RESEARCH PAPER

Quality by Design-Based Development and Evaluation of Itraconazole-Loaded Niosomal Gel for Topical Delivery

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ABSTRACT

Topical fungal infections are among the most common dermatological disorders worldwide. Conventional topical antifungal therapies often suffer from poor skin penetration, limited drug retention, and reduced therapeutic efficacy. Niosomal drug delivery systems have emerged as promising vesicular carriers capable of improving topical drug permeation, stability, and controlled release.

The present study aimed to formulate and evaluate itraconazole-loaded non-ionic surfactant vesicles (niosomes) for enhanced topical antifungal delivery using a Quality by Design (QbD)-based optimization approach.

Itraconazole-loaded niosomes were prepared by ultrasonication method using Span-60 and cholesterol. A Box–Behnken experimental design was employed to optimize formulation variables including surfactant concentration, cholesterol concentration, and mixing speed. The prepared formulations were evaluated for particle size, polydispersity index (PDI), zeta potential, % entrapment efficiency, and cumulative drug release. Optimized niosomes were incorporated into Carbopol 940 gel and further evaluated for pH, viscosity, and in vitro antifungal activity.

The prepared niosomal formulations exhibited particle size ranging from 237 nm to 1036 nm with PDI values indicating acceptable homogeneity. Entrapment efficiency ranged from 95.35% to 98.20%. The optimized formulation demonstrated sustained drug release up to 24 hours with cumulative drug release of approximately 73.82%. The formulated niosomal gel showed pH of 5.1 and viscosity of 9950 cps, indicating suitability for topical application. In the in-vitro antifungal studies, the maximum zone of inhibition after 72 hours, shown by niosomal gel, was 20.5 mm against Candida albicans.

Itraconazole-loaded niosomal gel demonstrated promising characteristics including high entrapment efficiency, controlled drug release, enhanced antifungal activity, and good skin compatibility. The developed formulation may serve as a potential alternative for effective topical management of fungal infections.

Keywords: Itraconazole, Niosomes, Topical drug delivery, Antifungal gel, Quality by Design, Box–Behnken Design.

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1. INTRODUCTION

Fungal infections represent a major global health problem affecting millions of individuals annually. Superficial fungal infections involving skin, hair, nails, and mucosal tissues are particularly common and are primarily caused by dermatophytes and opportunistic fungi such as *Candida albicans*. These infections are associated with discomfort, inflammation, itching, and reduced quality of life. [4]

Itraconazole is a broad-spectrum triazole antifungal drug widely used for the treatment of superficial and systemic fungal infections. The drug acts by inhibiting fungal cytochrome P450-dependent lanosterol 14α-demethylase enzyme, thereby blocking ergosterol biosynthesis and disrupting fungal cell membrane integrity. However, itraconazole possesses poor aqueous solubility and limited skin penetration, resulting in suboptimal topical delivery. [8,31]

Novel vesicular drug delivery systems such as niosomes have gained considerable attention for improving topical drug delivery. Niosomes are microscopic lamellar vesicles composed of non-ionic surfactants and cholesterol. These vesicles can encapsulate both hydrophilic and lipophilic drugs, enhance drug stability, improve penetration through the stratum corneum, and provide sustained drug release. [6]

Compared with liposomes, niosomes offer several advantages including improved chemical stability, lower cost, ease of preparation, biodegradability, and non-immunogenicity. Niosomal systems have demonstrated significant potential in topical delivery of antifungal agents by increasing residence time within skin layers and minimizing systemic absorption. [5,7]

Quality by Design (QbD) is a systematic pharmaceutical development approach involving predefined objectives and scientific understanding of formulation and process variables. Experimental design techniques such as Box–Behnken Design (BBD) enable optimization of formulation parameters with reduced experimental runs. [19]

The present investigation was therefore designed to formulate and optimize itraconazole-loaded niosomes using QbD approach and evaluate their suitability for topical antifungal delivery.

2. MATERIALS AND METHODS

2.1 Materials

Itraconazole was obtained from Alkem Laboratories. Span-60 and cholesterol were procured from Oxford Laboratory. Carbopol 940, triethanolamine, glycerin, methanol, chloroform, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, and other analytical grade chemicals were used throughout the study.

2.2 Preformulation Studies

2.2.1 Organoleptic Evaluation

Itraconazole was examined visually for color, odor, and texture.

2.2.2 Melting Point Determination

Melting point was determined using a digital melting point apparatus.

2.2.3 Solubility Studies

Solubility of itraconazole was evaluated in water, ethanol, chloroform, and dimethyl sulfoxide.

2.2.4 UV Spectrophotometric Analysis

A standard calibration curve of itraconazole was prepared in methanol and analyzed at 262 nm. [28,29]

2.2.5 FTIR Studies

Fourier Transform Infrared Spectroscopy (FTIR) was performed to evaluate compatibility between drug and excipients. [1,29]

2.3 Experimental Design

Using design expert software, the Box-Behnken three-factor, three-level experimental design optimized the formulation. Critical quality attributes (CQAs) desired in the final product, such as mean particle size (R1), PDI (R2), Zeta potential (R3), % Entrapment efficiency (R4), and cumulative drug release at 1 hour (R5), 2 hours (R6), 3 hours (R7), 5 hours (R8), and 24 hours (R9), were selected as response variables (dependent variables) as indicated in table 1. The critical formulation components that significantly affect the final product's quality and performance at three different levels: -1 (low), 0 (medium), and +1 (high). A three-factor, three-level Box–Behnken Design was employed using Design-Expert software. Table 2 illustrates the 17 experimental runs (F1 to F17) with five center point replicates that were suggested by the design expert system. Every batch of niosomal formulation was made using the general procedure mentioned above. [20,21]

Table 1: Independent and dependent variables were used to optimize niosomal formulation.

Independent variables	**Unit**	**Levels**		
		Low (-1)	**Medium (0)**	**High (+1)**
A: Span 60	mg	13.3	16.65	20
B: Cholesterol	mg	6.6	9.95	13.3
C: Mixing speed	RPM	450	550	650
Dependent variables	**Desired Constraint**			
R1: Mean particle size	Minimum			
R2: PDI	Minimum			
R3: Zeta potential	In range			
R4: % Entrapment efficiency	Maximum			
R5: Cumulative % drug release at 1hr	Minimum			
R6: Cumulative % drug release at 2hr	Minimum			
R7: Cumulative % drug release at 3hr	Minimum			
R8: Cumulative % drug release at 5hr	Maximum			
R9: Cumulative % drug release at 24hr	Maximum			

Table 2: 17 experimental formulations were prepared according to the design expert.

Formulation code	Amount of Span-60 (mg)	Amount of Cholesterol (mg)	Mixing speed (RPM)
F1	16.65	13.3	650
F2	13.3	6.6	550
F3	16.65	13.3	450
F4	20	9.95	450
F5	13.3	13.3	550
F6	20	6.6	550
F7	16.65	9.95	550
F8	16.65	9.95	550
F9	16.65	9.95	550
F10	16.65	9.95	550
F11	20	9.95	650
F12	16.65	9.95	550
F13	16.65	6.6	450
F14	16.65	6.6	650
F15	20	13.3	550
F16	13.3	9.95	450
F17	13.3	9.95	650

2.4 Preparation of Itraconazole-Loaded Niosomes

Itraconazole-loaded niosomes were prepared by ultrasonication method. Required quantities of Span-60, cholesterol, and itraconazole were dissolved in chloroform. Phosphate buffer saline (pH 7.4) was added with continuous stirring at 50–60°C. The resultant dispersion was probe-sonicated for 3 minutes to obtain niosomal vesicles. [9]

2.5 Characterization of Niosomes

2.5.1 Particle Size, PDI and zeta potential

The mean particle size, polydispersibility index and zeta potential of all the batches were determined by using a Horiba scientific nanoparticle size analyzer. All of the samples were diluted with distilled water prior to testing. The data was presented as the average of triplicate runs for each sample, and the measurements were performed at a

temperature of 25±0.5°C. [10]

2.5.2 Entrapment Efficiency

Entrapment efficiency of niosomes were calculated by ultracentrifugation method. 2ml drug loaded sample was centrifuged (Remi) at 12,500 rpm for 45 minutes at 20°C. The supernatant was diluted 10X, and the absorbance of the sample was measured at 262nm using a UV- Visible spectrophotometer. [11,18]

2.5.3 In-vitro Drug Release Study

The dialysis membrane was used to characterize Itraconazole loaded niosomes for in- vitro drug release. The niosomal formulation was sealed separately in dialysis membrane and immersed in 100ml release media. The experiment was carried out with constant stirring at 100 RPM for 24 hours at 37±0.5°C temperature. Aliquots of 1ml were collected at predetermined time intervals (1hr, 2hr, 3hr, 5hr, 24hr) and replenished with 1ml of fresh release media. The collected samples were diluted to 10ml and analyzed with a UV Spectrophotometer at 262nm. [12.18]

2.6 Preparation of optimized formulation of niosomes

After statistical analysis of obtained response data and consideration of desired constraints set for each response variables, i.e., minimum particle size and PDI, in range zeta potential, and maximum % EE, and *in-vitro* drug release at different time points in optimized formulation. Design expert software suggested a composition of optimized formulation based on criteria of highest desirability value. The maximum desirability (0.739) was predicted in optimized niosomal formulation composition of: span-60 content 20 mg, cholesterol content 9.95 mg, and mixing speed 450 RPM. The 2D contour plots depicting highest desirability value in optimized formulation are shown in figure 1. [9]

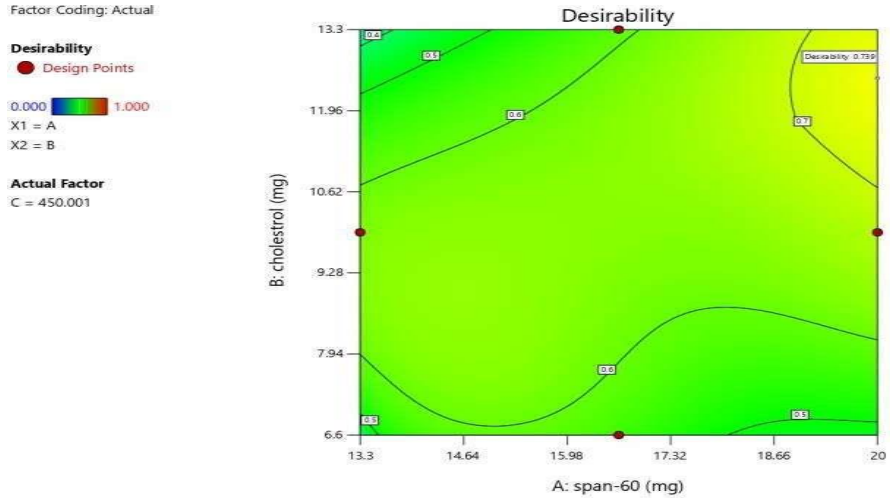


Fig.1: 2D – contour plot showing maximum desirability of optimized formulation of Itraconazole loaded niosomes.

2.7 Preparation of Niosomal Gel

Carbopol 940P was selected as a gelling agent to transform niosome dispersion into niosome gel formulation (optimized formulation). Carbopol was dispersed in water at a speed of 1200 rpm using a mechanical stirrer. The gel media was then filled with 20 ml of drug-loaded niosomes and glycerine, stirred for 15 minutes, neutralized with triethanolamine, and left to swell properly overnight. [13,30]

2.8 Evaluation of Niosomal Gel

2.8.1 pH Measurement

10 ml of the niosomal gel were placed in a beaker to measure the pH of gel. pH was measured at room temperature using a digital pH meter that had been calibrated. [14]

2.8.2 Viscosity

The prepared gel was put in a beaker underneath the spindle and rotated at room temperature in a Brookfield viscometer for determining its viscosity. [15]

2.9 In-vitro Antifungal Activity

Candida albicans was used in an antifungal bioassay; the standard strain was inoculated in a broth of yeast peptone and dextrose and kept at 35.2 C for aerobic fungi growth; spectrophotometric measurements of Candida colonies were then made; the plates were perforated aseptically in the middle with 8–10 mm diameter wells punched with a sterile tip; 0.5 ml of the formulation was injected in these wells; the plates were then incubated at 30±2°C for 48–72 hours. [16,23]

***In-Vitro* Experimental Protocol Design**

Table 3: *In-Vitro* Antifungal Assay Protocol

Plate No	Group	Formulation
01	Control group	No induction of fungal solution
02	Negative control group	Induction of fungal solution and no treatment
03	Standard group	Treated with itraconazole Suspension
04	Treatment group	Treated with itraconazole loaded niosomal gel

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

Table 4: Organoleptic Properties of Itraconazole

S. No.	Test	Observation
1	Colour	White
2	Odour	Odourless
3	Texture	White Powder

Table 5: Melting Point of Itraconazole

Drug	Reported Value	Observed Value
Itraconazole	166.2°C	168°C

Table 6: Solubility Profile of Itraconazole

S. No.	Solvent	Solubility
1	Ethanol	Soluble
2	Water	Insoluble
3	Chloroform	Soluble
4	Dimethyl sulfoxide	Freely soluble

Table 7: Calibration Curve Data of Itraconazole at 262 nm

Concentration (µg/ml)	Absorbance
2	0.145
4	0.183
6	0.229
8	0.271
10	0.316

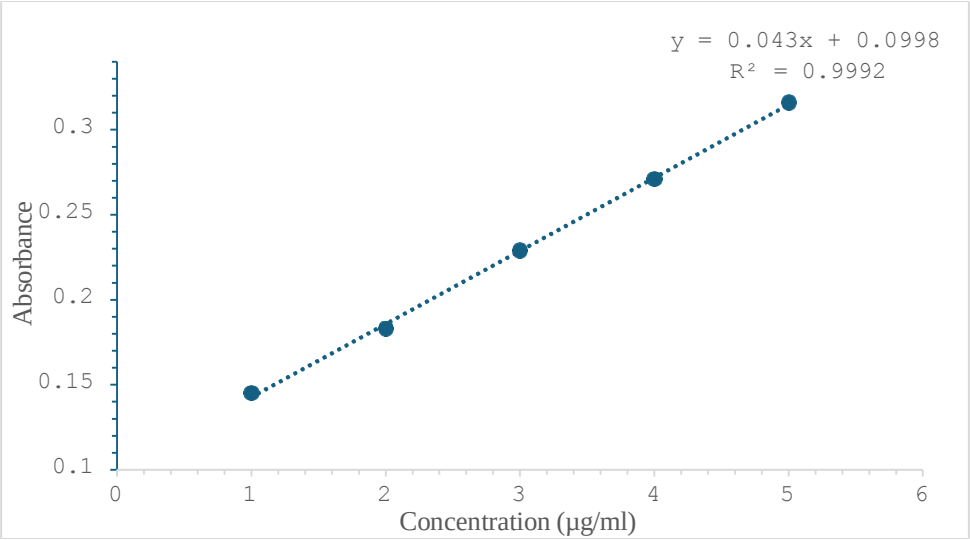


Fig.2: Calibration Curve of Itraconazole drug

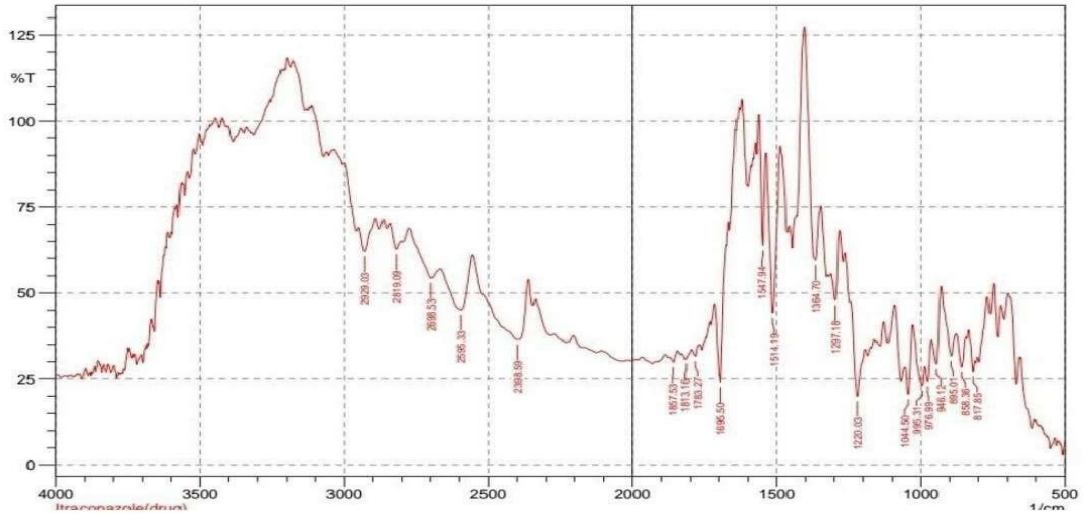


Fig. 3: FTIR Spectrum of the drug (Itraconazole)

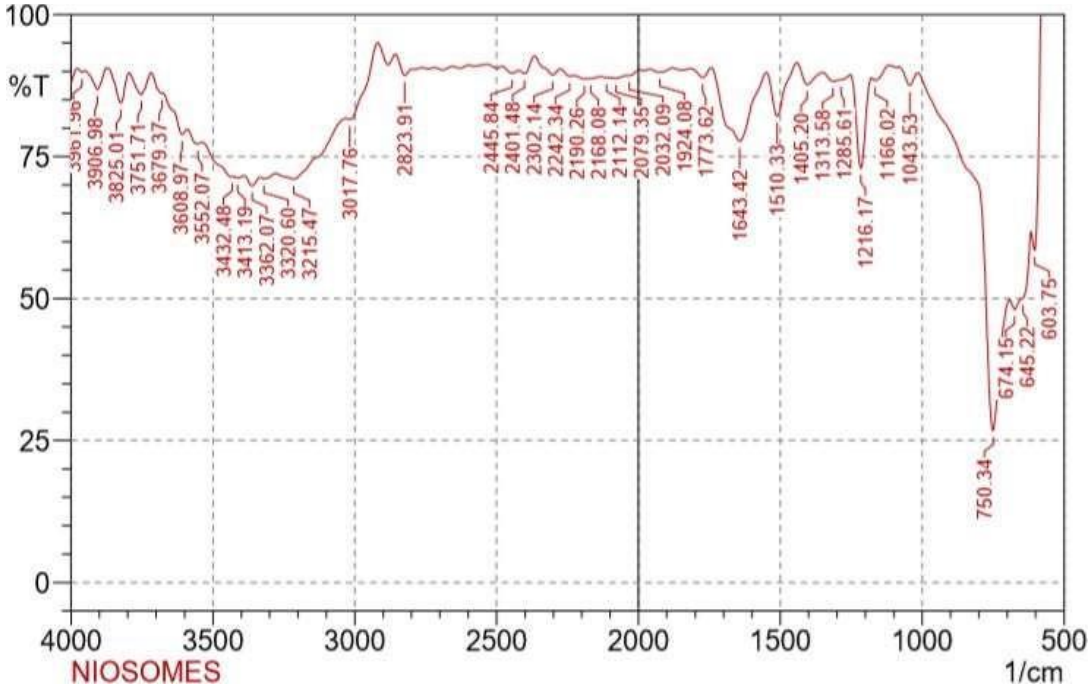


Fig. 4: FTIR Spectrum of optimized niosomal formulation

3.2 Evaluation of Niosomal formulation

3.2.1 Particle Size

Particle size ranged from 237 nm to 1036 nm. Increase in surfactant concentration and mixing speed significantly influenced vesicle size. The particle size of formulation is essential parameter that was investigated and listed in table 8, while the 3D response surface plots are depicted in fig.5. [24,25]

3.2.2 Polydispersity Index

PDI values indicated acceptable homogeneity of the prepared formulations as shown in table 8 and the 3D response surface plots are depicted in fig.5.

3.2.3 Zeta Potential

Zeta potential ranged from -19.5 mV to 9.9 mV, indicating moderate physical stability of vesicles. As shown in table 8 and the 3D response surface plots are depicted in fig.5. [24]

3.2.4 Entrapment Efficiency

The % Entrapment efficiency ranged between 95.35% and 98.20%, demonstrating high drug encapsulation ability of the niosomal system and the results are listed in table 8 and the 3D response surface plots are depicted in fig.5. [26]

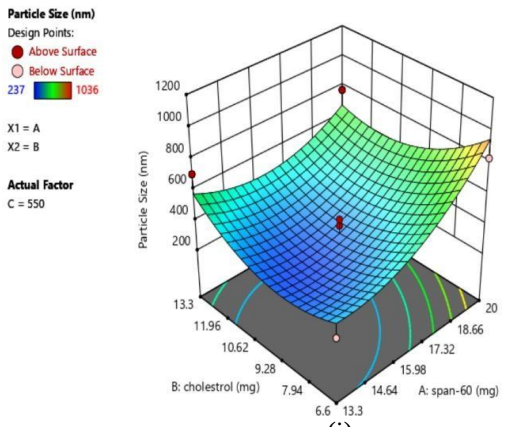
3.2.5 Cumulative % drug Release

The 17 optimization trial batches had cumulative drug release data ranging from 5.94 to 16.95% at 1 hour, 12.78 to 31.64% at 2 hours, 25.61 to 49.18% at 3 hours, 37.90 to 56.67% at 5 hours, and 44.44 to 73.82% at 24 hours. As seen in fig.8, the 3D response surface plots illustrated the drug release at 1, 2, 3, 5, and 24 hours. [13, 27]

Table 8: Box- Behnken experimental design of niosomal formulation and their measured responses

Run	Amount of Span-60	Amount of Cholesterol	Mixing Speed	Particle Size	P.I	Zeta Potential	Entrapment	Drug release 1hr	Drug release 2hr	Drug release 3hr	Drug release 5hr	Drug release 24hr
Unit	mg	mg	RPM	nm	unitless	mV	%	%	%	%	%	%
1	16.65	13.3	650	237	0.327	-4.9	98.08	12.78	22.64	32.12	37.90	46.34
2	13.3	6.6	550	296	0.282	9.9	96.31	11.27	20.38	25.61	41.33	50.38
3	16.65	13.3	450	544.9	0.585	-0.9	98.20	11.08	26.43	32.12	49.46	59.80

4	20	9.95	450	351	0.398	3.9	97.62	12.88	17.90	28.52	40.46	73.82
5	13.3	13.3	550	704.9	0.418	1.6	97.48	13.98	34.49	49.18	56.67	61.79
6	20	13.3	550	827.4	0.566	-0.9	97.35	14.68	28.71	34.77	38.18	44.44
7	16.65	9.95	550	262.3	0.167	5.6	96.40	16.95	24.44	36.19	44.25	73.54
8	16.65	9.95	550	273.5	0.286	1.2	97.24	16.95	24.44	36.19	44.25	73.54
9	16.65	9.95	550	273.7	0.229	-6.3	96.40	16.95	24.44	36.19	44.25	73.54
10	16.65	9.95	550	376.1	0.751	-1.9	97.06	16.95	24.44	36.19	44.25	73.54
11	20	9.95	650	1036	0.406	-0.2	96.40	5.94	25.01	36.10	50.89	63.04
12	16.65	9.95	550	418.9	0.431	-3.9	96.28	16.95	24.44	36.19	44.25	73.54
13	16.65	6.6	450	536.1	0.518	7.5	96.28	14.11	18.85	37.33	47.28	63.87
14	16.65	6.6	650	499.5	0.459	1.9	95.35	14.08	19.80	38.37	43.78	63.11
15	20	13.3	550	772.1	0.611	9.4	96.35	8.08	12.78	27.19	43.87	68.33
16	13.3	9.95	450	311.3	0.576	-3.2	96.30	7.43	18.75	28.04	40.46	63.87
17	13.3	9.95	650	378.2	0.444	-19.5	97.40	12.59	31.64	39.70	54.49	68.33



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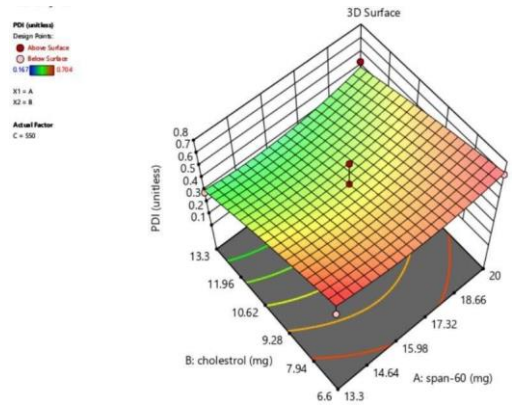

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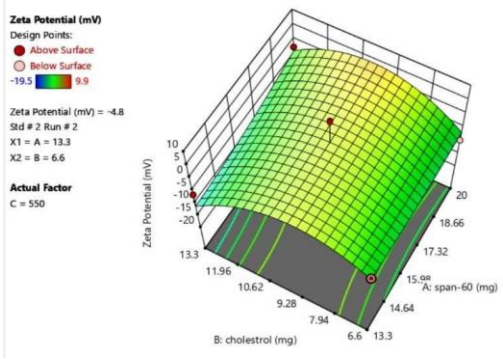

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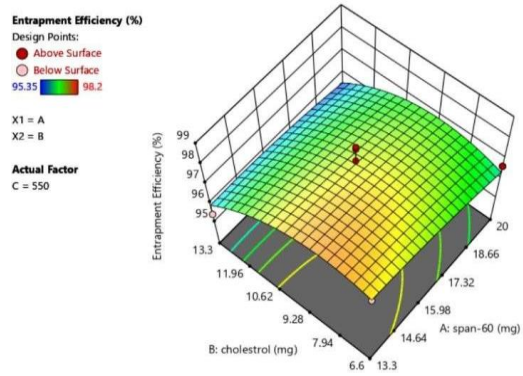

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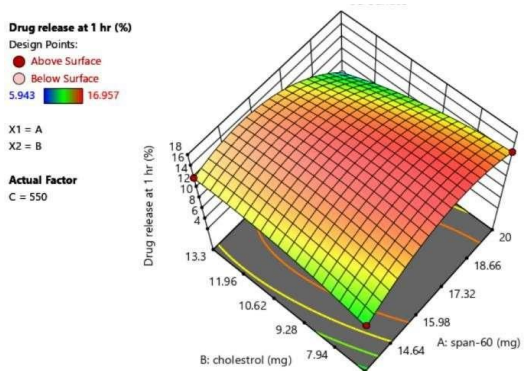

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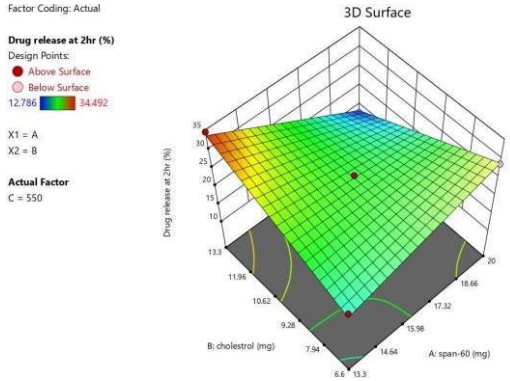

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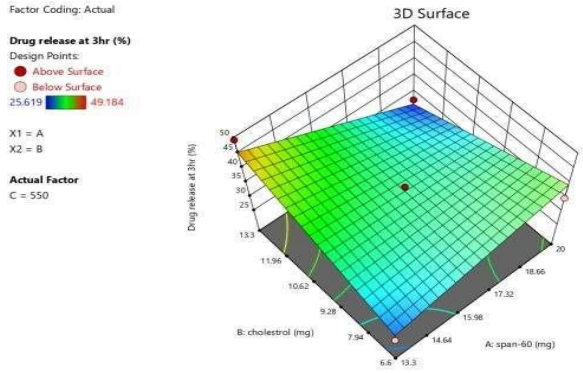

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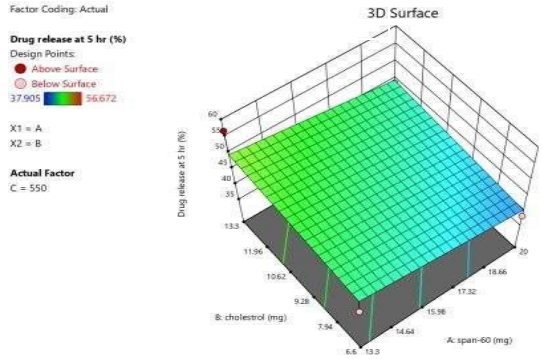

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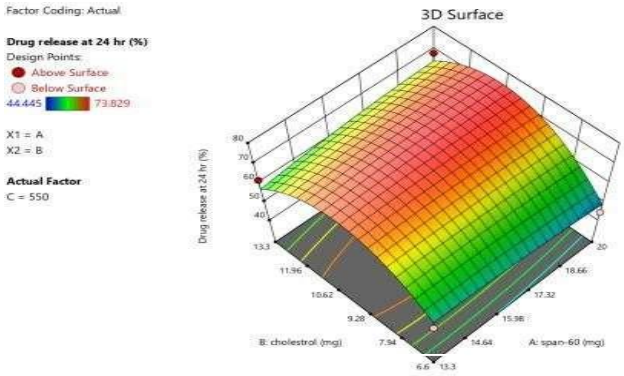

(ix)

Fig.5: 3D response surface plot of (i) particle size, (ii) PDI, (iii) zeta potential, (iv) Entrapment efficiency and cumulative drug release at (v) 1hr, (vi) 2hr, (vii) 3hrs, (viii) 5hrs, and (ix) 24 hrs.

3.3 Evaluation of Niosomal Gel

3.3.1 pH

The pH of the niosomal gel was found to be 5.1, which is suitable for topical application.

3.3.2 Viscosity

The viscosity of gel formulation was found to be 9950 cps, indicating appropriate consistency and spreadability. [12]

3.4 Evaluation of in-vitro Antifungal Activity

The in-vitro antifungal assay for the zone of inhibition was performed on the fungal strain *candida albicans*. The maximum zone of inhibition was 20.5 mm for the niosomal gel group. No zone of inhibition was seen for the standard group containing itraconazole suspension, result was depicted in fig. 6. The niosomal gel exhibited significant antifungal activity against *Candida albicans*. Enhanced zone of inhibition indicated improved antifungal efficacy compared to conventional formulation. [17,22]

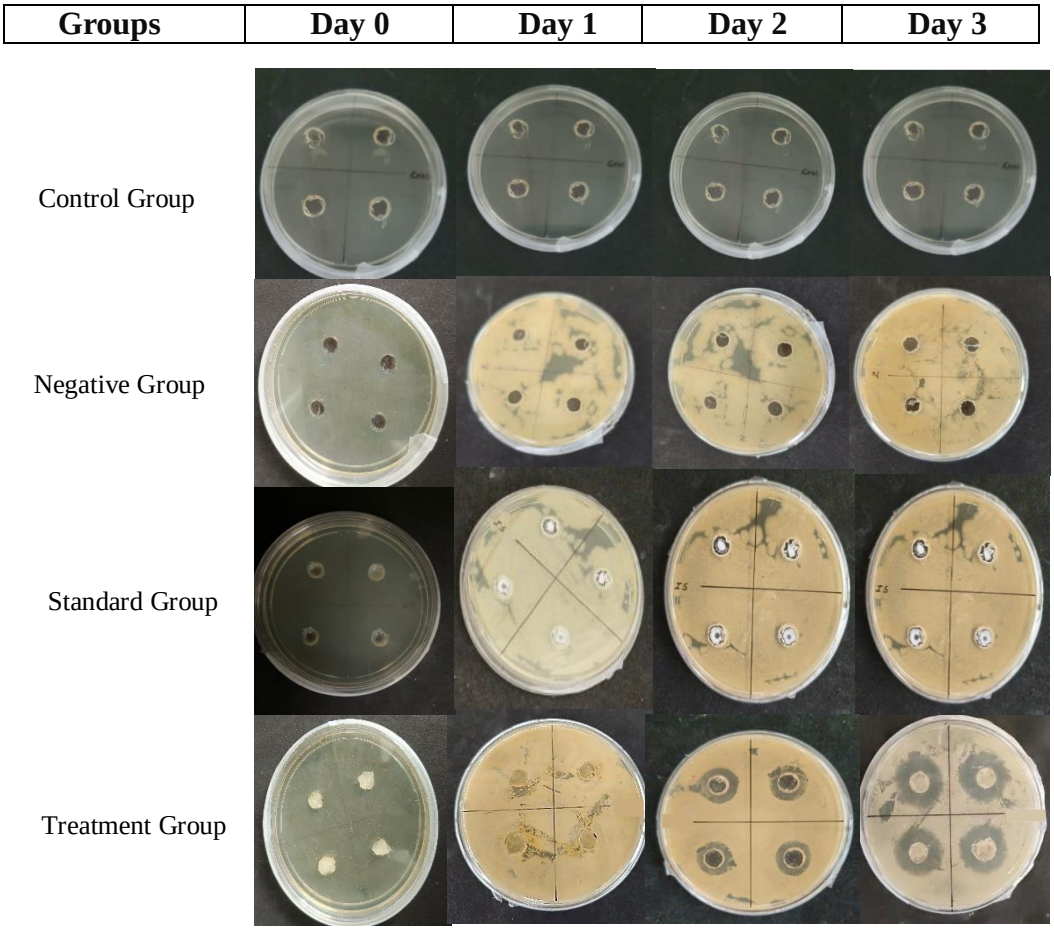

Fig.6: In vitro antifungal results of different groups from day 0 to day 3

4. CONCLUSION

The present study successfully developed itraconazole-loaded niosomal gel using a QbD-based optimization approach. The prepared niosomal formulations demonstrated favorable physicochemical characteristics including nanosized vesicles, high entrapment efficiency, controlled drug release, and acceptable stability.

The optimized niosomal gel exhibited enhanced antifungal activity against *Candida albicans* along with good skin compatibility. Incorporation of itraconazole into niosomal vesicles significantly improved drug release behavior and may enhance topical therapeutic effectiveness.

The findings suggest that niosomal gel represents a promising carrier system for topical delivery of

itraconazole and may provide an effective alternative for treatment of fungal skin infections.

Conflict of Interest

The authors declare no conflict of interest.

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