007; Williams *et al.,* 2003). Thus, an increase in solubility and dissolution rate of poorly water-soluble drugs will be a great challenge for the formulation scientist for improving the bioavailability and therapeutic efficacy of these drugs.

Many formulation strategies have been exploited to overcome the above issues, such as pH adjustment (Stephenson *et al.,* 2011) and prodrug design (Stella, 2010) (chemical methods) and whereas modification of solid state (Blagden *et al.,* 2007; Pudipeddi and Serajuddin, 2005), micronization (Liu *et al.,* 2006; Mosharraf and Nystrom, 1995), complexation (Loftsson and Brewster, 1996; Brewster and Loftsson, 2007) and lipid-based drug delivery

system (physical methods). Among all, lipid-based drug delivery system is one of the most popular approaches to improve dissolution and bioavailability of poorly water-soluble drugs (Saroy *et al.,* 2012; Porter *et al.,* 2007). Lipid-based drug delivery system offers a variety of options like emulsions, vesicular systems and lipid particulate systems (Pouton and Porter 2008). Under emulsions, self-emulsified drug delivery system has been successful commercially, and it consists of an isotropic mixture of drug, lipid, surfactant, co-surfactant which generate oil in water micro/nanoemulsion when exposed to GI fluids (Date and Nagarsenker, 2007; Gursoy and Benita, 2004).

QbD is a systematic, holistic and proactive approach that begins with predefined objectives and emphasises product and process understanding and process control in the development of pharmaceutical product development. QbD also helps us to understand the effect of various factors, their possible interactions and identification of optimal formulation composition utilizing design of experiments as one of the tools (Yu, 2008; Woodcock, 2004; Shivhare and McCreath, 2010).

Ritonavir is an HIV protease inhibitor indicated for the treatment of AIDS. It is practically insoluble in water and may potentially exhibit dissolution rate limited absorption (Robert and Richard, 2004). Thus in the present research work, an attempt was made to develop SNEDDS containing ritonavir as a poorly water-soluble model drug. Initially, screening studies were performed by using Plackett-Burman design to identify few significant factors out of the large set. Further, to identify an optimal condition/design space of multivariable system an efficient strategic experimental tool response surface methodology (RSM) was used.

MATERIALS & METHODS

A pharmaceutical grade of Ritonavir was a generous gift from M/s Strides Arco labs, Bangalore, India. Capmul® MCM and Captex® 355 EP from Abitec Corp., Janesville,

The USA. Pentaerythritol tetra caprylate tetra caprate (PTCTC), coco caprylate and caprate (CCC), Hariol® 538, Trimethylolpropane tricaprylate tricaprate (TPTT), Propylene glycol dicaprylate dicaprate (PGDD) from Subhash Chemical industries, Pvt. Ltd. Maharastra, India. Cremophor EL® (polyoxy 35 castor oil) from BASF Co. Germany. Transcutol HP® (diethylene glycol monoethyl ether) from Gattefosse Co. Lyon, France. Brij®35 from Sigma Aldrich, India. Ethyl oleate, linseed oil, sunflower oil, soyabean oil, isopropyl myristate, olive oil, rice bran oil, corn oil, oleic acid, Tween 20, Tween 60, Tween 80, Propylene glycol, polyethylene glycol 400 and 600, from Himedia Lab. Private Ltd., Mumbai, India. All the chemicals used were of analytical grade and were purchased from a local supplier.

Solubility studies

The solubility of Ritonavir in various oils, surfactants and co-surfactants was determined by shake flask method. Briefly, an excess amount of drug was added into each vials containing 2 mL of each of oils, surfactants and co-surfactants separately and vortexed for three minutes to get a homogeneous mixture. All the samples were shaken for 48 h at 30±0.5°C in a thermostatically controlled shaking water bath (Labline Equipments PVT. Ltd, model 05T.24C) and further kept for 24 h at room temperature to reach equilibrium. The equilibrated samples were then centrifuged at 3000 rpm for 15 min, and the supernatant liquid was diluted with methanol and drug concentration was subsequently quantified by UV-spectrophotometric method (UV-1601, Shimadzu, Japan).

Experimental Design

Screening design [Plakett-Burman design (PB design)]

To determine the variables that may have a significant effect in the development of SNEDDS, a PB design as screening design was used. The critical material attributes (CMAs) considered for this study were distinguished as categorical and numerical factors which were selected based on the results of solubility studies. As a categorical factors type of oil, surfactant and cosurfactant were included and as a numerical factors amount of oil, surfactant and cosurfactant were considered. Globule size (nm), self-emulsification time (sec) and percent dissolution efficiency at 15min were considered as critical quality attributes (CQAs).

The levels of six independent variables are as follows:
X_1= Type of oil (Oleic acid -Capmul MCM)
X_2= Amount of Oil (100- 500mg)
X_3= Type of Surfactant (Tween 80- Cremophor EL)
X_4= Amount of surfactant (100- 450mg)
X_5= Type of Co-surfactant (PEG 400-Transcutol HP)
X_6= Amount of Co-surfactant (50- 450mg)
The response variables tested include:
Y_1 = Globule size (nm)
Y_2 = Self-emulsification time (sec)
Y_3 = Percent dissolution efficiency 15min ($\%DE_{15min}$)

Response surface methodology [Central composite design (CCD)]

To find out the optimal level or design space of the selected variables from PB design and to study

their interactions, RSM using central composite design (face-centred of alpha 1) was applied. According to the model, it contains 2^3 factorial designs with six-axial and two centre points making it to 16 ex- periments.

The three independent variables studied include:
X_1= Amount of Oleic acid (400- 500mg)
X_2= Amount of Cremophor EL (100- 125mg)
X_3= Amount of Transcutol HP (50- 70mg)
The response variables tested include:
Y_1 = Globule size (nm)
Y_2 = Self emulsification time (sec)

Formulation of SNEDDS

Ritonavir loaded SNEDDS were prepared by adding ritonavir (50mg) to the isotropic mixture of oil, surfactant and co-surfactant at the predetermined amount as per the design. This isotropic mixture was vortexed and followed by sonication for 5min to get a transparent clear solution. The prepared formulations were equilibrated in a water bath at 37 ± 0.5^{0}C for 24hrs prior to characterisation studies.

Characterisation of SNEDDS

Measurement of globule size: Aliquots (100µL) of each formulation was diluted 100 times with distilled water in a beaker maintained at 37^{0}C and gently stirred on a magnetic stirrer. The globule size was measured by dynamic light scattering technique using ZetaPALS (Brookhaven Instruments Corporation, NY).

Self-emulsification time: Self-emulsification time (SET) was carried out by using USP type II dissolution apparatus (TDT-06T, Electrolab, India) containing distilled water as a medium. An aliquot (0.5ml) of each formulation was added dropwise to distilled water (500ml) which was maintained at 37^{0}C $\pm$ 0.5^{0}C under continuous stirring at 50rpm. The time required in seconds to obtain a uniform dispersion was recorded as the SET.

In vitro dissolution studies

In vitro dissolution studies for all the SEDDS were performed by using USP dissolution apparatus II paddle assembly (TDT-06T, Electrolab, India) at 37^{0}C $\pm$ 0.5^{0}C using 500ml of pH 1.2 buffer. The rotational paddle speed was set to 50rpm. Aliquots samples were withdrawn at specified time intervals, and the samples were analysed spectrophotometrically (UV-1601, Shimadzu, Japan) and the amount of drug released was determined from the calibration curve. The magnitude of dissolution efficiency at 15 min ($\%DE_{15\ min}$) for each formulation was computed as the percent ratio of area under the dissolution curve up to that time't' to that of the area of the rectangle described by 100% dissolution at the same time point and is defined as follows (Khan, 1975):

$$\%DE = \frac{AUC_o^T}{Q_{100T}}$$

Regression analysis

The effect of formulation variables on the response variables was statically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design-Expert® version 6.05 (Stat-Ease, Inc.). The design was evaluated by using a suitable model. The best fit model was selected based on the several statistical parameters including multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS). For the model to be chosen as best fit, the PRESS valve should be small relative to the other models.

PB design was evaluated by the linear model

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 \ldots\ldots b_6 X_6$$

RSM was evaluated by the quadratic model, to describe the response surface curvature

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_1^2 + b_5 X_2^2 + b_6 X_3^2 + b_7 X_1 X_2 + b_8 X_1 X_3 + b_8 X_2 X_3$$

Where Y is the response variable, b_0 the constant and b_1, b_2, b_3 …. b_8 is the regression coefficient. X_1, X_2 and X_3 stand for the main effect; X_1X_2, X_1X_3 and $X_2 X_3$ are the interaction terms, show how response changes when two factors are simultaneously changed. X_1^2, X_2^2 and X_3^2 are quadratic terms of the independent variables to evaluate the nonlinearity

RESULTS AND DISCUSSION

Solubility studies

The solubility of ritonavir was tested in various oils, surfactant and cosurfactant by shake flask method and the results are presented in Fig. 1. Amongst the various oils studied, maximum ritonavir solubility was observed in oleic acid with 80.52 ± 5.76mg/ml and Capmul MCM 79.09 ± 6.37mg/ml. High solubility in oleic acid may be due to long-chain fatty acid and help in the absorption of poorly soluble drugs through lymphatic pathway bypassing hepatic first-pass effect (Bandyopadhyay *et al.,* 2012). Whereas high solubility of the drug in Capmul MCM id due to lipophilic nature of esterified medium-chain mono//diglycerides and also exhibit better self-dispersing ability (Constantinides, 1995). Amongst the various surfactants screened maximum solubility was observed in Cremophor EL and Tween 80 with 236.18

Table 1: Design matrix as per Placket-Burman design along with response variables

Formulation code	X_1 Type	X_2 mg	X_3 Type	X_4 mg	X_5 Type	X_6 mg	Y_1 nm	Y_2 sec	Y_3 %
P1	C-MCM	100	C-EL	100	PEG 400	50	225	214	34.23
P2	C-MCM	500	T80	450	PEG 400	50	320	289	12.63
P3	OA	500	C-EL	100	Transcutol	50	184	153	42.88
P4	C-MCM	100	C-EL	450	PEG 400	450	280	152	32.89
P5	C-MCM	500	T80	450	Transcutol	50	340	218	21.43
P6	C-MCM	500	C-EL	100	Transcutol	450	225	93	43.45
P7	OA	500	C-EL	450	PEG 400	450	264	155	34.93
P8	OA	100	C-EL	450	Transcutol	50	302	142	43.32
P9	OA	100	T80	450	Transcutol	450	226	202	28.74
P10	C-MCM	100	T80	100	Transcutol	450	211	231	27.32
P11	OA	500	T80	100	PEG 400	450	168	252	18.45
P12	OA	100	T80	100	PEG 400	50	194	317	19.45

C-MCM=Capmul MCM, OA=Oleic acid, C-EL= Cremophor EL, T80= Tween80

Table 2: Statistical values along with estimated coefficient values for six variables on three response variables as per Plackett-Burman design

Factors	Y_1			Y_2			Y_3		
	F value	Coefficient	P value	F value	Coeff-cient	P value	F value	Coefficient	P value
X_1	20.22	21.92	0.0020	-	-	-	35.29	-1.32	0.0019
X_2	-	-	-	6.89	-8.17	0.0393	20.92	-1.02	0.0060
X_3	-	-	-	258.25	-50.00	<0.0001	1515.66	8.64	<0.0001
X_4	80.59	43.75	<0.0001	7.46	-8.50	0.0341	19.77	-0.99	0.0067
X_5	-	-	-	82.93	-28.33	<0.0001	419.72	4.55	<0.0001
X_6	10.67	-15.92	0.0114	44.12	-20.67	0.0006	19.77	0.99	0.0067

Table 3: Central design matrix along with response variables

Formulation code	Type	X_1	X_2	X_3	Y_1nm	Y_2sec
C1	Fact	-1	-1	-1	152	156
C2	Fact	1	-1	-1	255	214
C3	Fact	-1	1	-1	154	162
C4	Fact	1	1	-1	283	247
C5	Fact	-1	-1	1	240	196
C6	Fact	1	-1	1	257	206
C7	Fact	-1	1	1	95	117
C8	Fact	1	1	1	159	162
C9	Axial	-1	0	0	142	164
C10	Axial	1	0	0	243	231
C11	Axial	0	-1	0	146	123
C12	Axial	0	1	0	113	117
C13	Axial	0	0	-1	136	147
C14	Axial	0	0	1	129	139
C15	Center	0	0	0	135	142
C16	Center	0	0	0	126	128

±12.37mg/ml and 216.55 ±7.33 mg/ml respectively. High solubility in Cremophor EL and Tween 80 may be attributed due to characteristic amphiphilic nature and a high HLB value of more than 12 (Cannon, 2011). Similarly, among the co-surfactant Transcutol HP and PEG 400 exhibited maximum solubility with 168.23±14.05mg/ml and 157.11 ± 6.19mg/ml respectively. Based on the results of solubility studies Capmul MCM and oleic acid as type oil, Cremophor EL and Tween 80 as a type of surfactant and Transcutol HP and PEG 400 as a type of co-surfactant were selected for further studies.

PB design

In order to screen the variables such as the type of oils, surfactants and co-surfactants along with their respective amount in the development of SNEDDS a Plackett-Burman design was adopted.

Table 4: Summary of ANOVA results in analysing

Source	Sum square	d.f.	Mean square	F value	Prob > F
Globule size (nm) (Y_1)					
Model	54016.62	9	6001.85	61.89	< 0.0001*
Residual	581.82	6	96.97026	-	-
Lack of Fit	541.32	5	108.2643	2.673193	0.4325 ns
Pure Error	40.50	1	40.5	-	-
Cor Total	54598.44	15	-	-	-
Self-emulsification time (sec) (Y_2)					
Model	25040.38	9	2782.26	37.51	< 0.0001*
Residual	445.06	6	74.18	-	-
Lack of Fit	347.06	5	69.41	0.71	0.7119ns
Pure Error	98.00	1	98	-	-
Cor Total	25485.44	15	-	-	-

* = Significant (p< 0.05); ns = non-significant; d.f.= degree of freedom

Table 5: Summary of ANOVA table for dependent variables from CCD

Source	d.f.	Sum square	Mean square	F value	Probability
Y_1= Globule size (nm) R^2 = 0.9893					
X_1	1	17139.60	17139.60	61.89	< 0.0001
X_2	1	6051.60	6051.60	176.75	< 0.0001
X_3	1	1000.00	1000.00	62.41	0.0002
X_1^2	1	10944.49	10944.49	10.31	0.0183
$X_1 X_2$	1	666.13	666.13	6.87	0.0395
$X_1 X_3$	1	2850.13	2850.13	29.39	0.0016
$X_2 X_3$	1	9316.13	9316.13	96.07	< 0.0001
Y_2= Self-emulsification time (sec) R^2 = 0.9825					
X_1	1	7022.50	7022.50	94.67	< 0.0001
X_2	1	810.00	810.00	10.92	0.0163
X_3	1	1123.60	1123.60	15.15	0.0081
X_1^2	1	9236.28	9236.28	124.52	< 0.0001
X_2^2	1	883.89	883.89	11.92	0.0136
$X_1 X_2$	1	480.50	480.50	6.48	0.0438
$X_1 X_3$	1	968.00	968.00	13.05	0.0112
$X_2 X_3$	1	3280.50	3280.50	44.23	0.0006

Table 1 depicts the design matrix along with response variables. This design screens important variables that effect on the studied response variables as well as their significant levels but does not consider the interaction effects among the studied variables. A probability value of less than 0.05 indicated that the model terms are significant and only those variables which are significant are presented in Table 2 along with coefficient values.

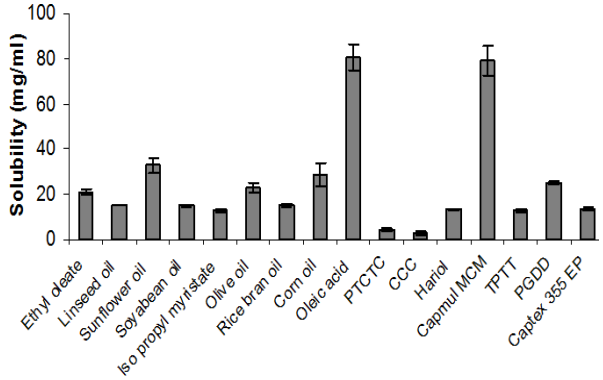

Figure 1: Solubility of ritonavir in various types of oil

Factor X_1, X_4 and X_6 were found to be significant on response globule size (Y_1). Probability value in

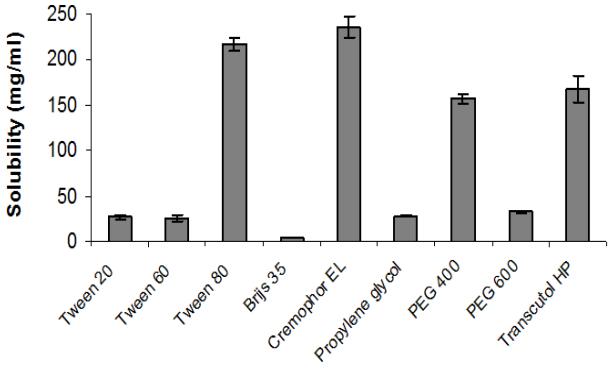

Figure 2: Solubility of ritonavir in various types of surfactant and Co-surfactant

Table 2 indicates that factor X_4 with p-value <0.0001 significantly affect the globule size followed by factor X_1 (p 0.0020). For response variable self-emulsification time, factor X_2, X_3, X_4, X_5, and X_6 found to be significant in a negative manner, i.e. decreases the self-emulsification time. Among the

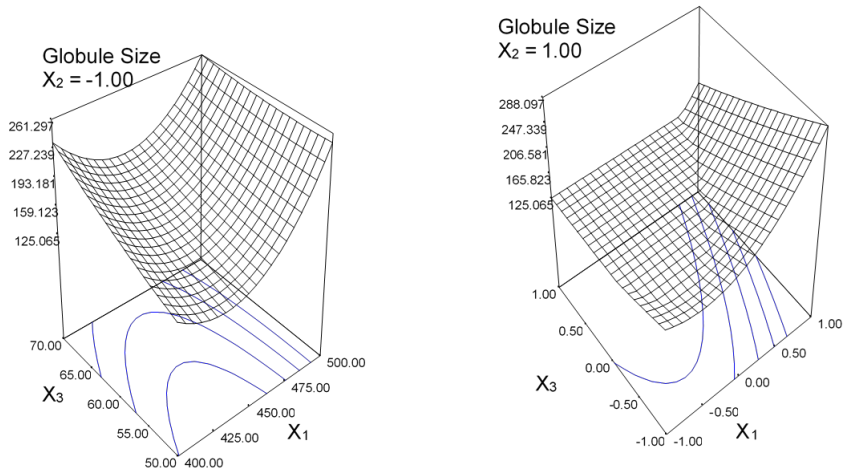

Figure 3: 3D-Response surface plots for interaction factor X1X2 on globule size

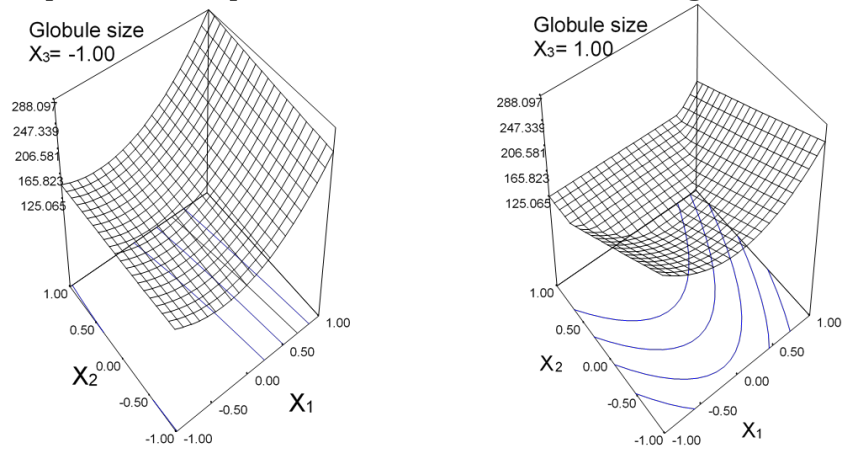

Figure 4:3D-Response surface plots for interaction factor X1X3 on globule size

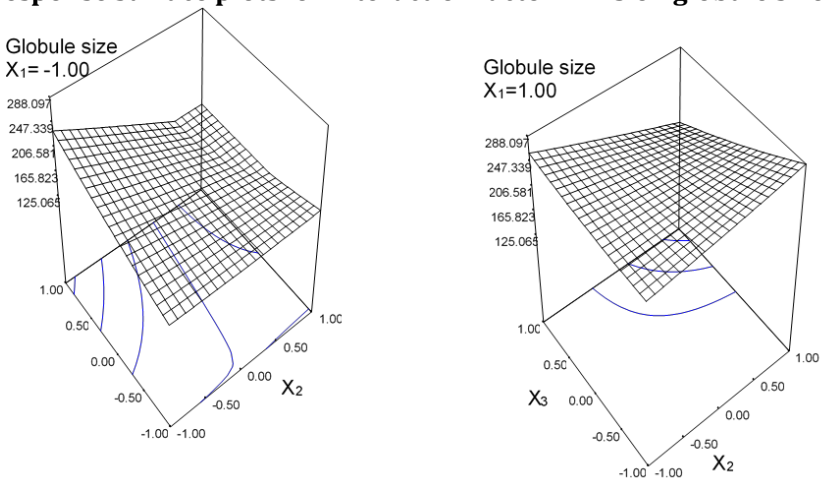

Figure 5: 3D-Response surface plots for interaction factor X2X3 on globule size

all, factor X_3 ($p < 0.0001$) was found to be highly significant followed by factor X_5 ($p < 0.0001$). In the case of $\%DE_{15min}$, all the studied independent variable was found to be significant and amongst all, factor X_3 ($p < 0.0001$) was more dominant followed by factor X_5 ($p < 0.0001$). Further, numerical optimisation technique was used to generate the optimum settings with predetermined constraints for SNEDDS. According to the statistical prediction, oleic acid as the oil phase, Cremophor RL as a surfactant and Transcutol HP as co-surfactant was identified and selected under categorical factors. But in the case of numerical factors, the results obtained was found to be in a wider range and suggesting further studies to arrive at the optimal settings/design space.

Response surface methodology

The selected variables from PB design was studied by RSM using face-centred CCD. The experiments were aimed towards the construction of the quadratic model and consist of 16 experimental trials

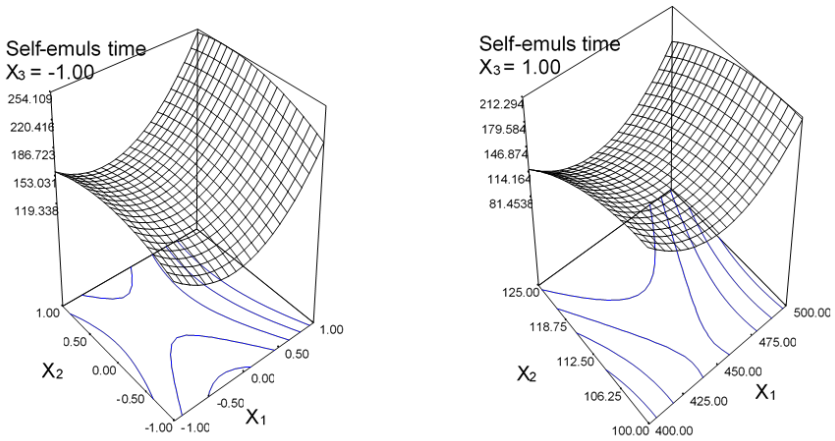

Figure 6: 3D-Response surface plots for interaction factor X1X2 on Self-emulsification time

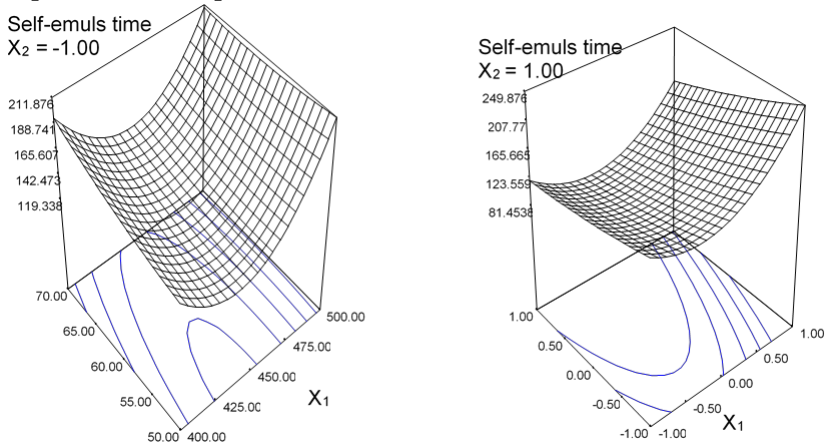

Figure 7: 3D-Response surface plots for interaction factor X1X3 on Self-emulsification time

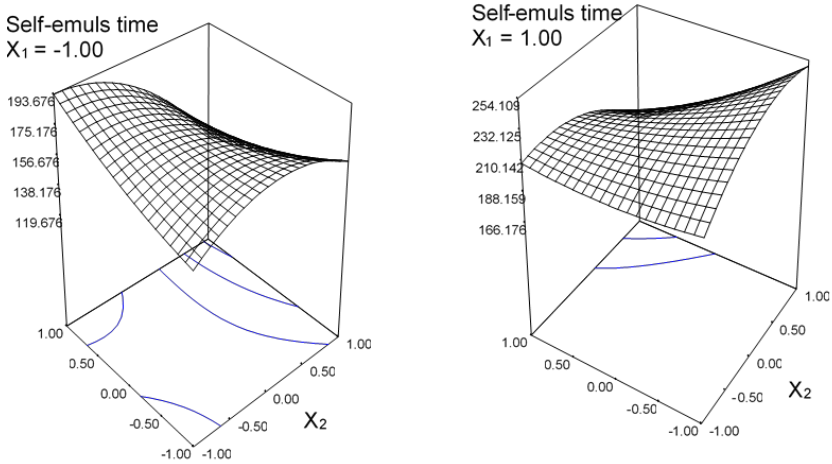

Figure 8: 3D-Response surface plots for interaction factor X2X3 on Self-emulsification time

along with the response, variables are presented in Table 3. The three independent variable studied includes amount of oleic acid (X_1= 400-500mg), amount of Cremophor EL (X_2= 105-125mg) and amount of Transcutol HP (X_3= 50- 75mg).

The model for response Y_1 and Y_2 were found to be significant with an F value of 61.89 ($p<0.0001$) and 37.51 ($p<0.0001$) respectively are shown in Table 4. The summary of ANOVA with significant model parameters affecting the response variables is shown in Table 5. Since R^2 values for the studied variables were found to be nearing to one, indicate the adequate fitting to the quadratic model.

Y_1= 128.88 +42.4X_1 -24.6X_2 -10X_3 +64.43X_1^2 +9.12X_1X_2 -18.87X_1X_3 -34.12X_2X_3

In this case, increasing the amount of oil increases the globule size whereas increasing the amount of surfactant and co-surfactant decreases the globule size. Further interaction factor between factors X_1X_2 can be studies with the help of 3D response surface plots in Fig. 3. A slanting line response was observed by increasing the amount of oleic acid

from lower to a higher level by keeping Cremophor EL and Transcutol HP at either lower or higher level. Similar results were also observed in case interaction factors X_1X_3 (Fig. 4). The results suggest that smaller globule size may be obtained at the intermediate level of the amount of oleic acid. Fig. 5 depicts the interaction effect between factors X_2X_3. Smaller globule size may be obtained if the amount of Cremophor EL and Transcutol HP are placed at a higher level with irrespective of the amount of oleic acid level.

Y_2= 137.21 +26.5X_1 -9X_2 -10.6X_3 +59.19X_1^2 -18.31X_2^2 +7.75X_1X_2 -11X_1X_3 -20.25X_2X_3

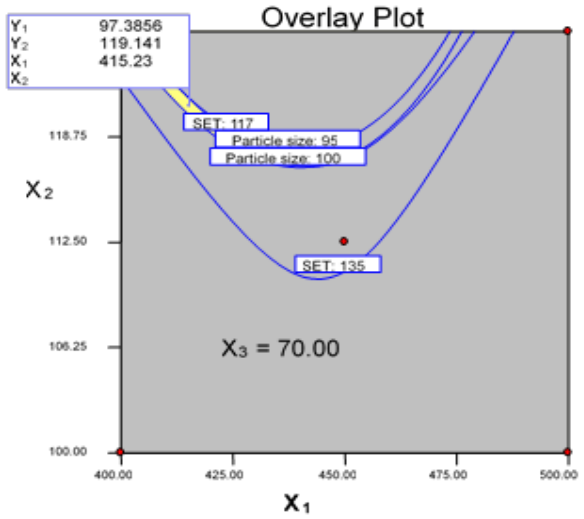

Figure 9: Overlay plot showing design space along with the optimal setting for independent and response variable

In this case, an increasing amount of oleic acid increases the self-emulsification time whereas increasing the amount of surfactant and co-surfactant decreases the self-emulsification time. Fig. 6 depicts the 3D response surface plot for interaction factors X_1X_2. When the factors X_2 and X_3 are kept at a lower or higher level and increasing the amount of oleic acid from lower to intermediate level, there was a significant decrease in self-emulsification time. But the same response variable increases by increasing the amount of oleic acid from the intermediate level to a higher level. A similar result was also observed with interaction factors between X_1X_3 (Fig.7). The 3D response surface plot for interaction factors X_2X_3 are presented in Fig 8. At a lower level of factor X_2 and X_1 and increasing the amount of co-surfactant from lower to higher level a significant increase in self-emulsification time is observed. But the same response variable decreases faintly as the factor X_3 is increased from lower level to higher level by keeping factor X_2 at a higher level with irrespective of the level of factor X_1. The result suggests that a less emulsification time may be obtained if the amount of oleic acid is at a lower level and the amount of Cremophor EL and Transcutol HP are at a higher level.

Optimisation studies: An optimal settings/ design space for SNEDDS must have a small globule size after dispersion and less emulsification time. Therefore, optimisation of an isotropic mixture of an amount of oleic acid, Cremophor RL and Transcutol HP is required in developing such dosage form. A numerical optimisation technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimised for the dependent (response) variables Y_1 and Y_2, and the optimised formula was arrived by restricting to 95%≤ Y_1 ≤100nm; 117≤ Y_2 ≤ 120 sec. The optimised levels of factor X_1, X_2 and X_3 were 415mg, 120mg and 70mg respectively with a maximum desirability value of 1 and the overlay plot are presented in Fig 9. To gainsay the reliability of the response surface model, new optimised formulations were prepared according to the predicted model and evaluated for the responses and was found to be 118nm for globule size (Fig 9) and 135 secs for self-emulsification time. Comparison of predicted and experimented values resulted in low residual errors indicating the successful application of DOE tool in the development of SNEDDS for poorly water-soluble drug by QbD approach.

CONCLUSION

The present investigation was aimed to develop a SNEDDS for poorly water-soluble drug by the application of QbD principles. PB design was found to highly beneficial in identifying potential CMAs affecting in the development of SNEDDS and RSM facilitated in identifying the optimal design space. The results of optimisation studies revealed us that an appropriated balance between the levels of the studied independent variables is imperative to acquire a globule size in nano range with significant improvement in emulsification time with a limited number of experiments. Though the research outcome is for a specific poorly water-soluble drug the same can be extrapolated to other drugs which come under BSC class II or IV.

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