

Quality by Design based development of Self Nano Emulsifying Drug Delivery System of Ritonavir

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ABSTRACT

Objectives: Ritonavir is an antiretroviral agent which belongs to Biopharmaceutical Classification System (BCS) II having poor water solubility. The purpose of this study was to design Self-Nano Emulsifying Drug Delivery System (SNEDDS) for a poorly water-soluble anti-retroviral drug-Ritonavir by implementing Quality by Design (QbD). **Methods:** In a DoE based development, Mixture design was used for the development and simultaneous optimization of the Ritonavir-SNEDDS. Droplet size (nm), Emulsification time (seconds), Polydispersity Index (PDI) and % Transmittance were the various responses selected for the study. Labrafil[®] M 1944 CS (oil), Tween 80 (surfactant) and PEG 6000 (cosurfactant) are the independent variables considered in the design. Eight formulations were prepared and tested for model fit. The simultaneous optimization of formulation was done by the Global desirability function approach obtained through Prediction profiler. **Results:** The developed optimal Ritonavir-SNEDDS through QbD approach resulted in a robust and sustainable method for improving the oral bioavailability of Ritonavir and confirmed by

the characterisation studies- droplet size (264.7 nm), emulsification time (46.1 sec), PDI (0.415) and % transmittance (94.8). **Conclusion:** The results conclude the potentiality of SNEDDS formulation to improve Ritonavir oral bioavailability under the QbD framework.

Key words: Critical Material attributes, Critical Quality Attributes, Quality by design Ritonavir, Self-Nano Emulsifying Drug Delivery System (SNEDDS), Smix, Risk Estimation Matrix.

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INTRODUCTION

Ritonavir (RTV) is an Antiretroviral medication used in the treatment of Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS).¹ RTV is the seventh approved antiretroviral drug and the second approved *protease inhibitor* in the United States. RTV shows its action against HIV1 by interfering with the reproductive cycle of virus through the inhibition of protease enzyme. RTV belongs to the Biopharmaceutical Classification System (BCS) II, which has poor aqueous solubility and good permeability characteristics.² The drug's low oral bioavailability may be due to poor solubility in the aqueous medium. Various formulation approaches have used to improve the solubility of drugs, such as solid dispersion, compaction, size reduction, pH adjustments; lipid based delivery systems (LBDS) etc. Among various approaches, LBDS found to be the promising approach for improving the bioavailability of lipophilic drugs. In the current study attempts have been made to convert lipophilic drug into an LBDS. Among the LBDS, Self-Nano Emulsifying Drug Delivery System (SNEDDS) is one of the most promising approach to enhance the oral bioavailability of poorly water-soluble drugs as it retains the medication in the GIT in a soluble state.³ SNEDDS is a mix of oil, surfactant and co-surfactant and sometimes cosolvent. In addition, the SNEDDS formulation is ideal for filling in gelatin capsules as a dosing unit container. Well précised and reproducible results obtained to achieve the required therapeutic goals of the formulation by the systematic approach called Quality by design (QbD).⁴ RTV loaded SNEDDS formulations were developed and optimized by Design of Experiments (DOE) approach called Mixture design.⁵ The mixture design was developed by using JMP[®] 13.2.1 software (Academic license from SAS, SAS Institute, Cary, NC,

USA). The Critical Material Attributes (CMAs) selected for the study were oil (Labrafil M1944 CS), surfactant (Tween 80) and cosurfactant (Polyethylene glycol 6000). The Critical Quality attributes (CQAs) chosen for optimization were droplet size, emulsification time, PDI and transmittance percentage.⁶

MATERIALS AND METHODS

Materials

Ritonavir was collected as a gift sample from Aurobindo Pharma Ltd, Hyderabad, India. Capryol TM 90 (propylene glycol monocaprylate NF), Transcutol[®] HP (diethylene glycol monoethyl ether EP / USP NF), Labrasol[®] (caprylocaproyl poloxyl-8 glycerides NF) and Labrafil[®] M 1944 CS (Oleoyl polyoxy-6 glycerides) were procured as gift samples from Gattefosse, Saint-Priest Cedex, France. Tween 80 (Polyoxyethylene sorbitan trioleate), Span 20 (Sorbitan monolaurate), PEG 400 (Polyoxyethylene monooleate) and PEG 6000 (Polyethylene glycol) were purchased from Sigma-Aldrich, Germany. All other chemicals have been of analytical quality.

Methods

Defining Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)

QTPP approach constitutes a design framework for product development and it starts with "design in mind" to guarantee the product efficacy and safety. The QTPP is products sketch that precise the characteristics which are expected during the development of product to respond to the

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therapeutic goal of the drug. Ultimately quality target product profile forms the root for development of the product. On the basis of QTTP (Table 1) the CQAs (Table 2) are well-defined for the product.

Risk assessment

Risk assessment is a continuum process for describing and quantifying the causes of variability and it was developed to identify the CMAs and CPPs affecting the CQAs of RTV loaded SNEDDS. The qualitative risk assessment tool called Fish Bone Diagram or Ishikawa diagram was created by using *JMP*[®] software to find the possible causes and sub-causes affecting the CQAs of the product. The factor with the great risk were selected by building the Risk Estimation Matrix (REM), which portrays the potential risks linked with the material attributes and the process attributes having greater impact on the CQAs of the product (Table 2). Each factor was allocated with risk grades of low, medium or high.⁷

Solubility study

The capability of oils, surfactants and cosurfactant to solubilise RTV was screened in the present solubility study. An excess amount of RTV was taken into an Eppendorf tube containing 2 ml of vehicle and agitated in vortex shaker for 10 min. After a thorough mixing, the samples were kept in a mechanical shaker (3000 rpm) for 48 hr at room temperature. After

centrifugation, the supernatant liquid was filtered through a 0.45 µm filter. The filtered supernatant liquid was diluted suitably with methanol and the absorbance was determined by using UV spectrophotometer (UV 1800, Shimadzu) at λ_{max} 266 nm to determine the amount of drug dissolved in the selected solvents. Solubility of RTV in selected oils, surfactant and cosurfactant was studied in triplicate and expressed as mg/ml \pm SD.⁸

Construction of Pseudo ternary phase diagram

The concentration range of oil, surfactant and cosurfactant which could give the nano or micro emulsion region was investigated by water titration method. The oil (Labrafil[®] M 1944 CS), surfactant (Tween 80) and cosurfactant (PEG 6000) were selected based on the initial solubility studies with RTV. The surfactant and cosurfactant (Smix) were mixed in different ratios (4:1 and 5:1). The ratios of oil: surfactant/cosurfactant were varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1w/w and taken in test tubes. These mixtures were homogenized in a vortex shaker for homogenization. The double distilled water was added at 5% increment in the range of 5 to 95 % of total volume. The mixtures were vortexed for 2 min in vortex mixer after each addition and allowed to equilibrate.⁹ A Pseudo ternary phase diagram was constructed for mixtures of oil, surfactant and cosurfactant by using Pro Sim[®] software and the ideal range for the excipients was identified through the pseudo ternary phase diagram.

Mixture design

Mixture design is a type of experimental statistical design which is used to develop and optimize formulations. Mixture design is used in the production of pharmaceuticals when the variables are proportion of the mixture.¹⁰ The mixture's components are expressed as a fraction equates to 1 (100 percent). In the mixture experiments; the response depends only on the relative proportion of the ingredients. The main aim of the mixture design is to model the blend ratios mathematically to predict the response(s) for any mixture in the system and to calculate the effect of each factor alone or in combination with other factors on the response.^{11,12} The established CQAs were factored as the selected responses for the study. These are droplet size (nm), emulsification time (seconds), PDI and % transmittance.

The independent variables selected for the study are oil (LabrafilM 1944 CS), Surfactant (Tween 80) and Cosurfactant (PEG 6000). The mixture design obtained by using *JMP*[®] 13.2.1 software. The different formulations obtained as per the design are subjected to characterization.

Table 1: Quality Target Product Profile (QTTP) for SEDDS of Ritonavir.

QTTP Elements	Target	Justification
Dosage type	Self-Emulsifying Drug Delivery system	Bioavailability improvement
Dosage form	Capsule	Ease of administration
Dosage strength	50 mg	Unit dose of 50 mg of Ritonavir is essential to target the viral load
Route of administration	Oral	Most suitable route for AIDS patients
Packaging	Alu- Alu Blister	Maximum protection and gives prolonged shelf life
Pharmacokinetic parameters	T_{max} , C_{max} , Area Under the Curve	For attaining the required therapeutic concentration in the systemic circulation
Stability	As per the conditions of ICH Q1B Long term stability studies	To maintain the therapeutic level of the drug during the shelf life period

Table 2: REM Matrix.

CMA /CPP CQAs	Oil	Surfactant	Cosurfactant	Stirring speed	Stirring time	Stirring temperature
Drug content	High	High	High	Low	Low	Low
Globule size	High	High	High	Medium	Medium	Medium
Zeta potential	High	High	High	Low	Low	Low
Emulsification Time	High	High	High	Medium	Medium	Medium
PDI	High	High	Medium	Medium	Medium	Medium
% Transmittance	High	High	High	Medium	Medium	Medium
Drug release in 15 min	High	High	High	Low	Low	Low
Permeability (45 mins)	High	High	High	Low	Low	Low

High Risk Factor
 Medium Risk Factor
 Low risk factor

Formulation of RTV-SNEDDS

RTV-SNEDDS were formulated using Labrafil[®] M 1944 CS as oil, Tween 80 as a surfactant and PEG 6000 as cosurfactant. The eight different formulations were prepared by adding 50mg of RTV into the mixture of Labrafil[®] M 1944 CS, Tween 80 and PEG 6000. The mixture was subjected to vigorous vortex mixing until the entire mass becomes clear and transparent. All formulations were stored in ambient temperature until use.¹³

Droplet size analysis

The formulations were diluted with HPLC grade water at the ratio of 1:100 (v/v) in volumetric flask (100 ml) and gently mixed by overturning the flask. The mean particle size and PDI of the diluted formulations was determined by photon correlation spectroscopy using Malvern Zetasizer Nano-ZS instrument. All studies were repeated in three trials.¹⁴

Emulsification time

All prepared formulations were assessed for emulsification time by using dissolution apparatus USP II in which 1 ml of the formulation was added drop wise into 200 ml of double distilled water maintained at 37 ± 0.5°C, under agitation provided by the paddle (50 rpm). The time taken (seconds) by each formulation to attain clear homogenous system was noted in triplicates.^{15,16}

Transmittance

The % transmittance was evaluated by diluting the RTV-SNEDDS with double distilled water (1:100). The diluted samples were checked in triplicate for the transmittance at 630 nm by using UV Spectrophotometer (UV 1800, Shimadzu).¹⁷

Model verification and optimization

The CQAs obtained for all eight formulations were integrated into the design to verify the model fit. The model validation conducted through the ternary mixture profiler. The ternary mixture profiler offers the optimal space in the ternary diagram. The different ratio of oil, surfactant and cosurfactant within the optimal space does not affect the responses of the SNEDDS formulation. The validation experiment or Verification formulation (VF) was conducted according the mixture profiler. The experimental values obtained for VF were compared with the predicted values. The lack of variations in the variances of the observed and predicted responses suggests better fit.

Design optimisation was performed via the contour profilers and by using prediction profiler. For each response, the contour profiler report shows a contour profiler plot, surface plot; factor (oil / surfactant /

cosurfactant) and response settings and their controls. The Optimized Formulation (OF) was prepared and evaluated as per the optimized prediction profiler. The experimental results obtained for the optimized formulation were compared with the model predicted responses and % difference was calculated.

RESULTS

The dosage form development under QbD frame work involves material evaluation as well as process attributes which have a greater impact on the quality of the drug. The possible factors influencing the product CQAs were defined through the fish bone diagram and REM (Table 2). As far as SNEDDS preparation is concerned, material attributes such as oil, surfactant and cosurfactant / cosolvent have a significant contribution to product responses than process attributes, since the preparation method is simple. Because of their limited contribution to product variability, the process attributes involved in the SNEDDS preparation such as stirring time, temperature and method of stirring were given less priority in the present work. Effective design of the SNEDDS formulation relies on appropriate selection of excipients in the formulation with their relative proportion.

The solubility of RTV in different excipients is presented in the Figure 1. Labrafil[®] M 1944 CS was selected as oil phase. Likewise, among various surfactants and cosurfactants, high drug solubility was observed with Tween 80 and PEG 6000 respectively. It was observed that Tween 80 in combination with PEG6000 at the ratio of 5:1 in combination with Labrafil[®] M 1944 CS shows better results in terms of clarity as well as accommodating maximum area in phase diagram as compared to 4:1

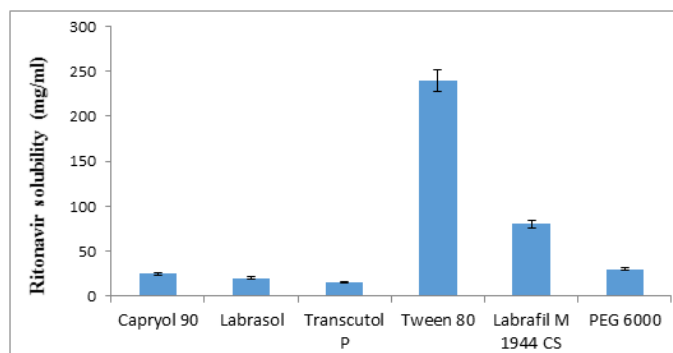


Figure 1: Solubility report for various vehicles. Values are expressed as mean ±SD, n=3

Table 3: Characterization of RTV-SNEDDS.

Formulations	Droplet size (nm)	Emulsification time (seconds)	PDI	% Transmittance
F1	380.6±8.12	38±0.42	0.262±0.55	88.453±10.26
F2	241.4±6.14	26±0.36	0.256±0.49	75.6±0.37
F3	231.7±4.71	41±0.45	0.411±0.57	93.929±10.69
F4	274.4±6.14	24±0.57	0.484±0.59	73.25±0.40
F5	187.2±2.56	42±0.13	0.513±0.56	98.669±10.55
F6	78±1.97	45±0.46	1±0.41	98.198±10.36
F7	230.8±7.23	24±0.32	0.472±0.59	78.13±0.45
F8	28.1±1.62	34±0.40	0.88±0.21	86.142±0.56

Values are expressed as mean ±SD, n=3

ratio. Amongst the different combinations, Labrafil[®] M 1944 CS with Tween 80 and PEG 6000 at the Smix ratio of 5:1 was able to give maximal region for stable nano/microemulsion.

As per the mixture design, eight formulations were obtained and evaluated for the CQAs considered in the design. The characterization report obtained for all the eight formulations is presented in the Table 3.

DISCUSSION

The dosage form development under QbD framework involves the identification of material attributes and process attributes, which have an influence on the quality attributes of the product.¹⁸ Risk assessment carried out by using Fish bone diagram and REM ensures CMAs are the independent variables leading to product variability and their appropriate limits were defined through the preformulation studies. By the application of statistical mixture design, eight different batches of SNEDDS were obtained and evaluated for the CQAs (Table 2). The mean droplet size obtained for the eight formulations were in the range of 28.10 to 380.60 nm. The least droplet size was observed with F8, whereas F1 shows highest droplet size. The reduced droplet size ensures the better absorption of drug from the GIT.¹⁹ Self-emulsifying systems should disperse uniformly and immediately once it comes in contact with the dispersion medium. This property of the formulation is assessed through *invitro* self-emulsification test; lesser the time taken, better is the emulsification process and faster the absorption of drug. The emulsification time for the all the formulations was less than 1 min, indicates the spontaneous emulsion formation.

The PDI values describe the size distribution of droplets and they were in the range of 0.256 to 1.0 and represent the formation of uniform emulsions with greater stability. The value obtained near zero represents the homogeneous droplets in the dispersion.

The % Transmittance in all the eight formulations was found to be in the range of 73.25 to 98.669 %. Among all the formulations F5 and F6 shows highest % Transmittance. The higher % transmittance ensures the formation of droplets size in the nano range.²⁰ The data obtained from all eight SNEDDS formulations was statistically analysed fitting multiple regression models with the intercept set to zero. The statistically significant models for droplet size (nm), emulsification time (sec), PDI, % transmittance were determined. The R^2 and p -value obtained for all the responses is used to evaluate the model fit. The predictive models, droplet size (nm) ($R^2=0.83$ and $p=0.3661$), emulsification time (sec) ($R^2=0.98$ and $p=0.0417$), PDI ($R^2= 0.74$ and $p=0.5215$) and % transmittance ($R^2= 0.98$ and $p=0.0521$) were statistically significant.

For the same model the effect test is used to check the fixed effects in the model. The effects test report obtained for droplet size indicates that Labrafil M 1944 CS ($p < 0.0563$) has significant effect on the model. The effect test ensures that Labrafil M 1944 CS ($p < 0.0066$), Tween 80 ($p < 0.0120$) and Labrafil M 1944 CS/Tween 80 ($p = 0.0422$) have significant effect on the emulsification process. The PDI depends on Tween 80 ($p < 0.0854$), whereas the % Transmittance is influenced by Labrafil M 1944 CS ($p < 0.0012$) and Tween 80 ($p = 0.0026$). Hence through effects test we can conclude that statistically significant models obtained for emulsification process, % transmittance followed by droplet size and PDI. The effects summary obtained for the whole model ensures that, the CQAs considered in the design are significantly influenced by the proportion of Labrafil M 1944, Tween 80 and the mixture proportion of Labrafil and Tween 80.

The model validation was done by conducting the experimental run as per the ternary profiler plot (Figure 2). The actual and the predicted values (Table 4) obtained for each response did not vary significantly (% Difference within ± 5), indicates the validity of the model.

The contour and surface plot obtained for each response is presented in Figure 3. The shaded area within the contour plot region shows the design's non-viable region and the white region offers the optimized

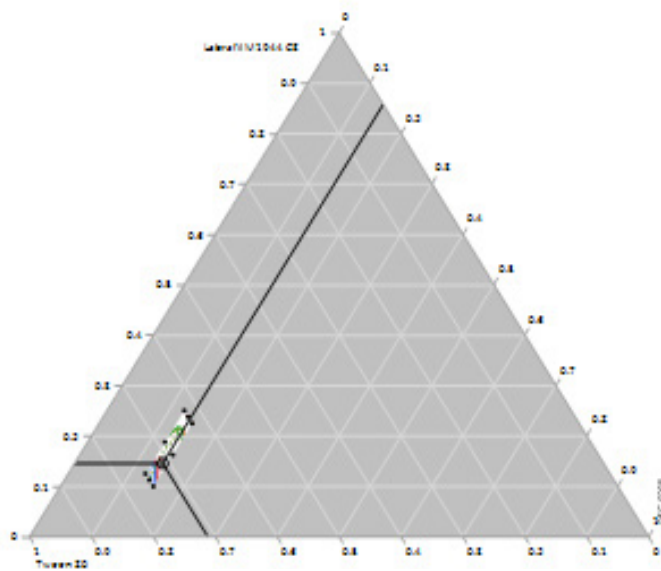


Figure 2: Ternary mixture diagram depicting the design space.

Table 4: Predicted and Experimental values for VF-SNEDDS and OF-SNEDDS.

Responses	VF-SNEDDS			OF-SNEDDS		
	Predicted value	Experimental value	% Difference	Predicted value	Experimental value	% Difference
Droplet size (nm)	245.6	249.3 \pm 5.56	1.506	263.09	264.7 \pm 6.12	0.61
Emulsification time (sec)	46.09	45 \pm 0.23	-2.36	45.68	46.18 \pm 0.13	1.09
PDI	0.4579	0.479 \pm 0.58	4.607	0.422	0.415 \pm 0.51	1.65
% Transmittance	97.95	98.4 \pm 1.26	0.459	96.73	96 \pm 0.56	-0.756

% Difference = [(Experimental value - Predicted Value) / (Predicted Value)] \times 100

Values are expressed as mean \pm SD, $n=3$

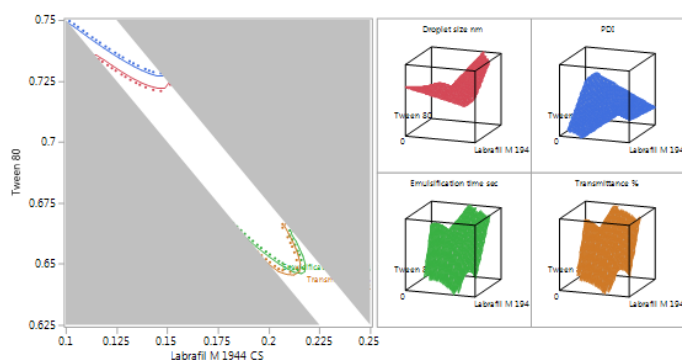


Figure 3: Contour and surface plots showing the effect of formulation components on the responses.

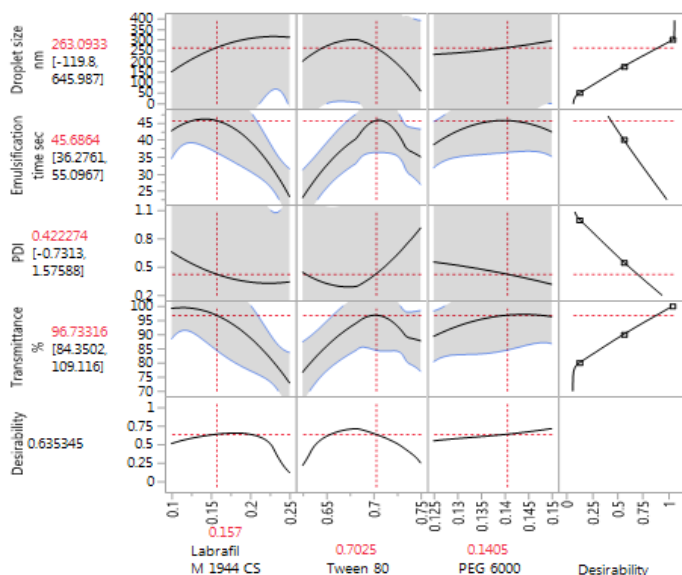


Figure 4: Prediction profiler for multiple responses.

space for operational design. The global desirability function obtained for the prediction profiler (Figure 4) is 63.53 %. The predicted and the experimental values obtained for OF-SMEDDS did not vary significantly (Table 4). The droplet size, PDI and zeta potential obtained for OF formulations ensure formation of SNEDDS with good stability characteristics. The statistical parameters obtained for the whole model ensures that the CMAs factored in the design have a significant effect on the CQAs.

CONCLUSION

The current studies effectively demonstrate the systematic QbD-based development of optimized SNEDDS formulations of Ritonavir, an antiretroviral, thus providing a fast, efficient and cost-effective approach to formulation of delivery systems with enhanced bioavailability potentials. The preliminary preformulation studies and the risk assessment carried out enabled the proper selection of independent variables for the optimization of dependent variables. This compact strategy to the development of formulations found to be reliably robust and can suit its predefined CQAs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AIDS: Acquired immunodeficiency syndrome; **BCS:** Biopharmaceutical classification system; **cART:** Combination antiretroviral therapy; **CMA:** Critical material attributes; **CPP:** Critical process parameters; **DoE:** Design of experiment; **HIV:** Human immunodeficiency virus; **HLB:** Hydrophilic lipophilic balance; **LBDDS:** Lipid based drug delivery system; **PDI:** Polydispersibility index; **QbD:** Quality by design; **QTPP:** Quality target product profile; **REM:** Risk estimation matrix; **SEDSS:** Self emulsifying drug delivery system; **SNEDDS:** Self nano emulsifying drug delivery system.

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