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Original Article

QbD Based Development of Novel Self Emulsifying Drug Delivery System of Rosuvastatin

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ABSTRACT

Objectives: The present study aims to systematically develop a Self-Emulsifying Drug Delivery System (SMEDDS) of Rosuvastatin using a (QbD) framework. **Materials and Methods:** The formulation development was initiated by defining the CQAs and QTPP with suitable justification. A statistical mixture design was employed, where Maisine CC, propylene glycol and labrasol, were chosen as independent variables. Emulsification time, transmittance, drug release at 15 min and drug content were found as important CQAs. Eight rosuvastatin self-emulsifying systems were prepared and assessed. The global desirability approach was used for simultaneous optimization. **Results:** The experimental data showed good fit to the regression models, with high correlation coefficient "R^2 values ranging from 0.95 to 0.98". Among the evaluated responses, transmittance was statistically significant ($p<0.05$), while other CQAs are not statistically significant ($p>0.05$). The zeta potential and particle size for optimized formulation were evaluated, which were found to be -38.5 mV and 112.3 nm, respectively. According to *in vitro* drug release studies, the formulation's best fit to the korsmeyer-peppas ($R^2=0.933$; $n=0.117$) suggested *Fiskian* diffusion. The global Desirability value of 0.7363 indicated good correlation between dependent and independent variables. **Conclusion:** The QbD-based development of Rosuvastatin SMEDDS successfully identified critical material attributes influencing formulation performance, demonstrating the effectiveness of QbD in building quality into oral drug delivery systems.

Keywords: Bioavailability, Quality by Design, Rosuvastatin, SMEDDS.

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INTRODUCTION

Oral Drug Delivery Systems (ODDSs) are widely used because they are safe, convenient, patient-friendly, non-invasive and self-administered easily.[1] Though the oral drug delivery system has numerous advantages but it comes with certain limitations, like poor drug solubility and low drug permeability.[2]

Rosuvastatin belongs to the statin class of HMG-COA reductase inhibitors, which are mainly used to lower LDL cholesterol levels in order to prevent and cure cardiovascular disease. Due to the first pass metabolism the bioavailability of RSV was approximately 20%. Hence, to overcome these limitations and to enhance the oral absorption, advanced formulation strategies are required.[3]

Lipid-Based Drug Delivery Systems (LBDDS) are innovative formulations in which drugs are dissolved or suspended in lipid excipients. This system transforms the drug in oil into a complicated design that, when combined with water, forms an emulsion.[4]

Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) are homogeneous mixture of solid or liquid surfactants, hydrophilic solvents and cosolvents, or natural or synthetic oils. These systems create fine Oil-in-Water (o/w) emulsion known as microemulsion When they are mixed with watery environment and gently stirred.[5] These are also adaptable for various routes of administration, depending on the therapeutic needs.[6]

Consequently, SMEEDS were formulated using systemic Quality by Design (QBD) strategy. In order to define the critical quality requirements of the formulation the quality target product profile was developed. The critical process essential material was effectively correlated to formulation responses through the use of the Ishikawa diagram to identify risks and the risk estimate matrix to determine the severity and probability of risk. Design of Experiment (DOE) was used to optimize formulation variables and interactions, saving development time and improving prediction of optimum compositions.

MATERIALS AND METHODS

Rosuvastatin calcium (analytical grade) was procured from MSN Laboratories Pvt. Ltd., Maisine CC, Labrasol and Transcutol HP (pharmaceutical grade) were obtained from Gattefossé, Mumbai,

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India. Cinnamon oil was purchased from SD Fine Chemicals Pvt. Ltd., Tween 80 and Tween 20 (analytical grade) procured from Merck India. PEG 6000 (analytical grade), span 20, and span 80 were acquired from Lobachemie Pvt. Ltd.

Methods

According to ICH Q8(R^2), Quality by Design is a structured approach to product creation that starts with a particular objective. It places strong emphasis on process and product control and is based on quality risk management. It creates appropriate manufacturing controls in order to ensure consistent product quality.[7] A thorough grasp of the product performance is provided by Quality Target Product Profile (QTPP) framework, identification Critical Quality Attributes (CQAs), and determination of Critical Material and process characteristics.[8]

Quality target product profile

It is the overall summary of drug product quality attributes that should ideally be achieved to ensure the desired quality while taking drug product efficacy into account.[9] An overview of QTPP components and their rationale for rosuvastatin formulation development is provided (Table 1).

Critical Quality Attributes

CQAs refers to the essential properties of the drug product that have a significant effect on the quality that must fall within the acceptable range. The process of identifying critical quality attributes must focus on those attributes that have the ability to affect overall quality and should be arranged in order of criticality depending on the level of possible effect.[10] CQAs represent the features of the final drug product. As a result, consistent product efficacy and process dependability are ensured by evaluating the CQAs throughout formulation or product development.[11] lists the CQAs and their explanations (Table 2).

Risk Assessment

The USFDA describes risk assessment as a proactive safe tool to measure and minimize the risk. It involves evaluating, tracking, communicating and updating risks to the pharmaceutical products performance throughout the product life cycle. [12] As demonstrated in Figure 1, the Ishikawa fish bone diagram is a graphical method that gives a possible cause for the specific risk involved in the formulation.[13]

Risk Estimation Matrix

The risk estimation matrix involves identifying and determining the relationship between the CQA vs QTTP and CQA vs CPP. The FMEA tool was utilized successfully to determine the RPN and to evaluate the components with high risk. Hence, REM illustrates the possible risks associated with material and process elements that could significantly impact the CQA. The individual critical risk factor was assessed based on three parameters, Occurrence, severity, and detectability. These risk characteristics were assigned a score using a three-level scale as high, low, medium.[14] The risk priority number were calculated with the help of the JMP software as:

$$RPN = S \times O \times D$$

Design of Experiment (DOE)

Further selecting the appropriate CMC through risk assessment for SMEEDS development, the formulation design was constructed using JMP® 13.2.1 software. A mixture design from the classical DOE category was chosen due to its suitability and the few numbers of the experimental runs, for a short-term study. The independent (mixture compounds) and dependent variables (responses) with their selected levels were listed in (Table 3). Based on these inputs, the software generated a D-optimal mixture design consisting of 8 randomized experimental runs. A D-optimal design was applied for the SMEEDS due to its suitability for the formulations involving components with the fixed compositional limits. The design generated 8 runs, which are statistically sufficient to study the impact of surfactant, oil and co-surfactant concentration on critical quality attributes while reducing the experimental workload and material utilization. The assessment of the quality attributes was done using the prepared formulations.

Preparation of Liquid SMEDDS formulation

According to the mixture design, the SMEDDS were formulated using different concentrations of co surfactant, surfactant, oil. About 40mg of RSV was dissolved in a solution of MssineCC, Labrasol, and propylene Glycol to create the eight distinct formulations (F1-F8). The prepared mixture was heated to 40° using a water bath. The mixture was a vertex mixed for 15 min at 2500 RPM until it was transparent and clear. Before being used, all formulations were placed in the glass sealed containers and kept at room temperature (between 25-30°C).[15]

Checking CQAs of RSV-SMEDDS

Drug loading efficiency

To determine the RSV content, 1 mL of SMEDDS formulations (equivalent to 40 mg drug) was diluted with methanol and emulsified under moderate agitation then further it is made up using 100 mL of the (0.4 mg/ mL). Then 0.1mL was taken into a 10 mL volumetric flask from previous stock and was diluted with buffer solution (4 µg/mL).[16] This sample was analyzed under UV at λ_{max} 244 nm. The amount of RSV was calculated from the equation obtained from the calibration plot.

Emulsification Time

The prepared formulations were evaluated for the emulsification time. The self-emulsification characteristics were evaluated using USP Type -2 dissolution equipment (LABIMDIA, DS 8000,

Mumbai, India).[16] About 500 mL of the double- distilled water was gently stirred using a rotating paddle at 50rpm while 1 mL of the formulation was poured dropwise at 37±°C. Each formulation "time taken (seconds)" for creating a distinct, homogenous system was recorded in triplicates.

Transmittance

It was assessed by mixing the formulation with double-distilled water at 1:100 ratio.[16] The transmittance of the sample in triplicates is measured using a UV spectrophotometer at 630 nm.[16]

Drug release

In vitro studies were conducted using the citrate buffer (pH 6.6), and USP 1-basket type dissolution apparatus used as outlined in IP.[16] The rotating speed was set to 50 rpm and temperature of the medium was maintained at 37°C±0.5. SMEEDS formulations corresponding to 40 mg of the drug and pure drug were placed into hard gelatin capsules which were then positioned in the cylindrical baskets made of non-reactive mesh to prevent buoyancy. At the time interval of 5, 15, 30, 45, 60 min samples were collected from the dissolution vessels and diluted with citrate buffer and analysed using Spectroscopy λ_{max} 244 nm.

Model evaluation

The design to assess the model fit comprised each of the eight RSV-SMEEDS preparation. Multiple regression models with the intercept set to zero were used to statistically assess the data.

The drug loading (mg/mL), emulsification time (sec) and droplet size in (nm) shown to be statistically significant. Variables with p values <0.05 were found significant. The different Three-Dimensional (3D) and contour graphs were designed, analyzed, and plotted using the JMP software.

Design Validation or Verification

The ternary mixture profiler was used to validate the model (Figure 9). The ideal space in the ternary diagram is provided by the ternary mixture profiler. The dependent variables of the SMEDDS are unaffected by the varying ratios of the surfactant, oil and co-surfactant within the optimal region. According to the mixture profiler (Table 4) verification formulation carried out. The experimental and predicted values for VF were compared. Better goodness of fit is shown by the absence of disparities between the variances of observed and expected responses.

Optimization of Formulation

The contour profiler plot can be used for simple formulation optimization; the desirability function approach was used for simultaneous formulation optimization by mixture design. The global desirability function value ranges from 0 to 1. In accordance with the prediction profiler the optimized formulation was prepared and evaluated for responses. The results obtained for the optimized formulation were correlated with the model predicted responses.

Droplet Size analysis

Formulation of the SMEDDS is mainly affected by the surfactant and oil content present. The size of SMEDDS droplets affects the lipolysis, drug release and consequently the absorption process.[15]

Determining the droplet size in oral lipid formulations is therefore essential. After the formulations were diluted 100 times using HPLC-grade water, the mean droplet size, Polydispersity Index (PDI), and Zeta potential of the diluted formulations were determined by photon correlation spectroscopy using Malvern Zetasizer Nano-ZS (Malvern Instruments, United Kingdom).

Drug release kinetics

The release data for improved formulations was fitted into a number of kinetic models in order to comprehend the drug release mechanism.

Zero order kinetics

The following equation can be used to describe drug dissolution from pharmaceutical dosage forms that release the drug gradually, provided the area stays constant and there are no equilibrium conditions.

$$At = A0 - k0t$$

First order release kinetics

First order describes that release rate from the system depends on the concentration which as follows:

$$\log C = \log \frac{C_0 - Kt}{2.30}$$

Higuchi Model

The release of poorly soluble and water-soluble medications integrated in semisolid using the above model.

$$Qt = \frac{KH.t1}{2}$$

Korsmeyer and Peppas Model

To comprehend the release process, *in vitro* data was analysed using the Peppas model. The exponent "n" was found using the linear plot's slope.

$$\frac{Mt}{M\alpha} = btn$$

RESULTS AND DISCUSSION

Risk estimation FMEA of CQA vs QTPP

The REM analysis Table 5 indicates that the drug content, drug release, globule size, and transmittance are essential quality parameters with higher potential impact on the final product.

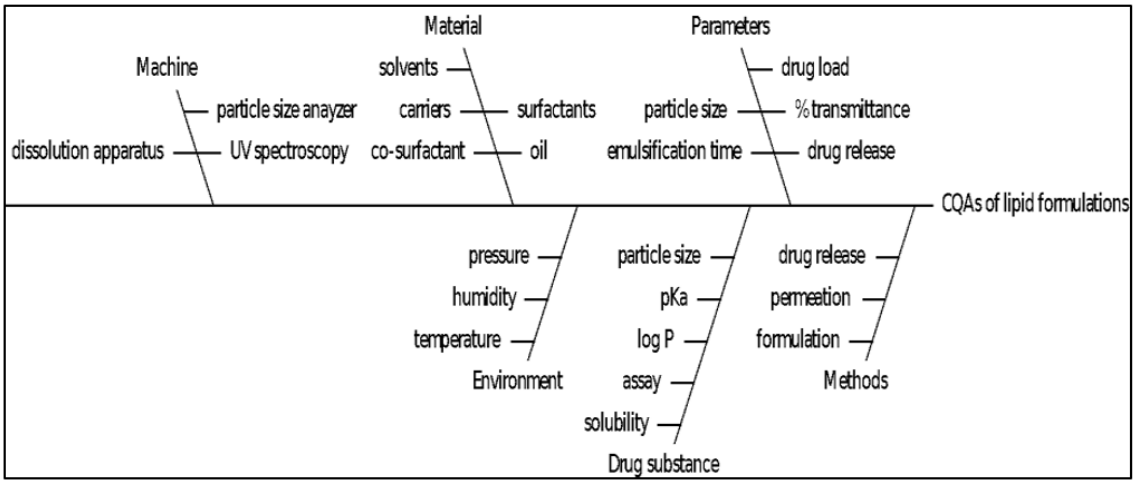

Figure 1: Ishikawa Diagram.

Table 1: QTPP of RSV-SMEDDS.

QTPP Elements	Target	Justification
Dosage type	Lipid based formulation	Bioavailability improvement.
Dosage form	Capsule	Ease of administration.
Dosage strength	40 mg	Required to show the therapeutic action at the target site.
Route of Administration	Oral	Most convenient route (Patient acceptability).
Packaging	Alu- Alu Blister	Maximum protection and gives prolonged shelf life.
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.
Pharmacokinetic parameters	T_{max}, C_{max}, AUC	Maximum drug levels in systemic circulation helps to improve the therapeutic efficiency.

These variables directly influence the formulation stability, self-emulsification behavior, and therapeutic efficiency hence they require strict control during the formulation.

CQA Pareto Graph

The CQA Pareto graph (Figure 2) shows that, primarily drug release, globule size were the major contributors to formulation risk. Therefore, precise optimization and control of variables are essential to achieve stable and reproducible SMEDD performances.

CQA VS CPP Heat Map

The heat map (Figure 3) interprets that cosurfactant, surfactant, oil are the largest risk parameters, which affect most of the CQA. While these process parameters are considered as low severity. Hence, excipient optimization is essential for regulating the product quality.

CPP Overall Pareto

The comprehensive Pareto chart reveals that formulation-related Critical Process Parameters (CPPs), accounts for the majority of the system's overall risk. These factors significantly influence the cumulative impact profile, clearly demonstrating that they are the primary sources of variability in quality and require strict control throughout the development process (Figure 4).

Formulation of SMEDDS by Mixture Design

Based on the extreme limits assigned to each factor, the JMP®13.2.1 program generated an 8-run design (Table 6) that was utilized for formulation construction and testing.

Characterization of formulations

The critical quality attributes report obtained for all the eight formulations was presented in Table 7. The same data has been utilized to conduct the design evaluation.

DOE Report

All the CQAs data has to be incorporated to the formulation design and the model report for the formulations was generated with the help of JMP software tool. A Variance Analysis (ANOVA) was used to assess the significance determined to evaluate the significance of the established design mixture. The regression

Table 2: Critical Quality Attributes of RSV- SMEDDS.

Quality attribute of product		Target	CQA	Justification
Physical attributes	Colour	Acceptable	No	The physical attributes were not considered critical, because they were not directly related to the efficacy and safety of the product, since the product will be enclosed in a capsule shell.
	Odour			
	Appearance			
Drug content (mg)		40 mg per dose	Yes	40 mg per unit dose of Rosuvastatin essential to treat high Cholesterol.
Transmittance (%)		>85%	Yes	Better clarity of the formulation confirms the Minimization of droplet size.
Particle size (nm)		<200nm	Yes	The stability of the product and better penetrability through gastro intestinal membrane ensured by the smaller and consistent globule.
Emulsification Efficiency (s)		<120	Yes	Has Direct correlation with onset of action and influences the size of the dispersed globules.
Drug release in 15 min		>80%	Yes	Faster the release of drug from the formulation, earlier the onset of action.

Table 3: Dependent and Independent Variables with their Limits.

Variables		Limits	
		Low	High
Independent variables	Maisine CC	0.1	0.2
	Labrasol	0.64	0.72
	Propylene glycol	0.16	0.18
Dependent variables	Drug loading (mg/mL)	35	40
	Emulsification time (s)	20	60
	Transmittance	70	100
	Drug release (%)	70	100

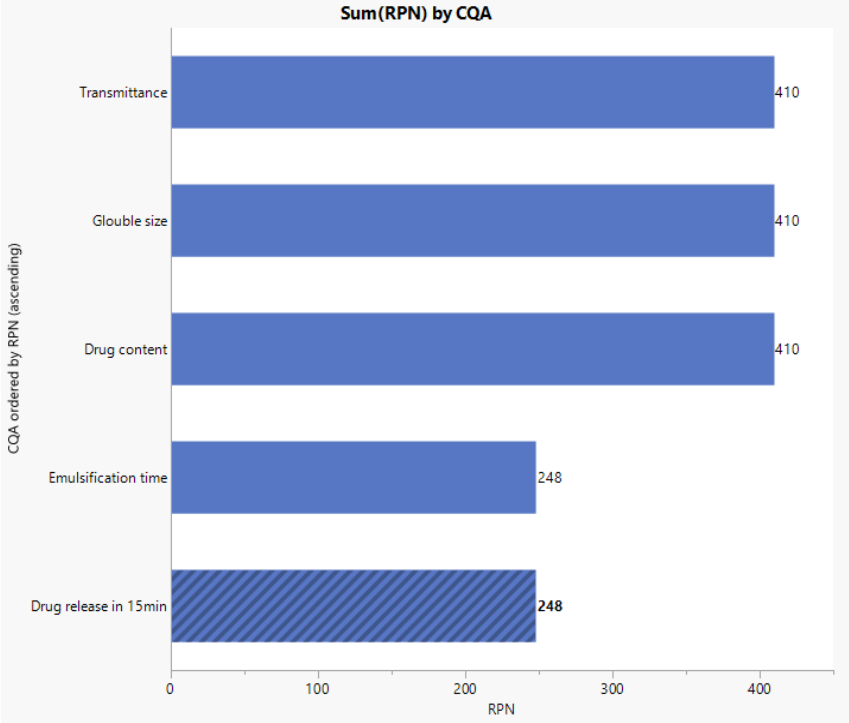

Figure 2: CQA Pareto Graph.

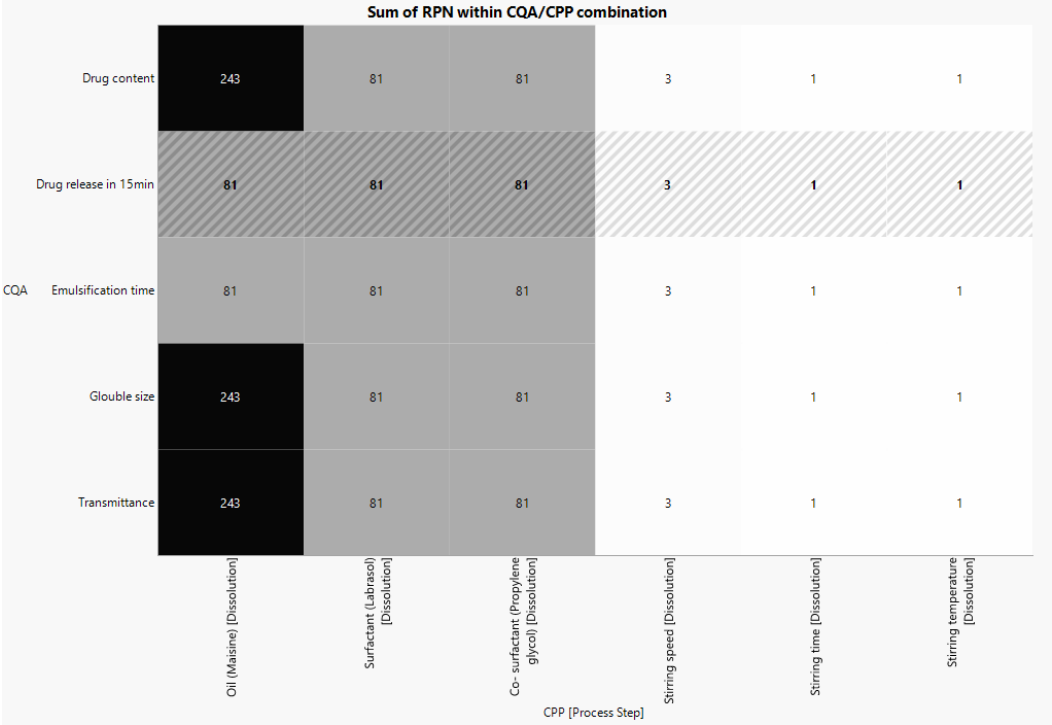

Figure 3: Heat Map of CQA vs CPP.

Table 4: Risk estimation matrix of CQA vs QTPP.

CQA QTTP	Dosage type	Dosage form	Dosage strength	Route of administration	Stability	Pharmacokinetics
Drug content	9	9	9	1	9	3
Globule size	9	9	3	1	9	9
Transmittance	9	9	3	1	3	1
Emulsification time	3	9	3	1	3	3
Drug release (15 min)	3	9	9	1	9	9

Table 5: SEDDS formulation table as per mixture design.

Formulation	Maisine CC	Labrasol	Propylene glycol
F1	0.18	0.64	0.18
F2	0.14	0.68	0.18
F3	0.12	0.72	0.16
F4	0.16	0.68	0.16
F5	0.19	0.64	0.17
F6	0.2	0.64	0.16
F7	0.1	0.72	0.18
F8	0.11	0.72	0.17

reveals strong model fitting, which shows strong model fitting, with R^2 value between 0.86 and 0.98. Among the evaluated responses, transmittance was statistically significant ($p< 0.05$), while drug content, emulsification time and drug release were not statistically significant ($p>0.05$) indicating adequate predictive ability within the design space. The actual Vs predicted plots obtained for each CQAs are shown in Figure 5, which validates the goodness of fit.

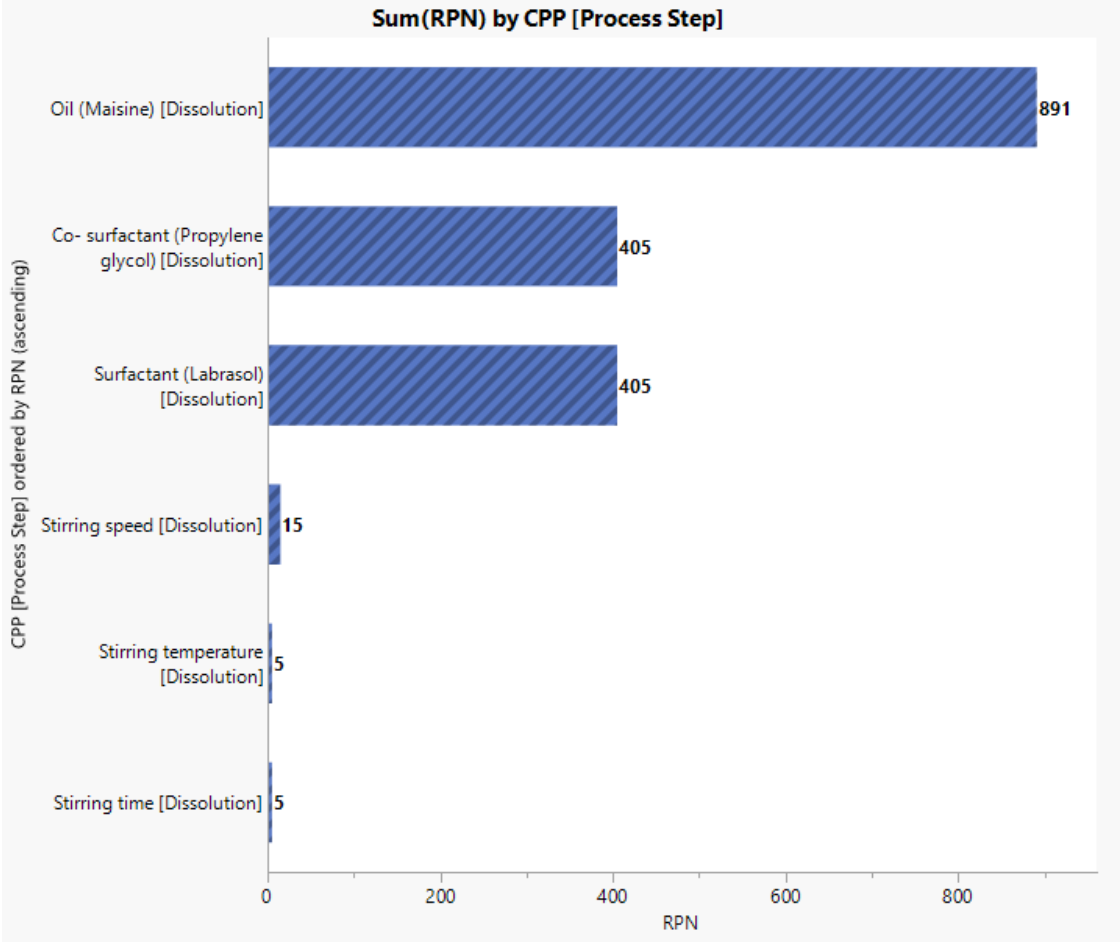

Figure 4: CPP Overall Pareto.

Table 7: **Predicted and Experimental values for VF-SMEDDS and OF- SMEDDS.**

Formulations		%Transmittance	Emulsification time (sec)	Drug load (mg/mL)	%Drug release
VF-RSV-SMEDDS	Predicted	87.9	23.7	40.1	86.63
	Experimental	86.02	24	86.63	86.99
OF-RSV-SMEDDS	Predicted	89.5	21.2	39.9	87.4
	Experimental	88.12	23.0	39.61	86.993

Table 6: **Characterization of RSV-SEDDS, Values are expressed as mean ±SD, *n*=3.**

Formulation	Drug Content (mg/mL)	Emulsification time sec	%Transmittance	%Drug release at 15 min
F1	39.96±2	10±2	88.96±1	88.94±0.83
F2	37.95±3	14±3	86.54±2	88.87±0.13
F3	36.96±1	17±3	85.46±2	87.07±0.13
F4	40.38±2	20±1	89.96±3	87.37±0.196
F5	39.89±3	22±3	89.12±2	86.24±0.127
F6	36.89±2	21±2	88.56±1	86.99±0.127
F7	32.23±1	23±1	81.23±2	85.04±0.155
F8	34.95±2	26±2	82.316±3	84.8±0.433

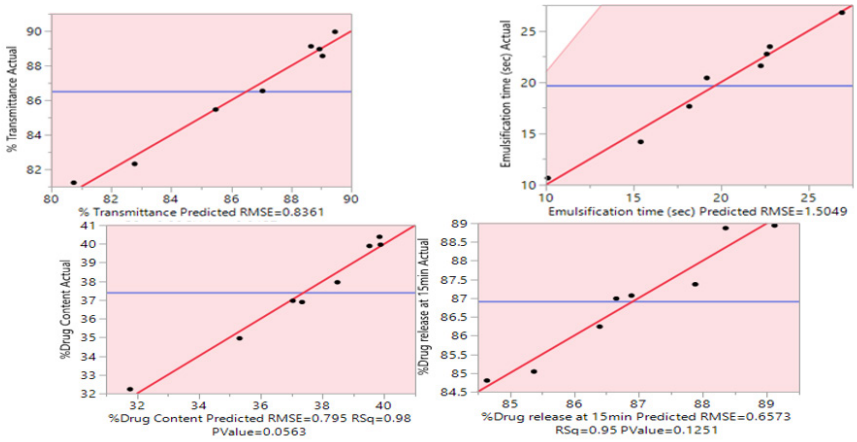

Figure 5: Actual vs. Predicted plots obtained for all the CQAs.

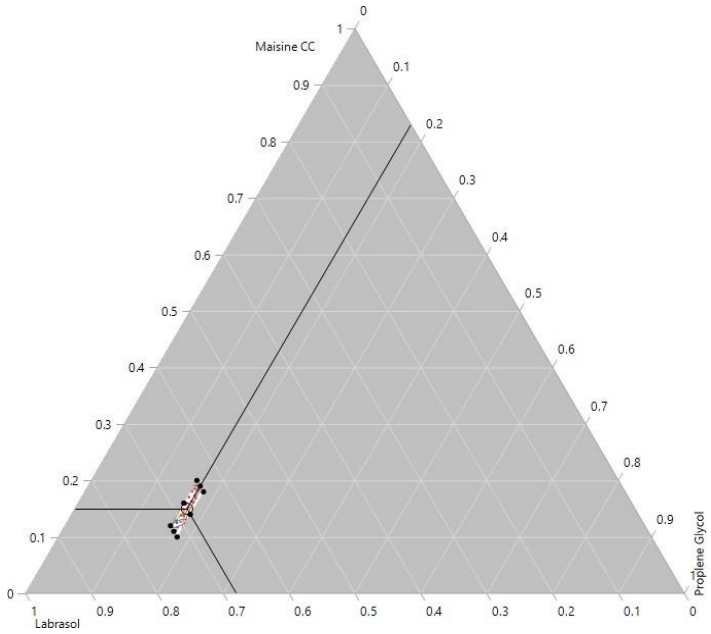

Figure 6: Ternary mixture plot.

Table 8: **Drug Release Kinetics Models.**

Release kinetics	R^2	*n*
Korsmeyer-Peppas	0.933	0.117
Zero-order kinetics	0.921	
First order kinetics	0.780	
Higuchi model	0.406	

Design Verification

The experimental batch was conducted in accordance with the ternary mixture profile plot (Figure 6), and the findings obtained confirms the design validation.

Optimization of Formulation

The model report produced a prediction profiler (Figure 7) that displayed a continuous connection between several parameters and different responses, providing an overall view of the variabilities which could exist within the selected extreme values.

Particle size and Zeta potential Report

The Improved formulation shows a homogeneous and narrow particle distribution with a mean particle size of "112.3" nm and a Polydispersity Index (PDI) of 0.25. The zeta potential was determined to be "-38.5" mV, indicating good physical stability because there is enough electrostatic repulsion between the dispersed globules to minimize aggregation and coalescence (Figures 8, 9).

In vitro Drug release

The Krosmeyer-Peppas model had the strongest correlation coefficient (R^2=0.933), indicating the best release mechanism Figures 8, 10. The release exponent (*n*=0.117) suggests a

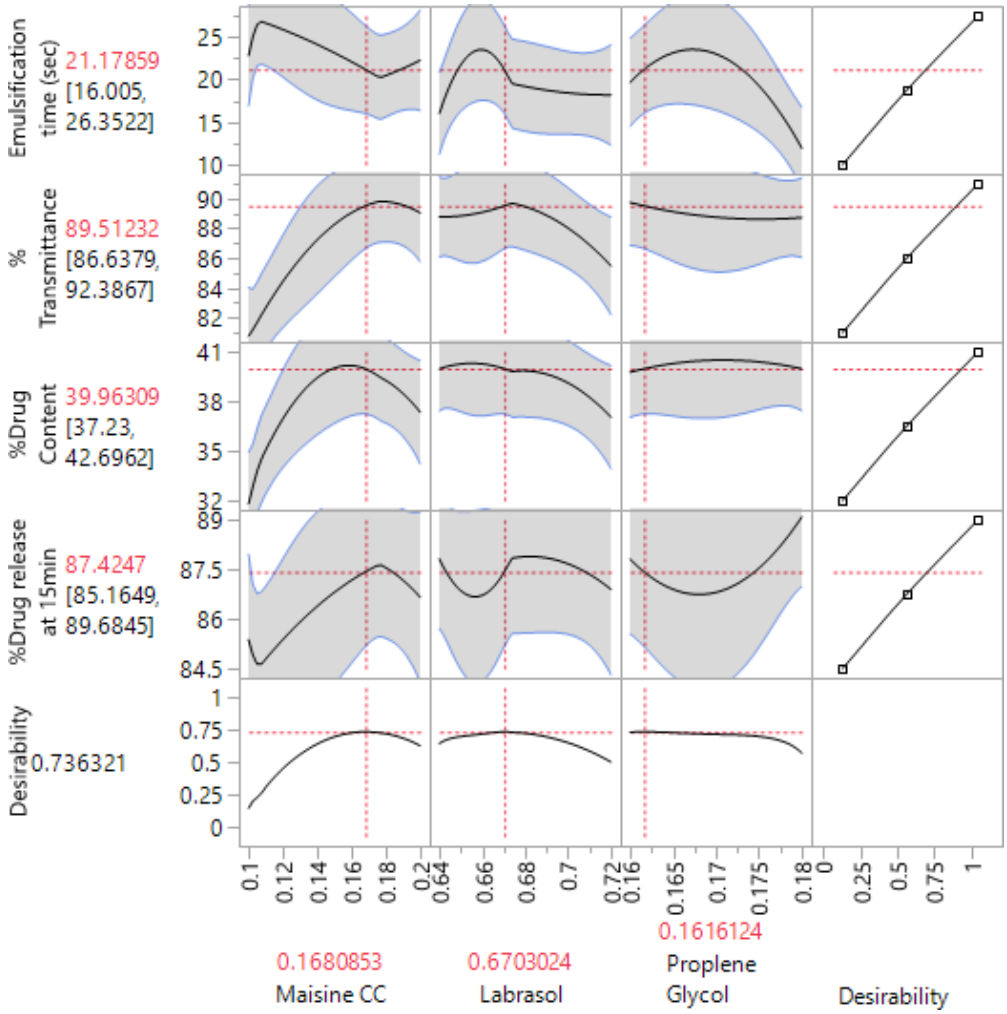

Figure 7: Prediction profiler after optimization.

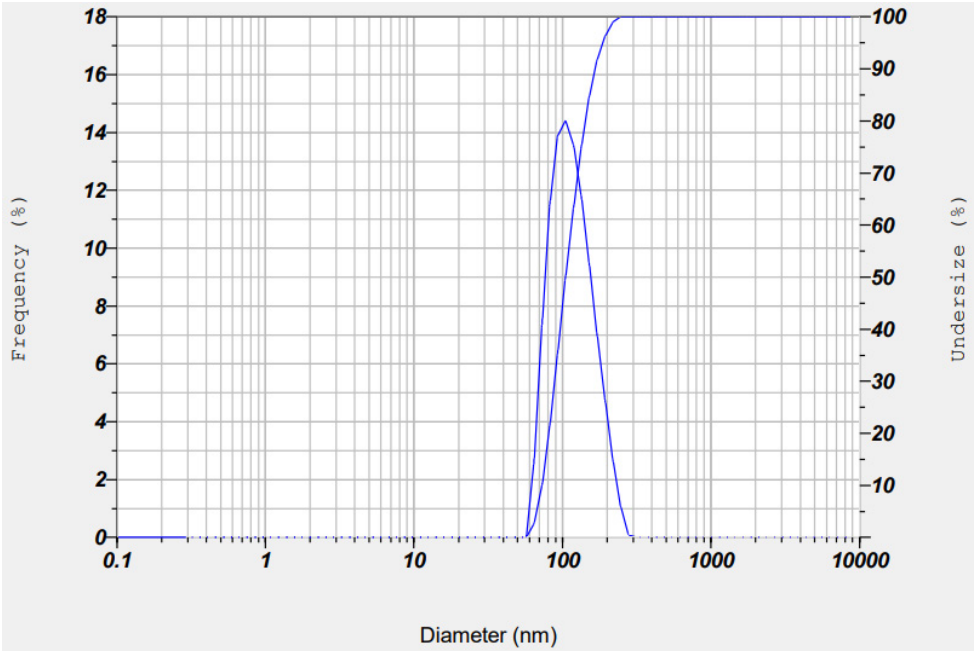

Figure 8: Particle size determination of OF-RSV-SMEDDS.

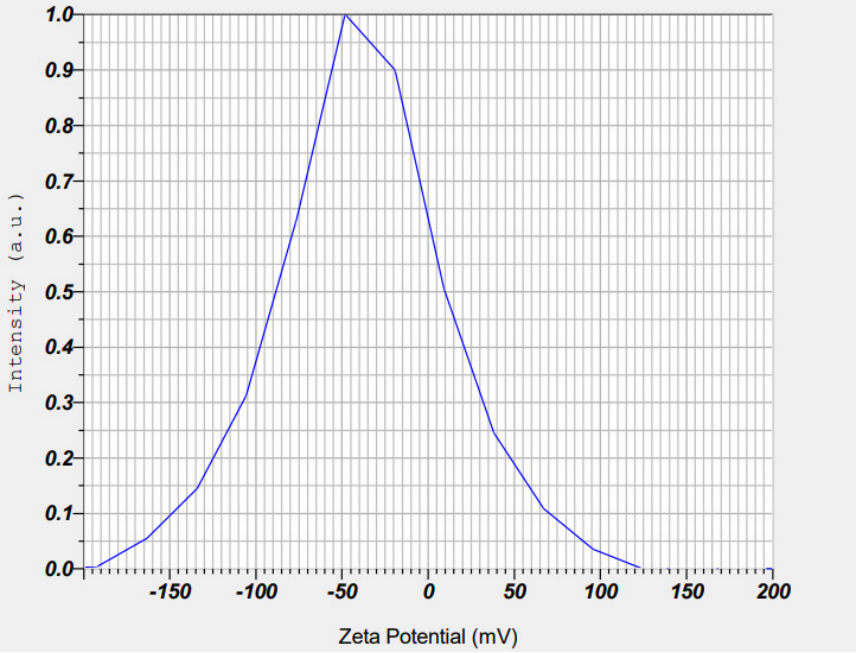

Figure 9: Zeta potential of OF-RSV-SMEDD.

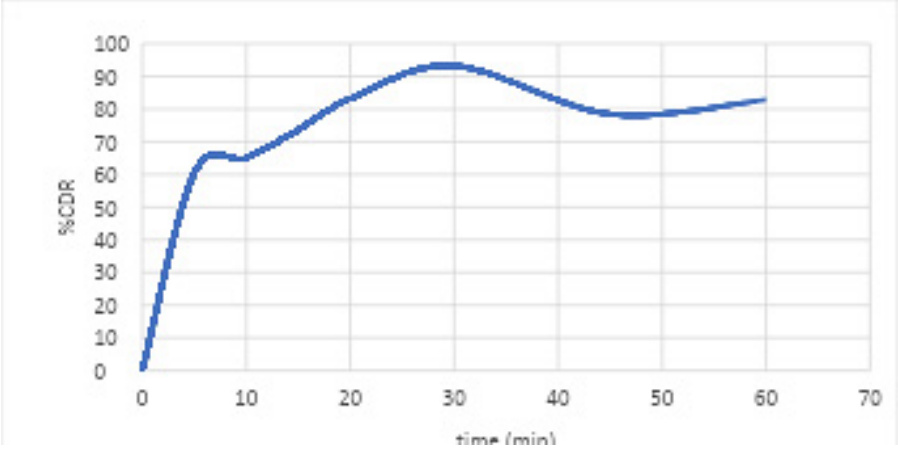

Figure 10: *In vitro* drug release graph for optimized formulations.

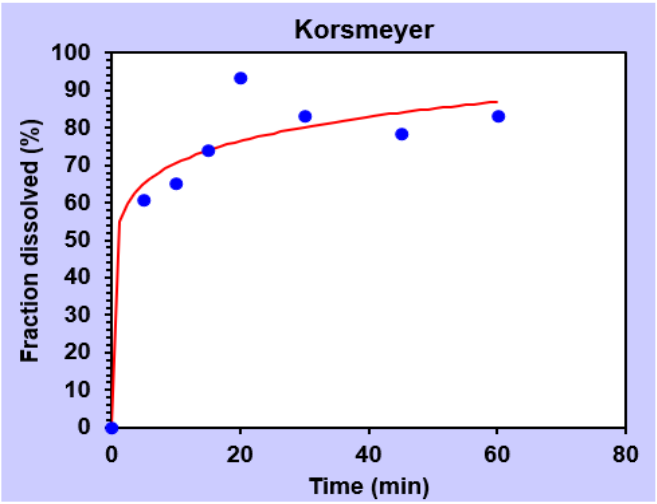

Figure 11: Krosmeyer Peppas model.

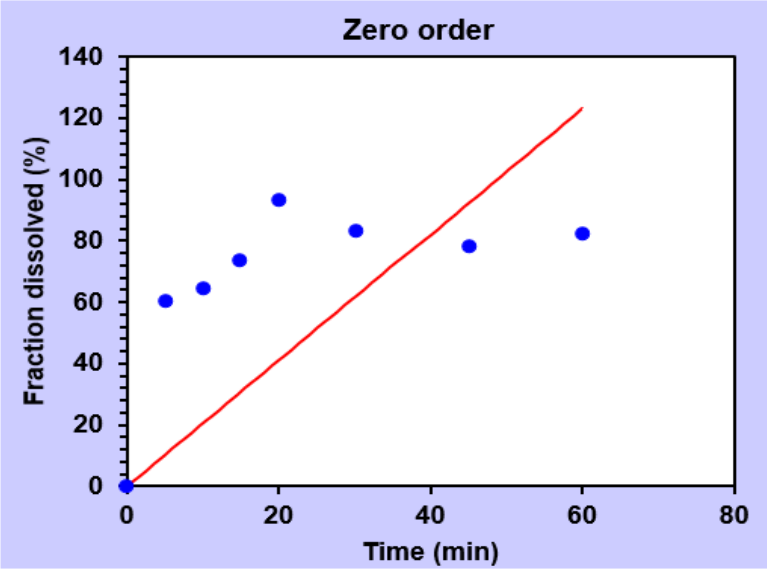

Figure 12: Zero -order model.

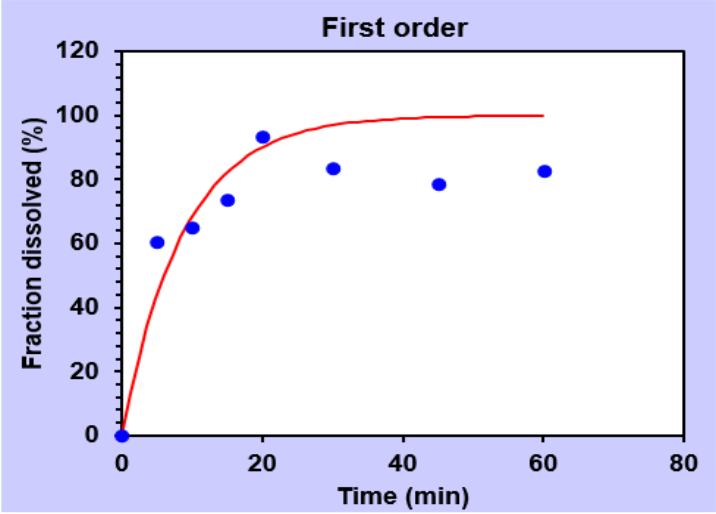

Figure 13: First order model.

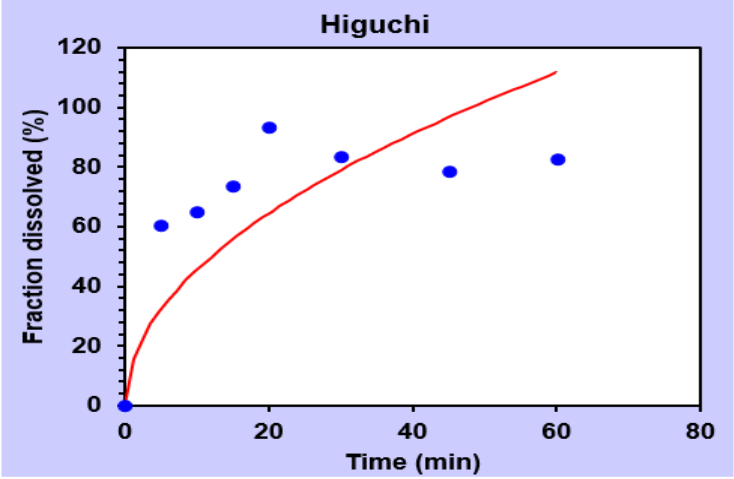

Figure 14: Higuchi model.

diffusion-controlled drug release mechanism. In comparison, zero-order kinetics (R^2=0.921) also showed good linearity, whereas first-order (R^2=0.780) and Higuchi model (R^2=0.406) demonstrated lower correlation. Therefore, the drug release predominantly follows the Korsmeyer–Peppas model with diffusion-controlled behaviour (Figures 11-14).

CONCLUSION

The increasing lipophilicity of modern drug candidates, driven by high-throughput screening and combinatorial chemistry, has resulted in many poorly water-soluble APIs, necessitating advanced formulation strategies to enhance solubility and bioavailability. Among these, SMEDDS offer an effective approach by improving solubility, enabling drug absorption, inhibiting P-gp efflux, and maintaining the drug in the solubilized state with nano-sized droplets. In this study, Rosuvastatin was successfully formulated as a liquid SEDDS using Maisine CC, Labrasol, and propylene glycol, demonstrating thermodynamic stability, good self-emulsification efficiency, with the minimal globule sizes below 200nm. The *in vitro* drug release studies followed Korsmeyer-Peppas model with the (R^2=0.933) (n=0.592). The results confirmed that novel lipid combinations can enhance formulation feasibility, although further permeability and pharmacokinetic studies are required to fully establish their potential. Overall, SMEDDS proved to be a promising strategy for RSV delivery, with all critical quality attributes achieved through a structured QbD approach involving QTPP definition, risk assessment, DOE application, and formulation optimization.

ABBREVIATIONS

RSV: Rosuvastatin; **SMEDDS:** Self-micro emulsifying drug delivery system; **QbD:** Quality by Design; **ODDSs:** Oral drug delivery systems; **LDL:** Low-density lipoprotein; **HMG-COA:** 3-hydroxy-3-methylglutaryl-coenzyme A; **LBDDS:** Lipid-based drug delivery systems; **QTPP:** Quality Target Product Profile; **CQAs:** Critical Quality Attributes; **REM:** Risk Estimation Matrix; **DOE:** Design of Experiment; **ICH:** International Council for Harmonisation; **FMEA:** Failure Mode and Effects Analysis; **RPN:** Risk Priority Number; **CMC:** Critical Material Characteristics; **PDI:** Polydispersity index; **VF:** Verification Formulation; **OF:** Optimized Formulation; **CDR:** Cumulative Drug Release.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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