RESEARCH PAPER

QbD assisted development and optimization of composite guar gum silver nanoparticle-based posaconazolehydrogel

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ABSTRACT

Objective(s): This study aimed to enhance the bioavailability and optimize a composite silver nanoparticle-based Posaconazole hydrogel using a Quality by Design (QbD) approach. A Box-Behnken design was employed as an independent quadratic model within the QbD framework. The primary goals were to improve antifungal efficacy, achieve controlled drug release, and ensure formulation stability and safety.

Materials and Methods: A systematic QbD strategy was applied, involving the identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) to develop a robust formulation. Silver nanoparticles were incorporated into the hydrogel matrix,and Posaconazole, the active pharmaceutical ingredient, was added. The formulation parameters were optimized using a Design of Experiments (DoE) approach, specifically the response surface methodology (RSM) via Box-Behnken design. The optimized hydrogel was characterized using Fourier-transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), differential scanning calorimetry (DSC), and invitro release studies.

Results: The optimized hydrogel exhibited an enhanced pharmacokinetic profile, sustained drug release, and improved quality attributes. Stability was confirmed through accelerated stability studies. Remarkably,invitro release studies demonstrated a 90.35% drug release within twelve minutes.

Conclusion*:* The Box-Behnken optimization technique successfully developed a silver nanoparticle-based Posaconazole hydrogel. The formulation showed significant potential for improved therapeutic efficacy in antifungal treatment.

Keywords: *Silver, Nanoparticles, Hydrogel, Optimization, Antifungal agent.*

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INTRODUCTION

Hydrogels are three-dimensional networks capable of absorbing and retaining substantial amounts of water while maintaining structural integrity through cross-linking. They can be derived from synthetic or natural sources and are classified based on cross-linking mechanisms, physical properties, structural characteristics, origin, and preparation methods [1]. Hydrogels offer several advantages, including high elasticity, stimuli-responsive (temperature- or pH-sensitive) drug release, bypassing of first-pass metabolism, and ease of chemical modification [2].

Posaconazole is a broad-spectrum antifungal agent belonging to the triazole class. It primarily prevents and treats invasive fungal infections caused by Aspergillus and Candida species in immunocompromised patients, such as those undergoing chemotherapy or stem cell transplantation [3]. Posaconazole exerts its antifungal activity by inhibiting the enzyme lanosterol 14α-demethylase, crucial for synthesizing the fungal cell membrane. Posaconazole and itraconazole share a similar molecular structure, with the former being modified from itraconazole through hydroxylation of the triazole side chain and substitution of fluorine atoms on the phenyl ring. These modifications enhance its potency and broaden its antifungal spectrum. Posaconazole exhibits both fungicidal and fungistatic properties [4]. Table 1 summarizes the physicochemical characteristics of Posaconazole, which play a critical role in the pharmacokinetic properties of the drug [3, 4].

Silver and its compounds have been used for millennia for antibacterial and therapeutic purposes. Recently, nanotechnology has revolutionized this field, particularly with the

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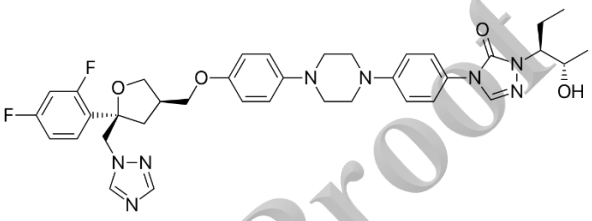
advent of silver nanoparticles (AgNPs). AgNPs are highly valued for their unique physical and chemical properties, which make them prominent in biomedicine, especially for their antifungal properties and controlled synthesis methods [5].

Table 1. General details and physicochemical characteristicsof Posaconazole

S.No.	Properties	Reported Data
1.	Drug category	Triazole antifungal
2.	Molar mass	700.792 g/mol.
3.	Empirical formula	$C_{37}H_{42}F_2N_8O_4$
4.	Metabolism	Liver (glucuronidation)
5.	Description	White to off white non hygroscopic powder
6.	Protein binding	98 to 99%
7.	Bioavailability	Low (8 to 47% oral)
8.	Excretion	Faecal (71-77%) and kidney (13-14%)
9.	Solubility	Methanol and dichloromethane
10.	BCS class	Class-II
11.	logP	5.5
12.	Melting point	170-172°C
13.	Structure	
14.	Trademarks	Noxafil

Quality by Design (QbD) was pioneered by Joseph M. Juran and outlined in the ICH Q8 guideline. This approach emphasizes that quality should be inherent in the product, not something that is tested afterwards. QbD is a systematic methodology that begins with clear objectives, focusing on a thorough understanding of the product and the processes involved. It relies on scientific principles and effective risk management strategies to ensure that quality is integrated into the product from the outset [6].

In 2002, the United States Food and Drug Administration (USFDA) released a foundational document outlining the modernized framework for current Good Manufacturing Practice (cGMP), termed "Quality by Design" (QbD), to facilitate the expeditious manufacturing of products that are not only safe and effective but also of high quality. Throughout the formulation development process, a range of QbD tools, including the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs) of the product, and Quality Risk Management (QRM), were utilized [7]. The fundamental steps of QbD are illustrated in the flow chart shown in Figure 1.

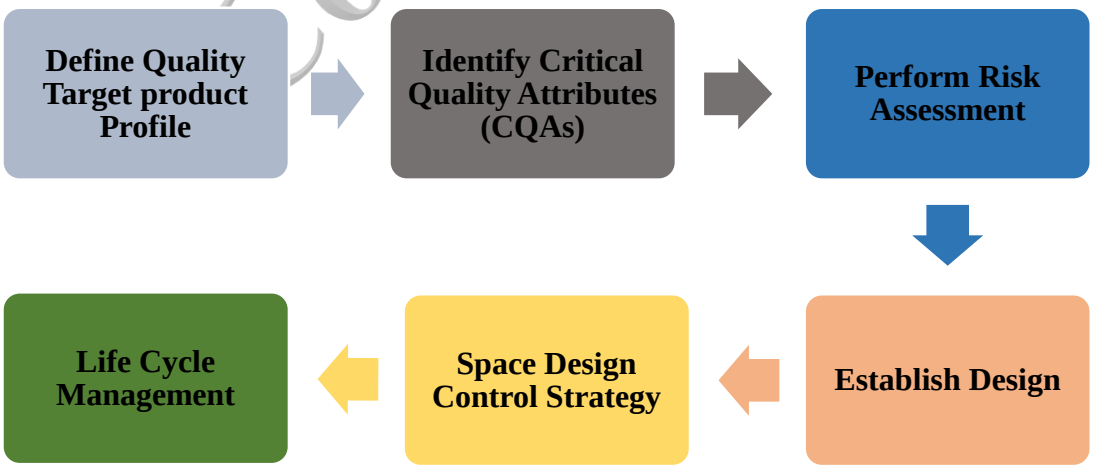


Fig. 1. Flow chart of steps of QbD.

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Box-Behnken design

The Box-Behnken Design (BBD) was chosen to explore the correlation between quality parameters and the factors affecting the quality of dosage forms. Box-Behnken is a design that provides an alternative to the resource-intensive complete factorial design [8]. Regarding experimental design, BBD is notably more efficient than Central Composite Design (CCD) and Full Factorial Design (FFD). The Box-Behnken design is particularly well-suited for response surface methodology because it can estimate quadratic model parameters and facilitate the construction of sequential designs. In contrast to BBD, which employs three levels per factor, the Central Composite Design requires more trials [9-11].

MATERIALS AND METHODS

Materials

Posaconazole was kindly provided as a gift sample by Allastir Pvt. Ltd., Tamil Nadu, India. Silver nanoparticles were purchased from Scitechesy Research and Technology, Varanasi, India. Carbopol 940, Guar Gum, Methylparaben, Propylparaben, Propylene Glycol, and Triethanolamine were obtained from Loba-Chemie, Mumbai, India. All chemicals used in the study were of analytical grade and were used without further purification.

Method

Chemical cross-linking of the polymer involves the radical polymerization of a polymer, such as Carbopol 940, with the cross-linker triethanolamine, forming stable, three-dimensional networks. In combination with the polymer and drug, other excipients were dissolved with continuous stirring using a mechanical stirrer at a speed of 500 rpm [12]. Various concentrations of the drug and excipients, as outlined in Table 2, were used to prepare the hydrogel.

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Table 2. Composition of hydrogel

S. No.	Category	Ingredient	Concentration
1.	Drug	Posaconazole	1%
2.	Anti-Microbial	Silver Nanoparticle	0.1Mz
3.	Gelling Agent	Carbopol 940	0.25 – 0.75 %
4.	Emulsion stabilizer	Guar Gum	0.5%
5.	Emollient	Propylene Glycol	0.5-1.5%
6.	Cross-linking agent	Triethanolamine	0.5-1.5%
7.	Preservative	Methyl Paraben, Propyl paraben	0.02 – 0.3 %
8.	Solvent	Distilled water, Methanol	Q. S

Statistical design

The optimization of the antifungal hydrogel was carried out using computer-aided methods, specifically utilizing Design Expert trial version 13 software and the Box-Behnken experimental design. This design approach incorporated three factors, each at three levels. The independent variables in this setup included the amounts of Carbopol 940 (g), propylene glycol (mL), and triethanolamine (mL) [13]. Key response variables, such as viscosity, pH, and percentage drug release, were identified as critical quality attributes. These variables and their respective levels and the response variables are detailed in Tables 3 and 4, respectively.

Table 3. Independent variables with level

S.No.	Variables	Unit	Lower level (-1)	Upper level (+1)
1.	Carbopol 940	g	0.25	0.75
2.	Propylene glycol	ml	0.5	1.5
3.	Triethanolamine	ml	0.5	1.5

Table 4. Dependent variables for hydrogel formulation

S.No.	Response variables	Unit
1.	Viscosity	Cps
2.	pH	-
3.	Cumulative % drug release	%

The Box-Behnken design with three factors and three responses suggested fifteen formulation trials, which were subsequently prepared and evaluated for their response variables. A response surface plot was then generated to illustrate the interactions between the independent and

dependent variables. The significance of the factors and the model was determined using an ANOVA test, with a significance threshold set at a p-value of < 0.05. Additionally, the model's adequacy was assessed through correlation coefficients (R^2) and adjusted R^2, providing statistical insights into the optimization process. The polynomial equation (1) derived from this experimental design is as follows:

$$\textit{Eqn. (1)} Yi = b0 + b1\,X1 + b2\,X2 + b3\,X3 + b12\,X1\,X2 + b13\,X1\,X3 + b23\,X2\,X3 + b11\,X12 + b22\,X22 + b33\,X\,32$$

In which, Yi represents the dependent variable, while b0 is the intercept. The regression coefficients b1 to b33 denote the weights assigned to each independent variable, which were determined based on preliminary experiments. The effects of independent variables X1 (Carbopol 940), X2 (Propylene glycol), and X3 (Triethanolamine)wereinvestigatedfurther in the study[9, 14, 15].

Characterization of hydrogel formulation

Organoleptic properties

Observations were made regarding the physical characteristics of the formulation, including color, odor, and texture.

Homogeneity

A visual inspection was performed to evaluate the hydrogel's transparency and to check for any phase separation. Tests were also conducted to identify the presence of any aggregates [16].

Determination of pH

One gram of hydrogel was dissolved in 100 mL of distilled water. The pH of the resulting hydrogel dispersion was measured after two hours using a digital pH meter. This process was repeated thrice, and the average pH value was calculated [17].

Determination of viscosity

The viscosity of the hydrogel formulations was measured at 25°C using a Brookfield viscometer (Model DV-II) with spindle number 64, operating at 100 rpm [17].

Spreadability

Two standard glass slides (6 cm by 2 cm) were used to assess the spreadability. The hydrogel was sandwiched between the slides with a 100 g weight, and a 20 g force was applied via a pulleysystem. The time the upper slide moved 6 cm was recorded [16, 17]. Spreadability was determined using the following formula:

$$Spreadability = M * l/t$$

Where M is the weight attached to the upper slide, l is the length of the glass slide, and t is the time taken in seconds.

Drug content

A beaker containing precisely one gram of topical hydrogel and 20 mL of methanol was prepared and mixed thoroughly. The resulting solution was then filtered using Whatman filter paper No. 1. After filtration, 1 mL of the strained solution was transferred to a 10 mL volumetric flask and diluted to 10 mL with methanol. Various aliquots of the stock solution were prepared and analyzed using a UV-Visible spectrophotometer (Shimadzu-1800) at a maximum absorption wavelength (λ_max) of 260 nm. A standard curve of Posaconazole in methanol at 260 nm is depicted in Figure 2

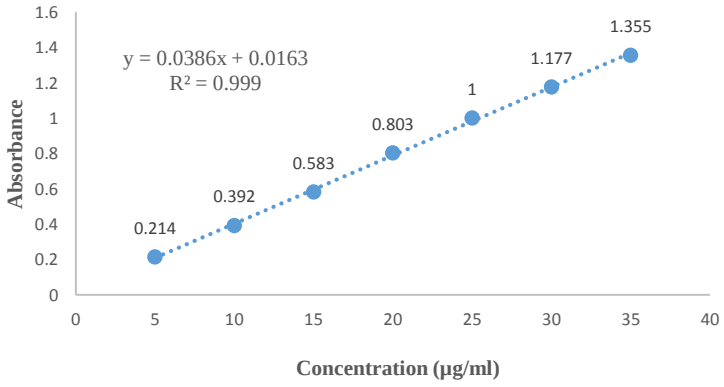

Fig. 2. Standard graph of Posaconazole in methanol

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In vitro drug release

The invitro drug study used a Franz diffusion cell with an egg membrane as the semi-permeable barrier. The donor compartment contained 1 gram of hydrogel, and methanol was used in the receptor compartment. Heating was performed with a magnetic stirrer and hot plate, and sampling involved replacing equal volumes of the receptor fluid. Samples of 3 mL were withdrawn at intervals of 2, 4, 6, 8, 10, and 12 minutes and analyzed spectrophotometrically at 260 nm.

Fourier Transform Infrared Spectrophotometry (FTIR) analysis

FTIR spectroscopy examined the individual ingredients and physical mixtures in various combinations to identify potential interactions within the final formulation. The analysis was performed over a 4000 to 400 cm^{-1} spectral range using an IR instrument (Shimadzu Corporation, Japan).

Differential Scanning Calorimetry (DSC) analysis

The hydrogel formulation underwent DSC analysis using the PerkinElmer DSC 6000 instrument, calibrated with indium. A 3 mg sample was heated in aluminum pans under dry nitrogen gas at 40°C/minute [18, 19].

Stability studies

The optimized hydrogel formulation was subjected to stability analysis to assess its temperature-related stability over a specifiedperiod. The formulation underwent three months of accelerated stability testing under International Conference on Harmonization (ICH) guidelines. It was placed in an aluminum tube and exposed to 40 ± 2°C conditionsand 75 ± 5% relative humidity. Samples were taken at defined intervals (0, 1, and 3 months), and various characteristics, such as homogeneity, pH, viscosity, drug release percentage, and drug content, were evaluated [17, 19].

Transmission Electron Microscopy (TEM)

TEM analysis was performed using Thermo Fisher Scientific Talos L120C equipment to examine the morphology, size, and dispersion pattern of various particles or entities present in the hydrogel formulation.

RESULT AND DISCUSSION

Quality Risk assessment (QRM) & fishbone diagram for hydrogel

Risk factors were identified using the Ishikawa diagram, also known as the Fishbone or cause-and-effect diagram, based on findings from the literature (Figure 3). This risk assessment, combined with Quality Risk Management (QRM), was further facilitated by the Risk Estimation Matrix (REM). In assessing risks related to hydrogel development, the Ishikawa diagram was used in conjunction with QRM (Table 5). The REM helped to understand the impact of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) on the product's Critical Quality Attributes (CQAs) by assigning risk grades (low, medium, or high) to individual parameters based on their influence. Parameters with high risk were then considered for the Design of Experiments to effectively determine the design space [21, 22].

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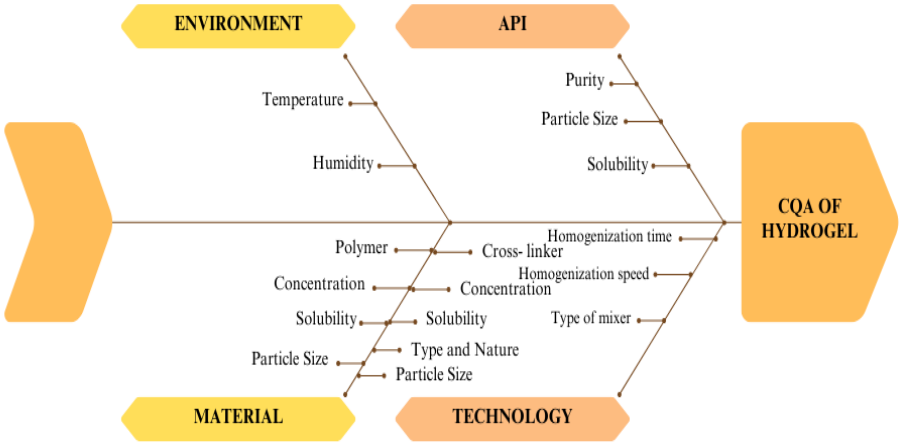

Fig. 3. Fish bone diagram illustrating risk factors that may affect CQA of hydrogel

Table 5. QRM matrix for hydrogel

CMAs/ CPPs		pH	Viscosity	Drug Release	Spreadability	Drug Content
Drug	Dose	H	M	H	H	H
	Solubility	H	L	H	H	H
Polymer	Dose	M	H	H	H	H
Emollient	Dose	L	H	H	H	L
Cross-linking Agent	Dose	H	M	H	H	H
Homogenization Time	Min.	L	H	M	M	H
Homogenization Speed	RPM	L	H	M	M	H

H = High M = Medium L =Low

Preparation of hydrogel with BBD

The Box-Behnken Design (BBD) generated fifteen batches, incorporating three center points, using multiple independent variables and three responses, as outlined in Table 6. These batches were designated as MQA501 to MQA515.

Table 6. The Box-Behnken Designed Composition of Antifungal Hydrogel

Run/ Batches	Independent variables			Dependent variables		
	X1	X2	X3	Y1	Y2	Y3
	Carbopol 940 (g)	Propylene glycol (ml)	Triethanolamine (ml)	Viscosity (cps)	pH	Cumulative drug release (%)
1.	0.75	1.5	1	19383	7.21	81.4
2.	0.5	1	1	17012	7.46	87.58
3.	0.75	1	1.5	19506	7.16	83.22
4.	0.5	0.5	0.5	17312	7.58	88.39
5.	0.75	0.5	1	19406	7.24	82.06
6.	0.5	1.5	0.5	17910	7.45	85.15
7.	0.25	1	1.5	7526	7.83	93.6
8.	0.5	0.5	1.5	17055	7.46	89.58
9.	0.25	0.5	1	7313	7.89	94
10.	0.5	1	1	17330	7.62	86.8
11.	0.75	1	0.5	19437	7.23	82.63
12.	0.5	1	1	17180	7.58	88.46
13.	0.5	1.5	1.5	17239	7.53	87.58
14.	0.25	1	0.5	7606	7.79	91.08
15.	0.25	1.5	1	7306	7.78	93.6

Effect of factors on responses

(A) Viscosity: The Design Expert software established the relationship between viscosity and the independent variables using a quadratic model, as shown in equation (2) below.

$$\textit{Eqn. (2):}\ Viscosity = +17174.00 + 5998.00A + 93.63B - 117.78C - 4.75AB + 37.25AC - 103.50BC - 3840.75A2 + 19.50B2 + 185.50C2$$

In this equation, A corresponds to Carbopol 940, B represents propylene glycol, and C represents triethanolamine. The independent variables with positive coefficients indicate an increase in viscosity, while those with negative coefficients suggest a decrease in viscosity.

The 3D response surface and 2D contour plots demonstrated that Carbopol 940 and triethanolamine concentrations significantly impactviscosity, ranging from 7313 cps to 19506 cps. In contrast, the concentration of propylene glycol has a relatively minimal effect on viscosity, as depicted in Figures 4(A), 4(B), 4(C), and 4(D). The perturbation graph of viscosity shown in Figure 5 indicates that A had a notably higher impact than B and C on viscosity, highlighting its significant effect ($p < 0.0001$).

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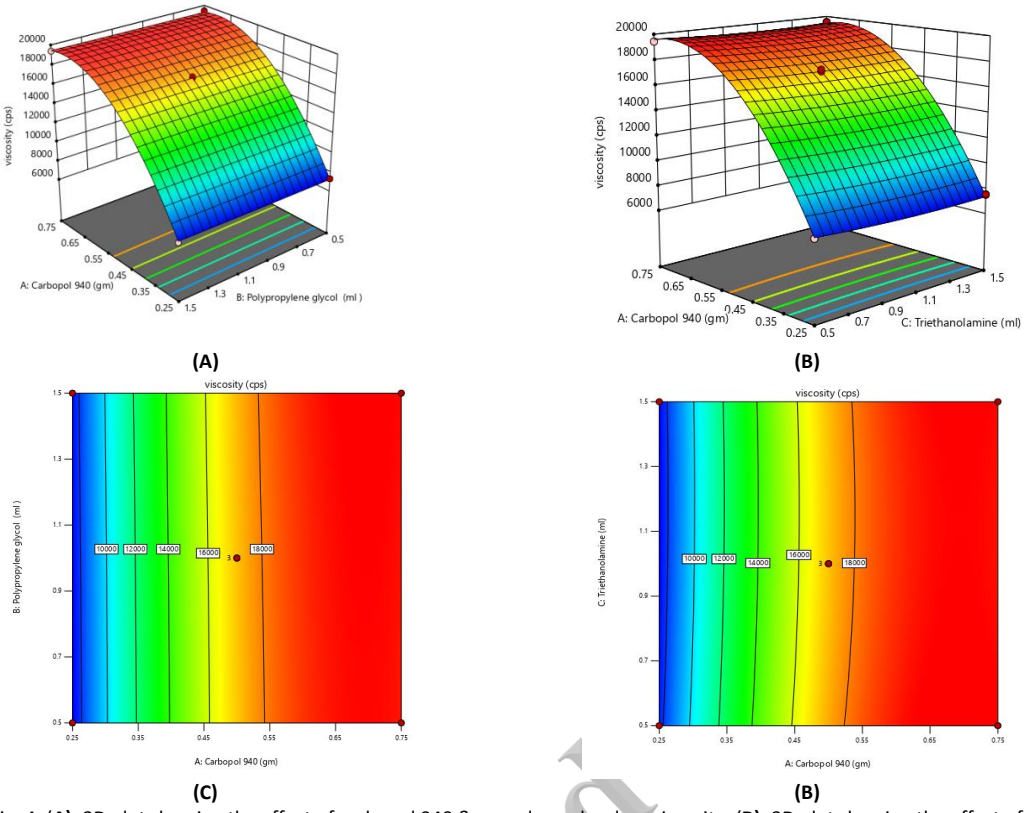

Fig. 4. **(A).** 3D plot showing the effect of carbopol 940 & propylene glycol on viscosity. (**B).** 3D plot showing the effect of Triethanolamine on viscosity. **(C).** 2D contour plot showing the effect of carbopol & propylene glycol on viscosity. (**D).** 2D contour plot showingtheeffect of Triethanolamine on viscosity.

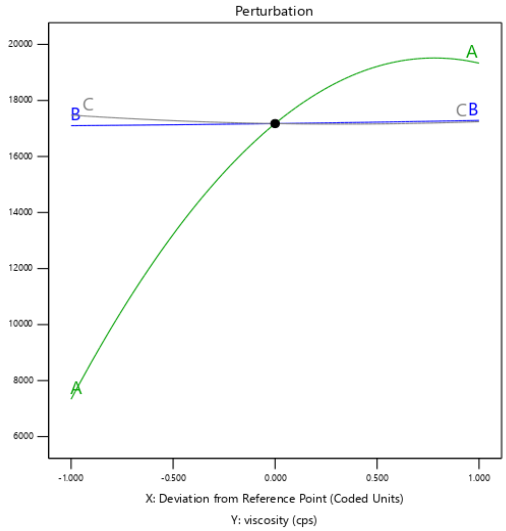

Fig. 5. Perturbation graph of Viscosity

(A) pH: The Design Expert software developed a linear model (equation 3) to describe the relationship between pH and the independent variables, as presented below.

Eqn. (3)

$$pH = +7.52 - 0.3063A - 0.0250B - 0.0088C$$

In this equation, A represents Carbopol 940, B stands for propylene glycol, and C corresponds to triethanolamine. Positive coefficients for the independent variables indicate an increase in pH, while negative coefficients suggest a decrease in pH.

The 3D response surface and 2D contourplots demonstrated that Carbopol 940 and triethanolamine concentrations significantly impactpH, ranging from 7.16 to 7.8. In contrast, the concentration of propylene glycol has a relatively minimal effect on pH, as depicted in Figures 6(A), (B), (C), and (D). The perturbation graph shows the effect of various factors on pH (Figure 7).

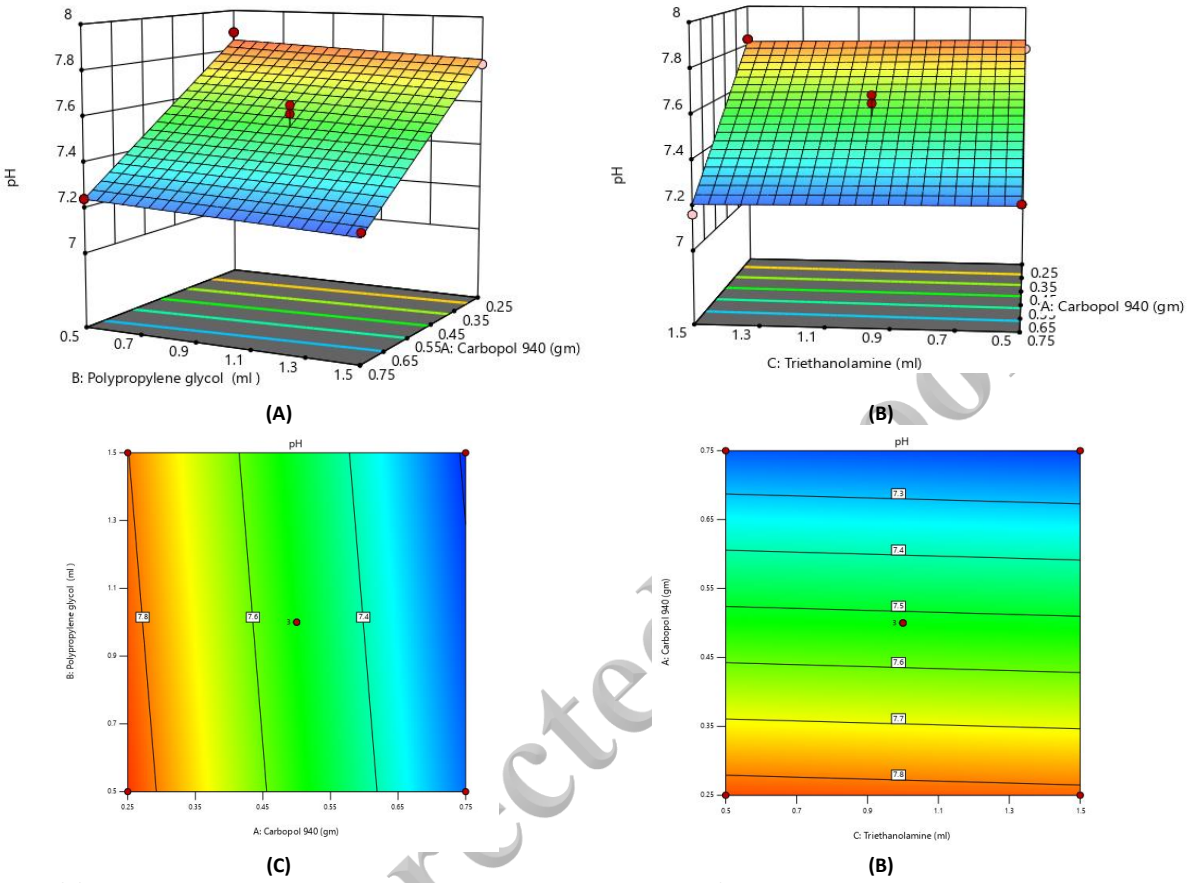

Fig. 6. **(A):** 3D plot showing the effect of carbopol 940 & propylene glycol on pH; (**B):** 3D plot showingthe effect of Triethanolamine on pH. **(C):** 2D contour plot showing the Effect of carbopol 940 & propylene glycol on pH; **(D):** 2D contour plot showingtheEffect of Triethanolamine on pH

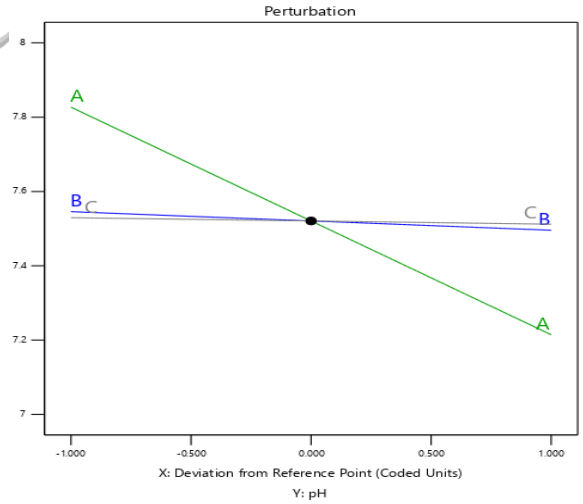

Fig. 7. Perturbation graph of pH

In-vitro drug release%

The Design Expert software established the relationship between viscosity and the independent variables using a quadratic model, as shown in equation (4) below.

$$\textbf{Eqn. (4): } \boldsymbol{Cumulative\ \%\ drug\ release} = +\mathbf{87.68} - \mathbf{5.37}\boldsymbol{A} - \mathbf{0.7875}\boldsymbol{B} + \mathbf{0.8412}\boldsymbol{C}$$

In this equation, A represents Carbopol 940, B stands for propylene glycol, and C corresponds to triethanolamine. Positive coefficients for the independent variables indicate increased drug release, while negative coefficients suggest decreased drug release.

The 3D response surface and 2D contourplots demonstrated that Carbopol 940 and triethanolamine concentrations significantly impactdrug release. An increase in the concentration of Carbopol and triethanolamine results in a decrease in % drug release, ranging from 94% to 81.4%. In contrast, the concentration of propylene glycol has no significant effect on % drug release, as depicted in Figures 8(A), (B), (C), and (D). The perturbation graph of cumulative % drug release is shown in Figure 9.

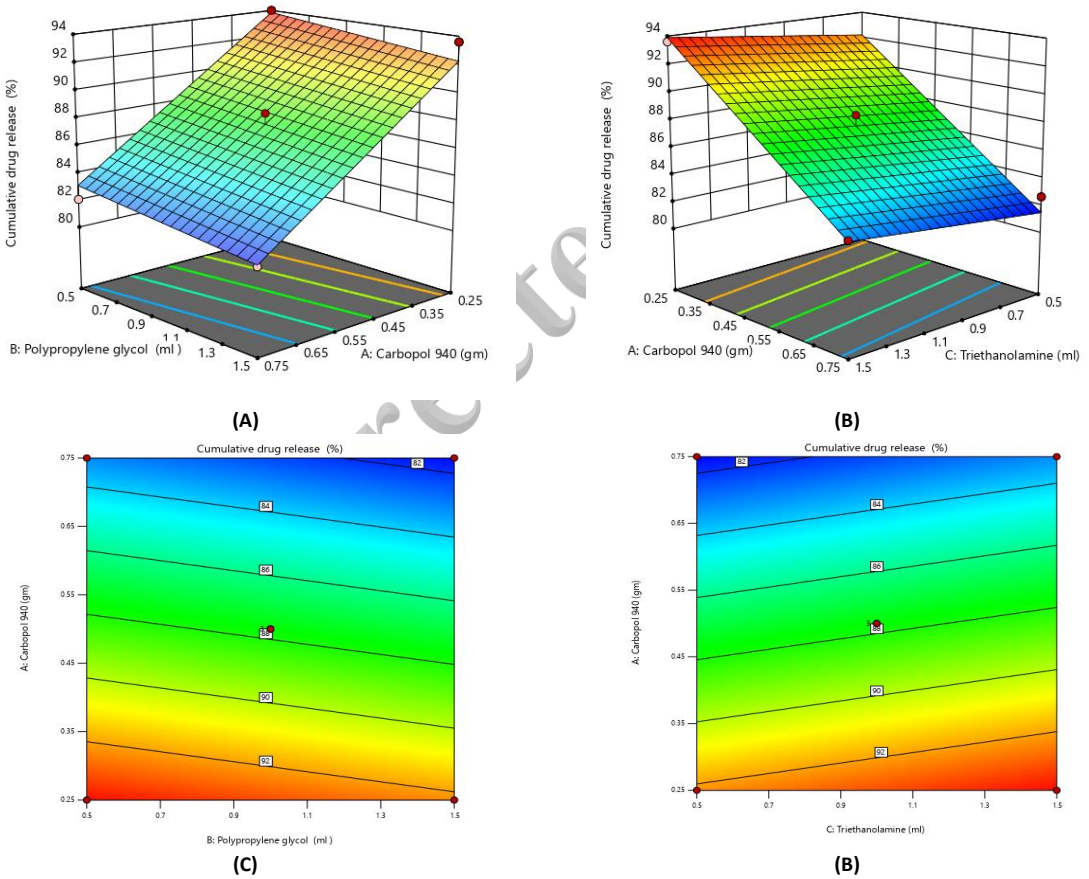

Fig. 8. **(A):** 3D plot showing effect of carbopol & propylene glycol on % drug release; **(B):** 3D plot showing the effect of Triethanolamine on % drug release; **(C):** 2D plot showing effect of carbopol & propylene glycol on % drug release; **(D):** 2D plot showing effect of Triethanolamine on % drug releases

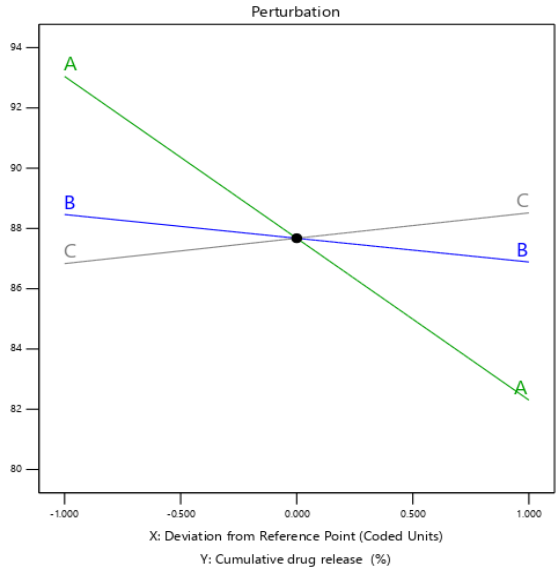

Fig. 9. Perturbation graph of cumulative drug release.

Result of statistical analysis of Antifungal Hydrogel

The fit summary and ANOVA analysis of the antifungal hydrogel provide essential insights into the effects of various factors on the response variables (Table 7). These insights are crucial for identifying significant factors and optimizing the formulation to meet quality standards. By understanding these relationships, the development process can bemore efficient, saving time and resources.

Table 7. Model fitting of measured response variables of software designed hydrogel

S. No.	Response Variable	Source	Sequential *P*-value	Lack of Fit *P*-value	Adjusted R^2	Predicted R^2	Remarks
1.	Viscosity	Linear	0.0001	0.0041	0.7930	0.6845	--
		2FI	0.9998	0.0027	0.7157	0.2724	--
		Quadratic	<0.0001	0.2823	0.9979	0.9902	Suggested
		Cubic	0.2823	--	0.9990	--	Aliased
2.	pH	Linear	0.0565	0.9555	0.9434	0.9262	Suggested
		2FI	0.0507	0.9740	0.9546	0.0381	--
		Quadratic	0.0542	0.9814	0.9480	0.0444	--
		Cubic	0.0833	0.9825	--	--	Aliased
3.	Drug release	Linear	<0.0001	0.5941	0.9567	0.9327	Suggested
		2FI	0.6954	0.4732	0.9498	0.8704	--
		Quadratic	0.9980	0.2760	0.9202	0.6200	--
		Cubic	0.2760	--	0.9614	--	Aliased

Predicted optimized antifungal hydrogel

The target objectives for the response variables in the proposed optimized formulation are outlined in Table 8. In contrast, Table 9 detailsthe concentrations of the independent variables, along with the expected and actual response values. The overlay plot for the final optimization is shown in Figure 10.

Table 8. Desirable objective of response variables for hydrogel batch

S. No.	Response variables	Criteria	Desired value
1.	Viscosity	Target	17088
2.	pH	Target	7.52
3.	Cumulative % drug release	Maximum	87.75

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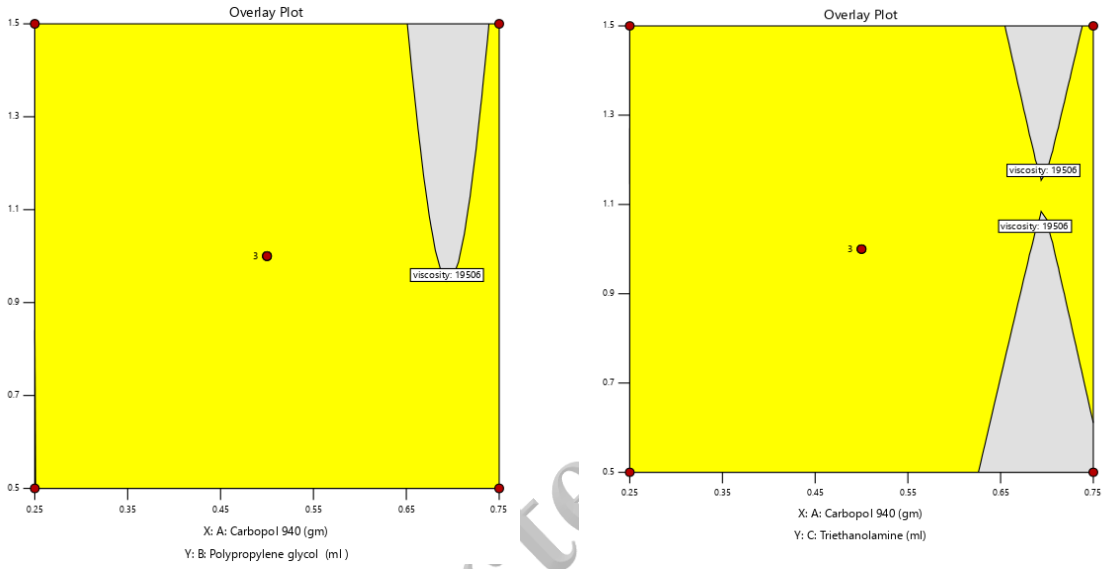
Table 9. Predicted dependent and independent variables values by the software

S. No.	Optimized formulation composition (MQA516)		Response		
	Component	*Quantity*	*Evaluation parameter*	*Software predicted*	*Experimentally observed value*
1.	Carbopol 940	0.5gm	Viscosity (cps)	17088	17058
2.	Propylene glycol	1ml	pH	7.52	7.56
3.	Triethanolamine	1ml	Cumulative drug release (%)	87.75	90.35



(A) **(B)**

Fig. 10. **(A):** Overlay plot of carbopol 940 and polypropylene glycol ; **(B):** Overlay plot of carbopol 940 and Triethanolamine of final optimization

Characteristic properties of antifungal hydrogel

Organoleptic properties

The physical characteristics of the trial batches included white color, odorlessness, and a smooth texture. Similarly, the optimized batch was found to be white in color, odorless, and to have a soft texture.

Homogeneity

A visual inspection was performed to evaluate the hydrogel's transparency and check for any phase separation. The study observed no phase separation in both the trial and optimized batches. The formulations exhibited transparency characteristics typical of gel formulations.

pH

The pH values of the antifungal hydrogel batches were measured using a calibrated pH meter. The optimized formulation had a pH of 7.56, which falls within the acceptable range of 7.16 to 7.89.

Viscosity

The viscosity of the hydrogel formulations was assessed using a Brookfield viscometer (Model DV-II) with spindle number 64 at a rotation speed of 50 rpm. The optimized hydrogel formulation exhibited a viscosity of 17,058 cps, which falls within the acceptable range of 7,306 to 19,506 cps.

Spreadability

The spreadability of the hydrogel formulations was evaluated. The optimized hydrogel formulation exhibited a spreadability of 35 g/cm, within the acceptable range of 6 to 46 g/cm.

Drug content

The drug content of the optimized formulation was found to be 96.23%, which falls within the acceptable range of 90.18% to 97.79%.

***In vitro* drug release**

The percentage of drug release for various trial batches and the optimized batch are depicted in Figures 11 and 12, respectively.

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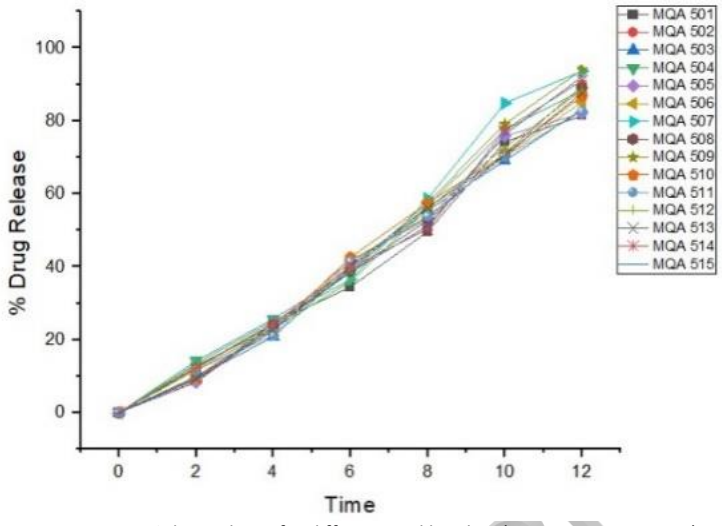


Fig. 11. In-vitro % drug release for different trial batches (MQA501 to MQA515)

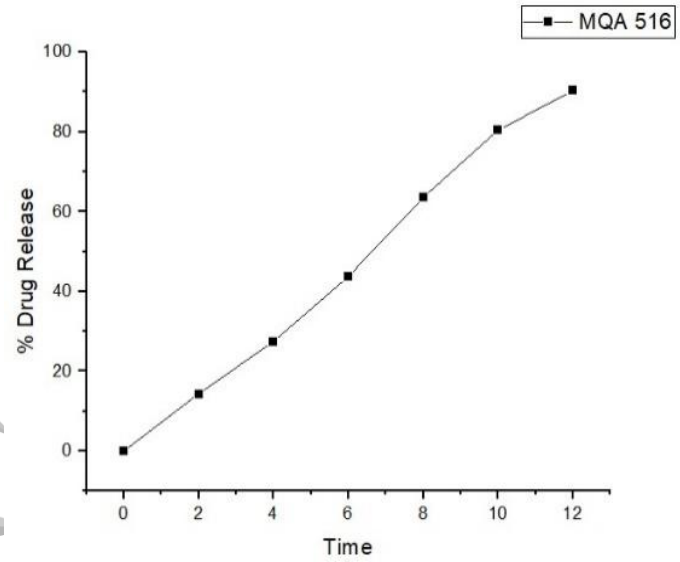


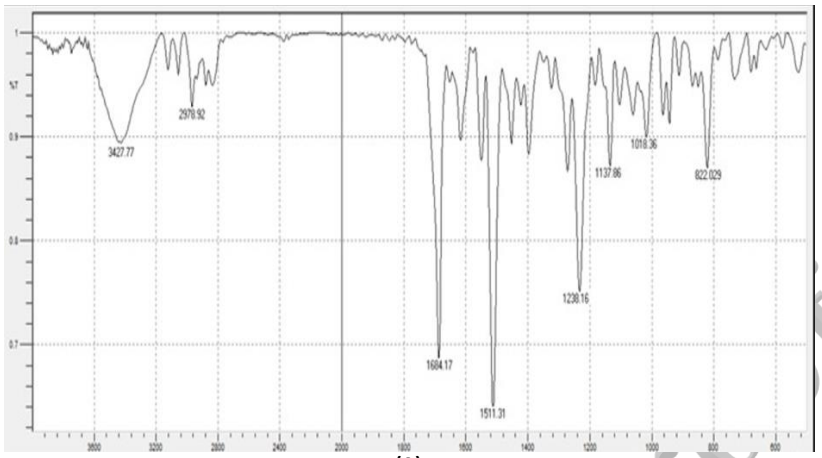
Fig. 12. In-vitro % drug profiles for optimized formulation (MQA516)

Fourier Transform Infrared Spectrophotometry (FTIR) Analysis

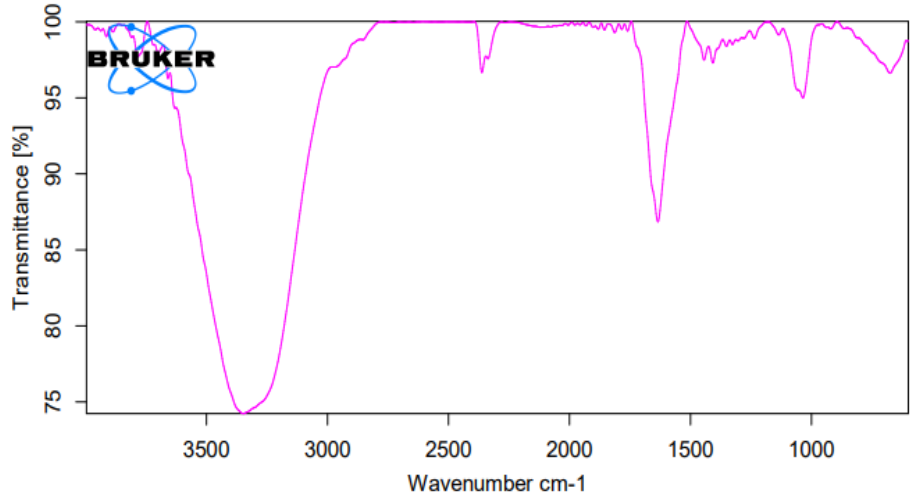
The intensity of the peaks in the hydrogel formulation was reduced compared to those of the pure API (Table 10). This reduction in intensity suggests a change in the physical form of the drug when incorporated into the hydrogel formulation. Figure 13A depicts the FTIR spectra of the pure drug, while Figure 13B depicts the FTIR spectra of the drug incorporated into the hydrogel formulation (optimized batch).

Table 10. Interpretation of FTIR spectra

S. No.	Functional group	Observed frequency (cm^{-1}) of pure drug	Observed frequency (cm^{-1}) in Posaconazole loaded hydrogel
1.	C=O stretching	1684.17	1634.66
2.	C-H bending	1238.16	1236.00
3.	C-O-C stretching	1137.86	1135.75
4.	C-F bending	1018.36	1035.22
5.	C-H aromatic bending	822.029	675.79



(A)



(B)

Fig. 13. **(A).** FTIR spectra of pure drug (Posaconazole); **(B).** FTIR spectra of Posaconazole loaded hydrogel formulation (optimized batch)

Differential Scanning Calorimetry (DSC) analysis

Figure 14 shows that the pure drug exhibits a notable endothermic peak at 171.93°C. In contrast, the DSC thermogram for the drug-loaded hydrogel formulation revealed a shift to an amorphous state, indicated by the absence of the melting peak. This suggests water exclusion during the formation of the complex, potentially enhancing the formulation's bioavailability through improved solubility and dissolution rates. The reduction in crystallinity is further evidenced by Figure 15, which illustrates the transition of the pure drug to the hydrogel formulation.

Stability studies

An accelerated stability study was conducted over three months for the optimized batch (MQA516). The findings of the study are summarized in Table 11. The formulation was stable throughout the study period, suggesting a robust drug shelf lifeduring storage.

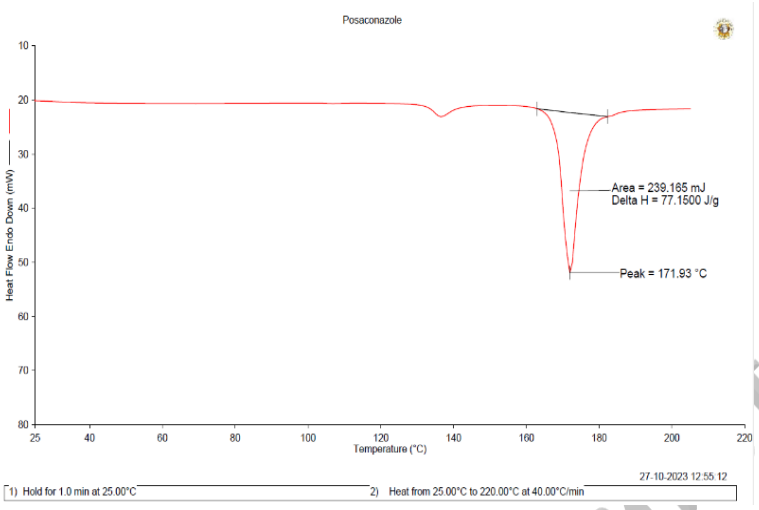


Fig.14. DSC Thermogram of pure drug

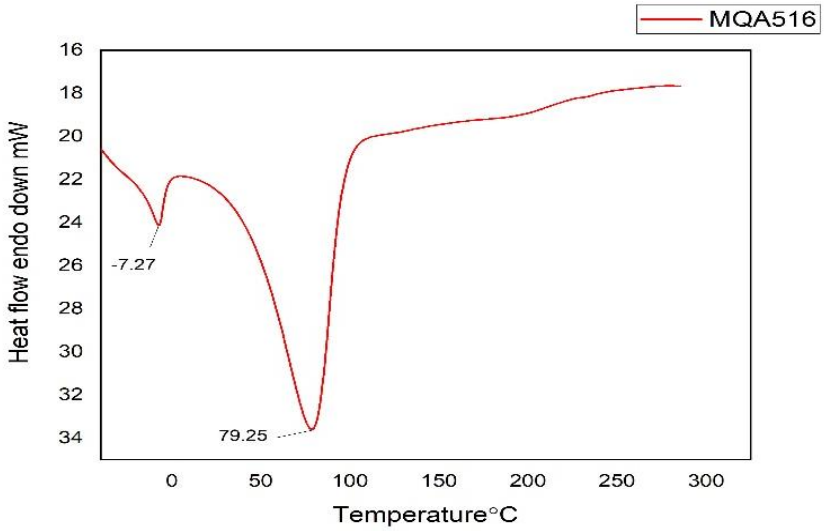


Fig.15. DSC Thermogram of drug loaded hydrogel formulation (optimized batch)

Table 11. Results of accelerated stability study

S. No.	Parameters	Temperature: 40°±2°C / Relative humidity (RH): 75 ± 5%RH			
		Initial	***After 1 Month***	***Ater 2 Months***	***After 3 months***
1.	Color	White	White	White	White
2.	Odour	Odorless	Odorless	Odorless	Odorless
3.	Weight (g)	90.213	90.149	89.924	89.814
4.	Homogeneity	Translucent/ No phase separation	Translucent/ No phase separation	Translucent/ No phase separation	Translucent/ No phase separation
5.	pH	7.56	7.54	7.52	7.50
6.	Viscosity (cps)	17058	16924	16758	16626
7.	Spreadability (gcm/sec)	35	33	30	29
8.	Drug content (%)	96.23	96.00	95.5	95.2
9.	*In-vitro* drug release (%)	90.35	90.15	89.93	89.75

Transmission Electron Microscopy (TEM)

The findings of the TEM analysis, as shown in Figure 16, revealed a smooth surface of the optimized hydrogel batch, indicating a uniform distribution of silver nanoparticles throughout the formulation.

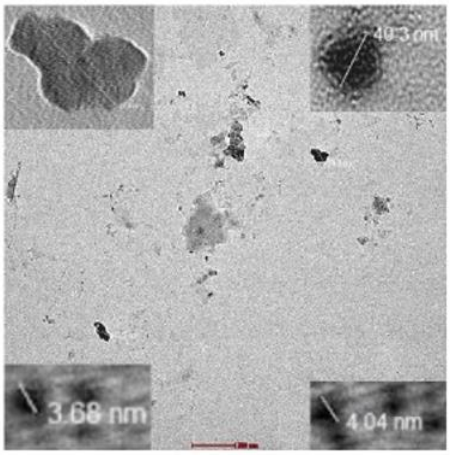


Fig.16. TEM images of optimized hydrogel formulation (MQA516)

CONCLUSION

Developing and optimizing an antifungal hydrogel using a Box-Behnken Design resulted in a formulation that met the predefined quality targets for viscosity, pH, and drug release. The optimized hydrogel comprised 0.5 g Carbopol 940, 1 mL propylene glycol, and 1 mL triethanolamine. This formulation exhibited desirable organoleptic properties, homogeneity, and stability over three months of accelerated testing. FTIR and DSC analyses characterized the successful incorporation of Posaconazole with reduced crystallinity, enhanced solubility, and dissolution rates. Additionally, TEM analysis confirmed the uniform distribution of silver nanoparticles within the hydrogel. These findings suggest the suitability of the QbD approach for developinga potent antifungal hydrogel with the desired quality parameters.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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Corrected Proof

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LIST OF ABBREVIATIONS

QbD	Quality by design	DoE	Design of Experiment
CQA	Critical Quality Attributes	RSM	Response surface methodology
QTPP	Quality Target Product Profile	PCZ	Posaconazole
CPP	Critical Process Parameters	AgNP	Silver Nano-particles
QRM	Quality Risk Management	FTIR	Fourier Transform Infrared Spectrophotometry
BBD	Box Behnken Design	DSC	Differential Scanning Calorimetry
CCD	Central Composite Design	TEM	Transmission Electron Microscopy
FFD	Full Factorial Design	cGMP	Current Good Manufacturing Practice
ANOVA	Analysis of Variance	API	Active pharmaceutical ingredient

Corrected Proof