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Optimization of Quality by Design Engineered Nanoformulation of an Antifungal Drug

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ABSTRACT:

Aim: This study aimed to employ a Quality by design (QbD) based approach for the development and optimization of stable voriconazole (VCZ) nanoemulsion (NE).

Materials and Methods: The NE was developed using Tween 80 as a surfactant, PEG 400 as a cosurfactant and sesame as oil phase. The Design of the Experiment (DoE) consisted Central composite design for the optimization. The independent variables were the concentration of surfactant mix (Smix), oil phase and RPM while globule size, zeta potential and polydispersity index (PDI) were the dependent variables. The NE was evaluated for particle size, zeta potential, pH, viscosity, transmittance, drug content, in-vitro drug release, and stability studies.

Results: The optimized formulation showed an approximate globule size of 34.39 nm, zeta potential of 63.62 and polydispersity index of 0.27 and was stable for three months at room temperature. *in vitro***. Conclusion:** A QbD-based approach can aid in the development of robust and thermodynamically stable NEs.

Keywords: QbD, Nanoemulsion, Voriconazole, Antifungal, Optimization

INTRODUCTION

"Quality by Design" (QbD) is a systematic approach to pharmaceutical development that emphasizes the importance of designing quality into the product from the beginning[1-5]. When applied to the development of nanoformulations, particularly for antifungal drugs, this approach ensures that the final product is both effective and safe for use. Antifungal drugs target fungal infections, which can be difficult to treat due to the fungal cell wall and biofilm formation, which often makes them resistant to conventional therapies[6-9]. Poor solubility, low bioavailability, and toxicity at effective doses are common issues with antifungal drugs. Nanoformulation can help overcome these challenges by enhancing drug delivery and targeting[10].

The QTPP outlines the desired characteristics of the final product, such as dosage form, route of administration, therapeutic index, and stability[11-15]. For an antifungal nanoformulation, key aspects might include targeted delivery to the infection site, sustained release, reduced toxicity, and improved patient compliance. CQAs are the physical, chemical, biological, and microbiological properties that must be controlled to ensure the product meets its QTPP[16,17]. For a nanoformulation, CQAs might include particle size, drug loading efficiency, zeta potential, release profile, and stability. Identify and assess risks associated with the formulation process that could impact the CQAs[18-21]. Critical Process Parameters include aspects like mixing time, temperature, and solvent choice, which can affect particle size and drug encapsulation efficiency. DoE is used to investigate the relationship between CPPs and CQAs systematically. It involves planning experiments to efficiently explore the design space[22,23]. For example, varying the concentration of the surfactant and the mixing speed might help determine the optimal conditions for producing nanoparticles of the desired size. Based on DoE results, the formulation and process parameters are optimized to achieve the desired CQAs[24-30]. A control strategy is established to monitor and maintain these parameters during manufacturing, ensuring consistent product quality[31-35].

The optimized process is scaled up from the laboratory to commercial production, with validation to ensure the product retains its quality attributes[36]. The QbD approach aligns with regulatory expectations for demonstrating a thorough understanding of the product and process. Regulatory submissions for nanoformulated antifungal drugs will require detailed documentation of the QbD process, including risk assessments, DoE, and control strategies[37-39]. Advantages of QbD in Antifungal nanoformulation include[40]:

Enhanced Efficacy: Nanoparticles can improve drug solubility and bioavailability, leading to better therapeutic outcomes.

-Reduced Toxicity: Targeted delivery and controlled release minimize side effects.

Regulatory Compliance: QbD facilitates smoother regulatory approval by providing a well-documented, scientifically sound approach to product development.

Applying QbD to the engineered nanoformulation of an antifungal drug result in a robust, high-quality product designed to meet specific therapeutic needs. This approach not only improves the drug's performance but also enhances patient safety and regulatory acceptance.

MATERIALS

Dr. Reddy's Laboratories Ltd. (Hyderabad, India) provided the voriconazole, while Abitech Corporation Limited (Janesvile, WI, USA) provided gift samples of Capmul MCM® (glycerol monodicaprylate) and Captex 100®. Gattefosse (Saint Priest, Cedex, France) donated Labrafil M 1944 CS® (oleoyl macrogoglyceride), Labrafil M 2125CS® (linoleoyl macrogolglycerides), Labrasol® (caprylo caproyl macrogol-8-glyceride), Peceol® (glyceryl oleate), Plurol oleique® (polyglycerol oleate), Lauroglucol 90® (propylene glycol

monolaurate), and Transcutol® P (diethylene glycol monoethyl ether). We purchased ethanol, polyethylene glycol 400 (PEG 400), Tween 80® (polyoxyethylene sorbitan monooleate), and Tween 20® (polyoxyethylene sorbitan monolaurate) from S.D. Fine-Chemicals Ltd. (Mumbai, India). Sesame oil and castor oil were purchased from Veda Oils (Gurugram, India). Analytical-grade chemicals were all that were used.

METHODS

Quality by Design (QbD) approach in formulation development

To prepare the nanoemulsion formulation, a design of experiment (DoE) was conducted to determine the ideal concentration of Smix and oil, together with the ideal mixing speed. The DESIGN EXPERT® (version 10) was utilized to illustrate the response surface model. To optimize process parameters and experimental repeatability while reducing experimentation time and costs, this technique aims to decrease experimental errors, process variance, and enhance efficiency. Using Central Composite Design (CCD), the nanoemulsion formulation was optimized. The selection of the mixing speed and the concentration of Smix and Oil served as independent variables. The dependent variables that were selected were globule size, zeta potential, and polydispersibility index (PDI).

RESULT AND DISCUSSION

Finally, the formulation variables were analyzed and optimized using a ternary phase diagram and design expert software for analyzing the data statistically and graphically using response surface plots. The Central Composite Design (CCD) was applied for the optimization of variables when experimental responses were dependent on the proportions of the variables only. In the present studies, the experimental designing of nanoemulsion formulation was done using the DESIGN EXPERT® (version 10). The independent variables of the nanoemulsion formulation selected were oil, S_{mix}, and RPM, i.e., A, B, and C respectively. The restrictions of the component proportion were selected from the boundaries of the nanoemulsion region of pseudo-ternary phase diagram. According to the FDA's Inactive Ingredient Database (IID), sesame oil is commonly used in various pharmaceutical formulations, including topical applications. The database indicates that sesame oil is used in concentrations up to 25% in topical formulations. It was therefore planned to keep the amount of oil as minimal as possible (≤10.0%) and the proportion of water at the maximum (≥70%). Smix (Tween 80 and PEG 400) were selected as an emulsifier and their amount was also kept in the optimum range (between 5-15%) and mixing speed was kept in the range of 1000 to 2500 rpm. Accordingly, as a design constraint A (S_{mix}), B (oil), and C (RPM) were taken at high and low levels as shown in the table … and the sum of A, B, and C was fixed at 100 %.

Table 1: Independent variables and responses for Central Composite Design

Factor	Name	Unit	Coded level			Response
			-	0	+	
A	Smix	%	5.00	6.23	15.00	Globule size (nm) R1 Zeta Potential (mV) R2 PDI (%) R3
B	Oil concentration	%	5.00	5.00	10.00	
C	RPM	rev/min	1000.00	1000.00	2500.00	

The Design Expert® software suggested a 20 CCD experimental design plan (Table 2) to

describe the effect of formulation components (independent variables) on Globule size (R1), Zeta potential (R2) and Polydispersibility Index (PDI) (R3). Out of 20 formulations 08 factorial, 06 axial, and 06 were central space type.

Table 2: Design Expert® software suggested formulation designs

Run	Space type	Independent variable			Response variable		
		A: Smix (%)	B: Oil concentration (%)	C: RPM (rev/min)	Response 1 (R1): Globule size (nm)	Response 2 (R2): Zeta potential (mV)	Response 3 (R3): PDI
1.	Factorial	5	5	1000	47.82	51.46	0.63
2.	Factorial	15	10	1000	55.34	38.11	0.79
3.	Axial	10	7.5	3011.34	105.35	59.78	0.51
4.	Factorial	15	5	2500	68.45	34.34	0.33
5.	Center	10	7.5	1750	64.23	49.65	0.32
6.	Factorial	5	5	2500	68.46	50.34	0.33
7.	Axial	1.59104	7.5	1750	99.34	51.56	0.91
8.	Axial	10	7.5	488.655	43.46	49.94	0.45
9.	Axial	10	11.7045	1750	64.92	34.54	0.58
10.	Factorial	15	10	2500	74.91	55.65	0.16
11.	Axial	18.409	7.5	1750	62.47	45.32	0.54
12.	Factorial	5	10	1000	34.39	63.62	0.27
13.	Factorial	5	10	2500	76.95	48.47	0.84
14.	Factorial	15	5	1000	46.95	23.13	0.21
15.	Axial	10	3.29552	1750	55.36	27.24	0.72

Optimization of NE components

Analysis of the data for globule size

CCD analysis of the fit summary response for globule size suggested the 2FI model with a sequential p-value of <0.0001, lack of fit p-value of 0.3608, adjusted R^2 of 0.9700 and predicted R^2 of 0.9360. The Sequential Model Sum of Square (SMSS) suggested the highest-order polynomial as 2FI vs Linear with 1409.96 sums of the square, 3 degrees of freedom, 469.99 mean square, 22.77 F-value and <0.0001 p-value. The lack of fit test also suggested the 2FI model with 186.71 sums of the square, 8 degrees of freedom, 23.34 mean square, 1.43 F-value and <0.3608 p-value. The summary statistics show the 2FI model with 4,54 standard deviation, 0.9795 R^2, 0.9700 adjusted R^2 and 0.9360 predicted R^2 values.

ANOVA for 2FI model
Factor coding was **Coded**.
The sum of squares was **Type III – Partial**
The **Model F-value** of 103.27 implies the model was significant. There was only a 0.01% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant. In this case, A, B, C, AB, AC, and BC are considerable model terms (values greater than 0.1000 indicate the model terms are not significant).
The **Lack of Fit F-value** of 1.43 implies the Lack of Fit is not significant relative to the pure error. There is a 36.08% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good to fit the model.
Fit statistics show the **predicted R^2** of 0.9360 is in reasonable agreement with the **adjusted R^2** of 0.9700; i.e. the difference is less than 0.2. The **Adeq Precision** measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio of 40.397 indicates an adequate signal. This model can be used to navigate the design space.

Table 3: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	56.42	1	1.02	54.23	58.62	
A-Smix Concentration	-22.61	1	1.23	-25.27	-19.96	1.0000
B-RPM	-13.23	1	1.23	-15.89	-10.58	1.0000
C-Oil Concentration	12.11	1	1.23	9.46	14.77	1.0000
AB	9.04	1	1.61	5.57	12.51	1.0000
AC	-5.60	1	1.61	-9.07	-2.13	1.0000
BC	-7.95	1	1.61	-11.42	-4.48	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, and the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

The final equation in terms of coded factors
Globule size = 56.42-22.61A-13.23B+12.11C+9.04AB-5.60AC-7.95BC
The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors
Globule size = 49.1571-5.3843 Smix conentartion-0.0099 RPM+16.7417 Oil concentration-0.0024 Smix concentration x RPM-0.4477 Smix concentration x Oil concentration-0.0042 Oil concertation

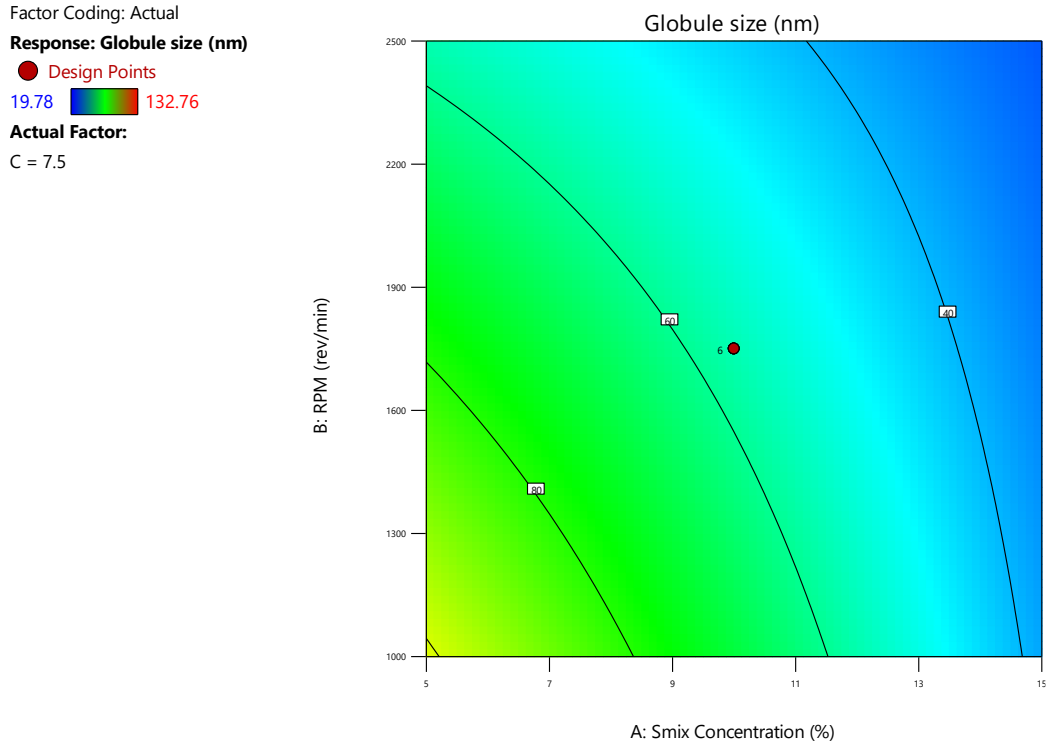

Fig. 1. 2-D Response surface plot showing the effect of formulation variable and prediction of Optimumresponse of globule size

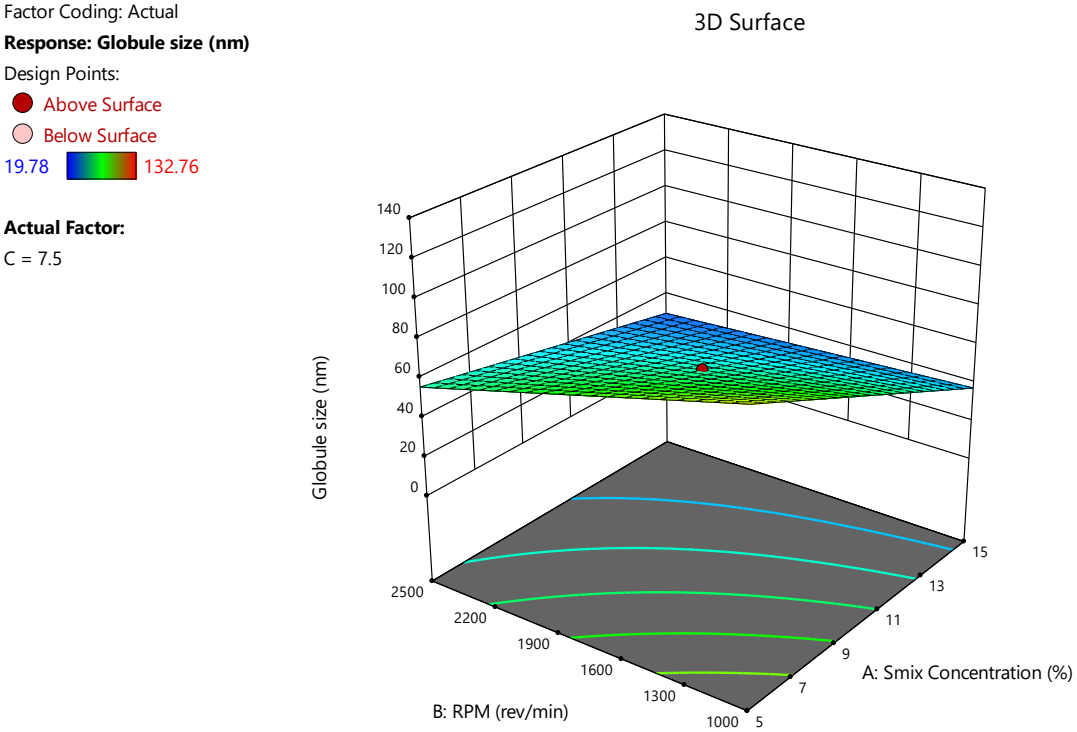

Fig. 2. 3D Response surface plot showing the effect of formulation variable & prediction of Optimum response ofglobule size

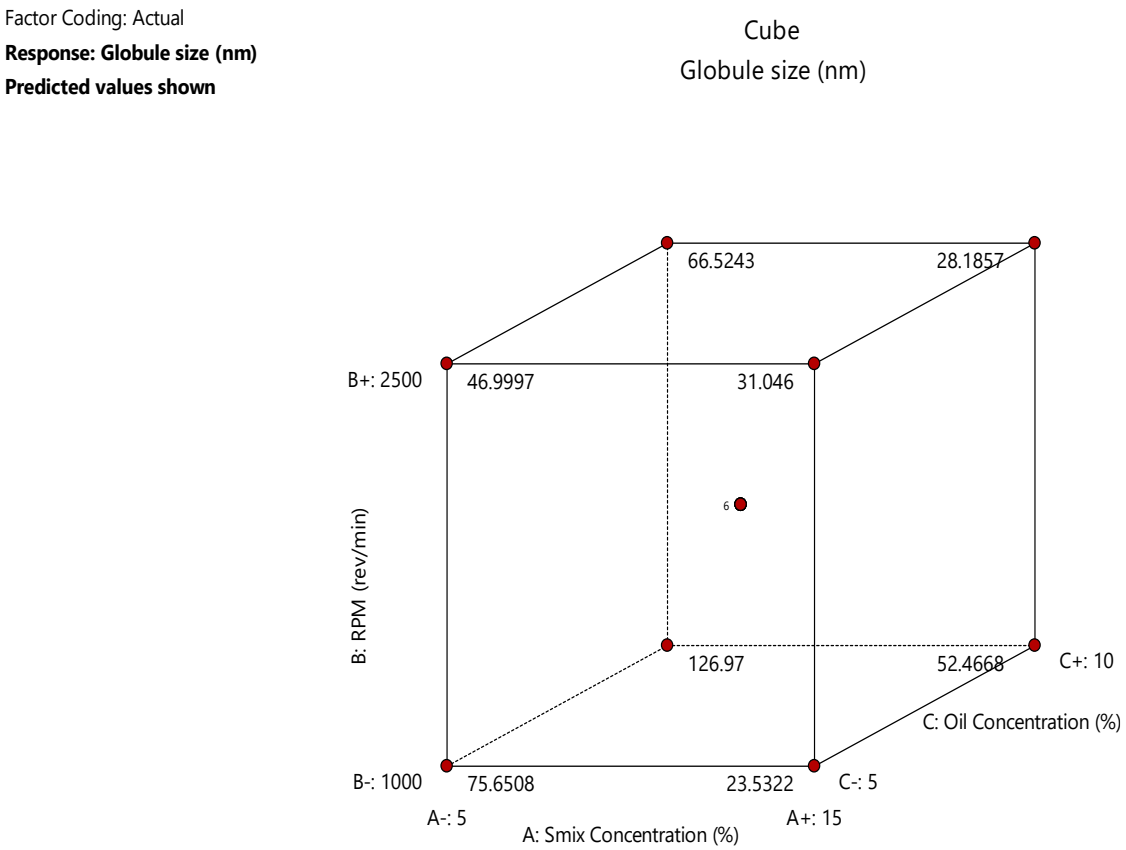

Fig. 3. Cube -Plot showing the effect of formulation variable & prediction of Optimum response ofglobule size

Analysis of the data for the polydispersibility index (PDI)

The CCD analysis of the fit summary response for PDI suggested the quadratic model with a sequential p-value of < 0.0001, adjusted R^2 of 0.9906 and predicted R^2 of 0.9617. The SMSS suggested the highest-order polynomial as Quadratic vs 2FI where the additional terms were significant and the model was not aliased. The selected polynomial had a 0.6010 sum of squares, 3 degrees of freedom, 0.2003 mean square value, 431.05 F-value and <0.0001 p-value. The summary statistics show a quadratic model with a standard deviation of 0.0216**,** R^2 value of 0.9950, adjusted R^2 of 0.9906, predicted R^2 of 0.9611 and PRESS value of 0.0358.

ANOVA for Quadratic model

Factor coding was **Coded**.

The sum of squares was **Type III - Partial**

The **Model F-value** of 222.53 implies the model was significant. There was only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicated model terms were significant. B, C, AB, BC, A^2, B^2 and C^2 were considerable model terms in this case.

Table 4: Fit Statistics

Std. Dev.	0.0216		**R^2**	0.9950
Mean	0.4048		**Adjusted R^2**	0.9906
C.V. %	5.33		**Predicted R^2**	0.9617
			Adeq Precision	41.6322

The data from fit statistics show a predicted R^2 value of 0.9617 9617 was in reasonable agreement with the **Adjusted R²** of 0.9906; i.e. the difference is less than 0.2. **Adequate Precision** measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio of 41.632 indicates an adequate signal so this model can be used to navigate the design space.

Table 5: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	0.1635	1	0.0088	0.1439	0.1831	
A-Smix Concentration	-0.0070	1	0.0058	-0.0200	0.0060	1.0000
B-RPM	-0.1036	1	0.0058	-0.1166	-0.0906	1.0000
C-Oil Concentration	0.0221	1	0.0058	0.0091	0.0351	1.0000
AB	-0.1428	1	0.0076	-0.1597	-0.1258	1.0000
AC	-0.0168	1	0.0076	-0.0337	0.0002	1.0000
BC	-0.0365	1	0.0076	-0.0535	-0.0195	1.0000
A^2	0.1825	1	0.0057	0.1699	0.1952	1.02
B^2	0.0858	1	0.0057	0.0732	0.0985	1.02
C^2	0.0851	1	0.0057	0.0724	0.0978	1.02

The coefficient estimated represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients were adjustments around that average based on the factor settings. When the factors were orthogonal the VIFs were 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. The final equation in terms of coded factors

PDI = +0.1635-0.0070 A -0.1036 B +0.0221 C -0.1428 AB -0.0168 AC -0.0365BC +0.1825 A^2 +0.0858 B^2 +0.0851 C^2

The coded factors equation can be used to predict the response for given levels of each factor. By default, the high levels of the factors were coded as +1 and the low levels were coded as -1. The coded equation was useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

PDI = +1.29366-0.0707 Smix concentration -0.00014 RPM – 0.1479 Oil concentration -0.000038 Smix x RPM -0.0013 Smix concentration x Oil concentration -0.00019 RMP x Oil concentration +0.0073 Smix concentration^2 +1.525-0.07 RPM^2 +0.0136 Oil concentration^2

The equation in terms of actual factors can be used to predict the response for given levels of each factor. Here, the levels should be specified in the original units for each factor.

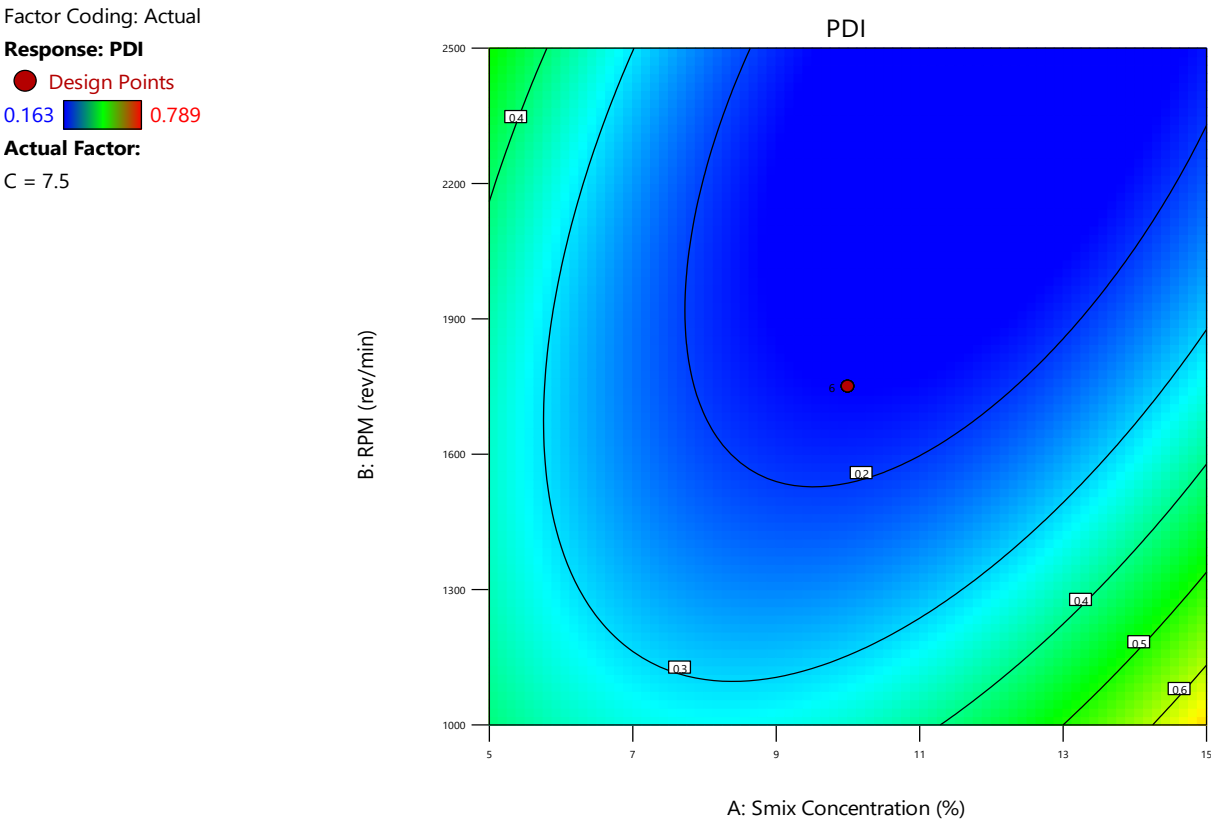

Fig. 4. 2-D Response surface plot showing the effect of formulation variable and prediction of Optimumresponse of PDI

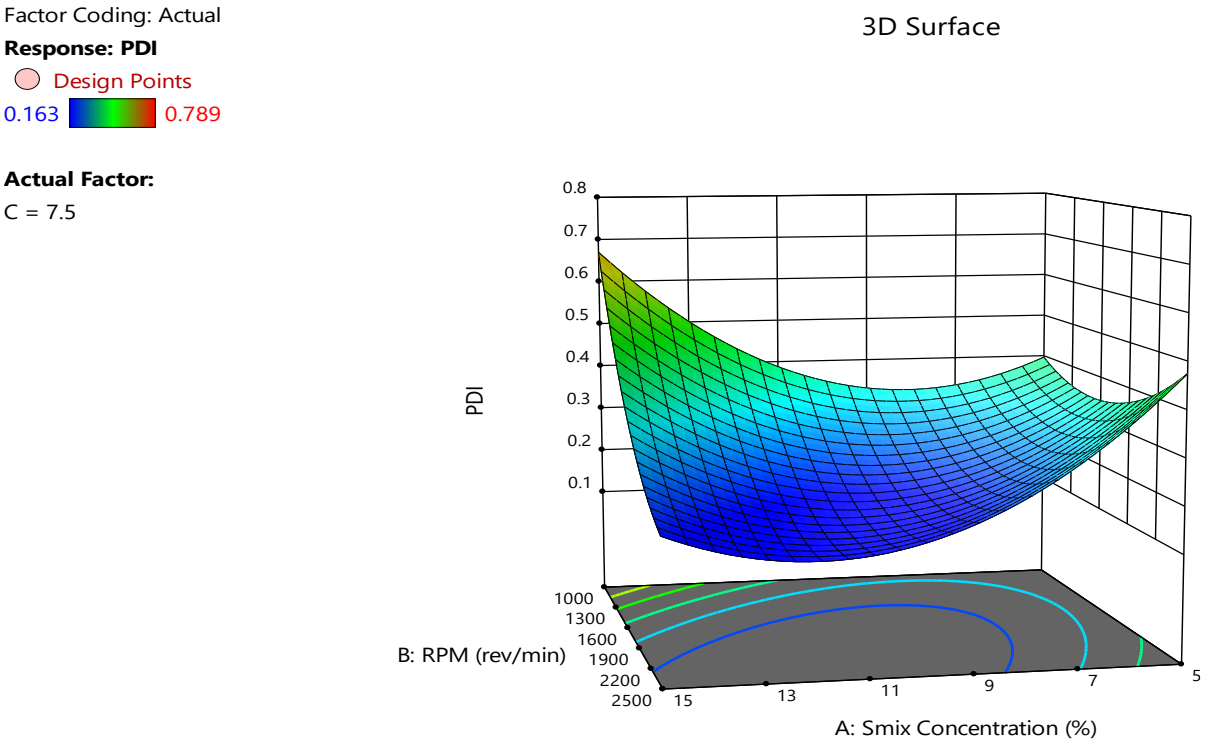

Fig.5. 3D Response surface plot showing the effect of formulation variable & prediction of Optimum response of PDI

Analysis of the data for the zeta potential

The CCD analysis of the fit summary response for zeta potential suggested the quadratic model with a sequential p-value of < 0.0001, a p-value of 0.0048, adjusted R^2 of 0.9402 and predicted R^2 of 0.7727. The SMSS suggested the highest-order polynomial as Quadratic vs 2FI where the additional terms were significant and the model was not aliased. The selected polynomial had a 0520.80 sum of squares, 3 degrees of freedom, 173.60 mean square value, 28.81 F-value and <0.0001 p-value. The model summary statistics show a quadratic model with a standard deviation of 2.45, R2 value of 0.9685, adjusted R2 of 0.9402, predicted R2 of 0.7727 and PRESS of 435.44.

ANOVA for Quadratic model

Factor coding was **Coded**.

The sum of squares was **Type III - Partial**

The **Model F-value** of 34.21 implies the model was significant. There was only a 0.01% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicated model terms were significant. In this case, A, B, C, AB, AC, A^2, B^2, and C^2 were significant model terms. Values greater than 0.1000 indicate the model terms were not significant. The **Lack of Fit F-value** of 15.24 implies the Lack of Fit is significant. There was only a 0.48% chance that a Lack of Fit F-value this large could occur due to noise.

Table 6: Fit Statistics

Std. Dev.	2.45		**R^2**	0.9685
Mean	41.34		**Adjusted R^2**	0.9402
C.V. %	5.94		**Predicted R^2**	0.7727
			Adeq Precision	17.6219

The **Predicted R^2** of 0.7727 was in reasonable agreement with the **Adjusted R^2** of 0.9402; i.e. the difference was less than 0.2. **Adeq Precision** measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio of 17.622 indicated an adequate signal so the model can be used to navigate the design space.

Table 7: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	34.45	1	1.00	32.22	36.68	
A-Smix Concentration	2.20	1	0.6642	0.7222	3.68	1.0000
B-RPM	6.78	1	0.6642	5.30	8.26	1.0000
C-Oil Concentration	4.22	1	0.6642	2.74	5.70	1.0000
AB	2.52	1	0.8678	0.5901	4.46	1.0000
AC	-6.47	1	0.8678	-8.40	-4.54	1.0000
BC	1.20	1	0.8678	-0.7349	3.13	1.0000
A^2	2.97	1	0.6466	1.53	4.41	1.02
B^2	1.71	1	0.6466	0.2741	3.16	1.02
C^2	5.41	1	0.6466	3.97	6.85	1.02

The coefficient estimated represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients were adjustments around that average

based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, and the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Final Equation in Terms of Coded Factors

Zeta potential = +34.45+2.20 A +6.78 B+4.22 C+2.52AB -6.47 AC+1.20 BC+2.97 A^2+1.71 B^2+5.41C^2

The coded factors equation can be used to predict the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation was useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Zeta potential = 52.7966+0.7708 Smix concentration -0.0131 RPM -7.2358 Oil concentration +0.00067 Smix concentration x RPM -0.5175 Smix concentration x Oil concentration + 0.00063 RPM x Oil concentration +0.1186 Smix concentration^2 +3.0484 RPM^2 +0.8652 Oil concentration^2

The equation in terms of actual factors can be used to predict the response for given levels of each factor. Here, the levels should be specified in the original units for each factor.

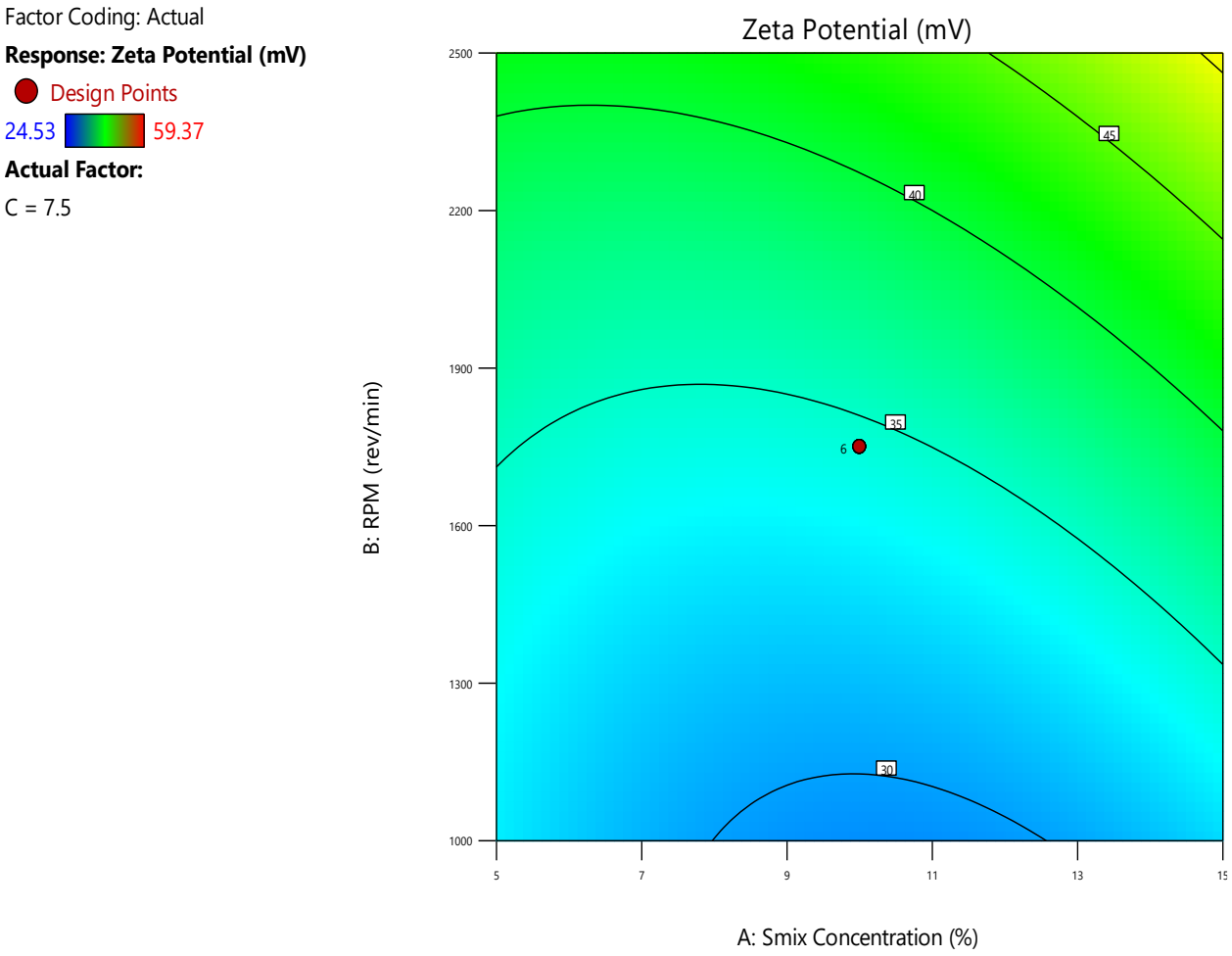

Fig.6. 2-D Response surface plot showing the effect of formulation variable and prediction of Optimumresponse of Zeta potential

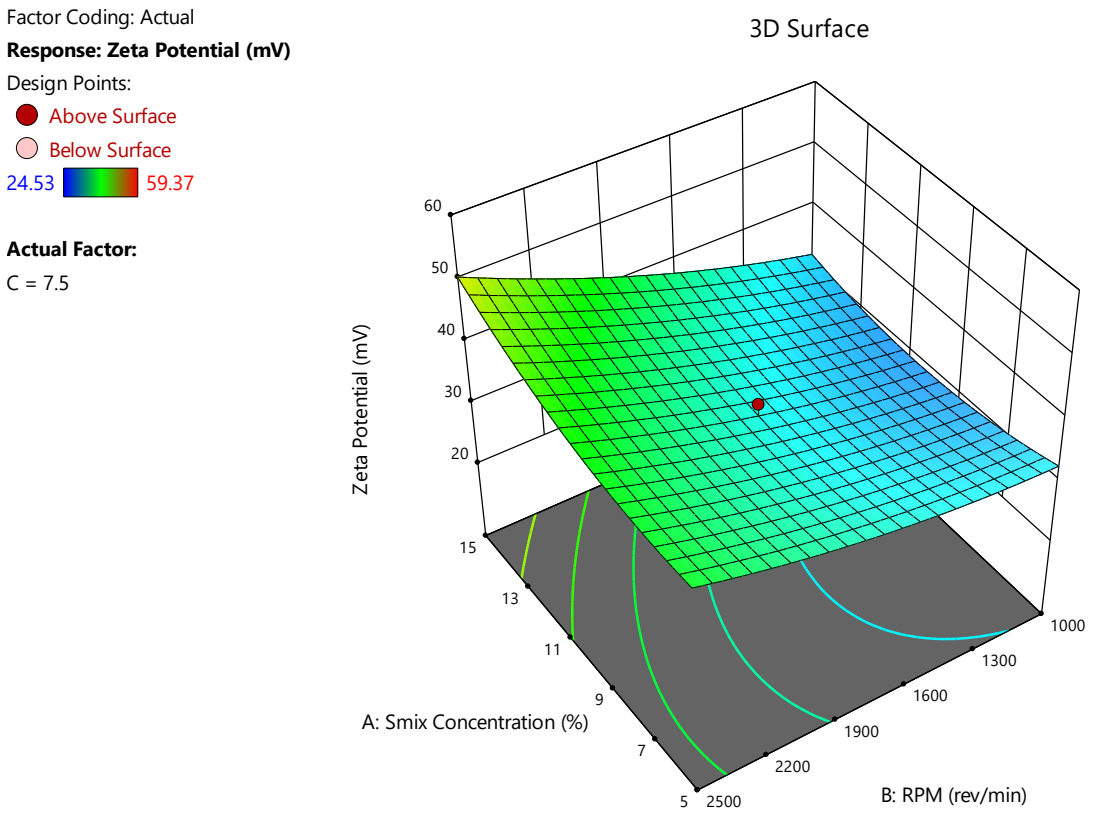

Fig.7. 3D Response surface plot showing the effect of formulation variable & prediction of Optimum response of Zeta potential

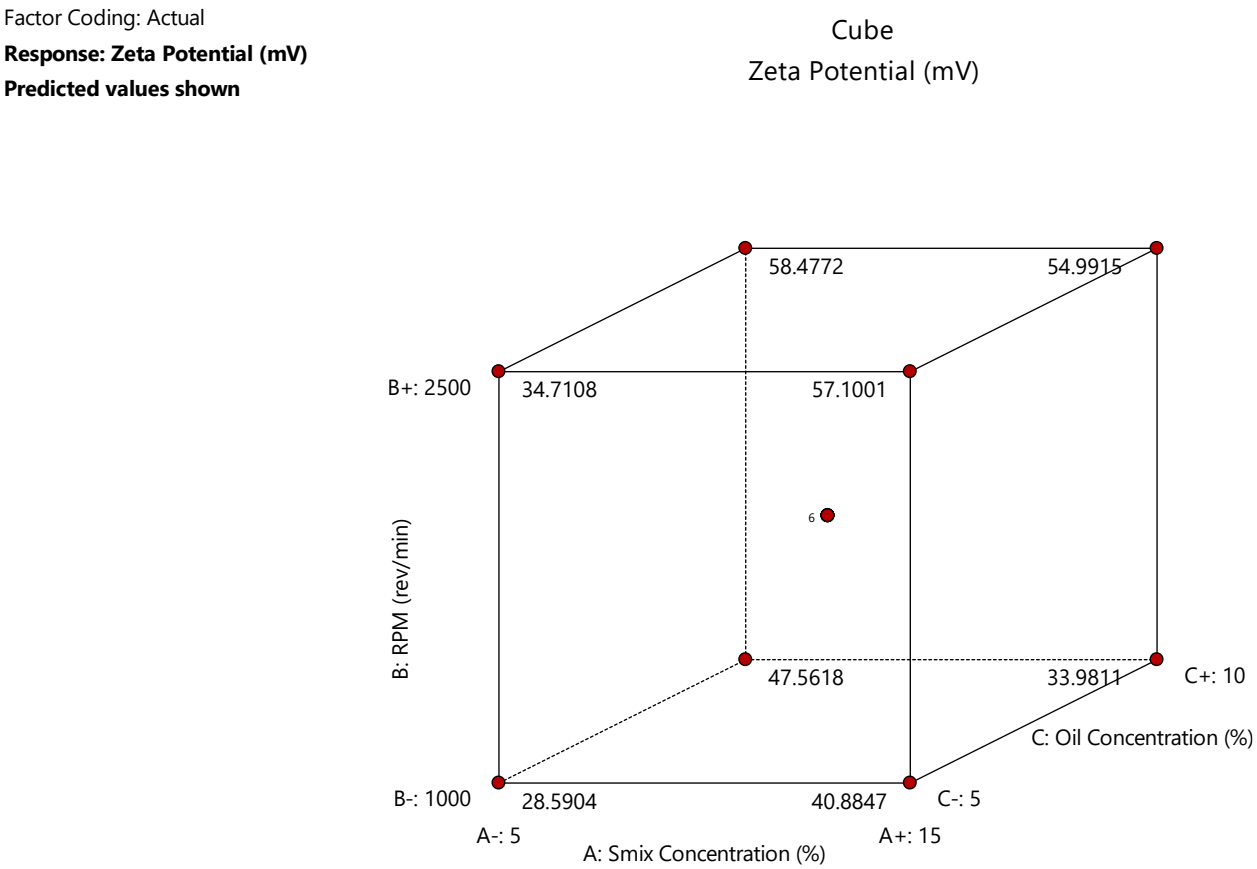

Fig.8. Cube -Plot showing the effect of formulation variable & prediction of Optimum response of Zeta potential

Prediction of optimized NE formulation

A numerical optimization technique predicted optimized NE formulation. In the first step, the formulation constraints within which the formulation optimization was to be done were defined as (a) the globule size should be minimum (b) the Zeta potential should be maximum (c) the PDI value should be minimum. The Design Expert software analyzed these inputs. To achieve these desired responses, the software proposed two optimized solutions in Table and fig..

Table 8: Formulation constraints for numerical optimization

S. No.	Variable	Formulation constraints		
		Goal	Lower limit	Upper limit
1	A, Smix (%)	Minimize	5.0	15.0
2	B, Oil concentration (%)	Minimum	5.0	10.0
3	C, RPM	In range	1000	2500
4	R_1, Globule size (nm)	Minimum	34.39	105.35
5	R_2, PDI	Minimum	23.13	59.78
6	R3, Zeta potential (meV)	Maximum	0.21	0.91

Table 9: Optimized solutions anticipated by Design Expert software

Proposed solution	Independent variable			Response variable			Desirability value
	A Smix (%)	B Oil conc. (%)	C RPM	R1 Globule size (nm)	R2 Zeta potential (meV)	R3 PDI	
	5.00	10.00	1000	34.39	63.62	0.27	0.964

Outcome: To achieve the desired formulation response one solution was anticipated by the Design Expert® software, the solution showed a desirability value of 0.964. As the proposed solution containing 5% w/w Smix, 10% w/w Oil and 1000 RPM showed the highest desirability value (0.964), it was selected as the optimized nanoemulsion formulation composition for further formulation development trials.

Based on the development trial batches and predefined QTPP for nanoemulsion CQA and justification of initial risk assessment are presented in Table and Table .

Table 10: Quality target product profile (QTPP)

S. No.	QTPP parameter	Target	Could it be QTPP?	Justification
	Therapeutic effect	For topical delivery of VCZ, it will be useful to treat infection caused by Candida and Aspergillus species infection and prevent skin damage due to infection	Yes	Localized delivery of VCZ can be achieved which may result in better efficacy and treatment

	Dosage form	Nanoemulsion based gel	Yes	Optimized nano emulsion-based formulation will improve the skin penetration. Further with the help of nanoemulsion based delivery, prolonged period of drug release will be attained which may result in improved efficacy of the formulation.
	Route of administration	Topical	Yes	The developed formulation aims for local delivery of the drug hence topical route was selected
	Strength of VCZ	1%	Yes	For topical route the amount of dose administered is limited due to various barriers and hence given limit is set.
	Dissolution profile	*In vitro* drug release up to 12 h	Yes	Development of a Nanoemulsion based formulation for topical delivery was aimed to be with improved efficacy.
	Appearance	Transparent to translucent formulation	Yes	This parameter is known to establish safety and efficacy along with patient compliance.
	Physicochemical properties	pH, globule size, zeta potential, viscosity, refractive index, % drug content, etc.	Yes	It is required to establish safety and efficacy along with patient compliance.
	Stability	Stable at room temperature	Yes	Required to ensure optimum

				safety and efficacy of the formulation.

Table 11: Rationale for the initial risk assessment

S. No.	CPPs	CQAs	Supporting arguments and initial strategy
1.	Fine and stable emulsion formation	Globule size, Zeta potential	The formation of fine emulsion is carried out by aqueous titration. The risk of fine emulsion formation impacting the drug product CQAs like globule size and zeta potential are high.
2.	Uniform and clear emulsion formation	PDI	The formation of uniform and clear emulsion formation to impact the PDI is high.
3.	Drug entrapment	% Drug content, *In vitro* drug release	The drug entrapment to impact the % drug content and in vitro drug release is high.

CONCLUSION

A NE loaded with VCZ and having excipients including, Tween 80, PEG 400 and sesame oil was optimized using a central composite design. The optimized NE was stable and showed improved in vitro antifungal activity as compared to pure drug. The qbD-based approach in formulation development can lead to robustness, thermodynamical stability and more effective NEs.

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