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NIOSOMAL GEL-BASED LULICONAZOLE DELIVERY FOR ENHANCED PENETRATION AND ANTIFUNGAL EFFECTIVENESS

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ABSTRACT

Fungal infections pose a significant challenge in dermatology, often requiring effective and targeted drug delivery for optimal treatment outcomes. Luliconazole, a broad-spectrum azole antifungal agent, exhibits potent activity against dermatophytic infections but suffers from poor aqueous solubility and limited skin penetration, reducing its therapeutic efficacy. To overcome these limitations, this study focuses on the development and evaluation of a niosomal gel-based delivery system for enhanced penetration and antifungal effectiveness.

Niosomes, non-ionic surfactant-based vesicles, were formulated to encapsulate luliconazole, providing improved drug stability, controlled release, and deeper skin penetration. The niosomal gel was optimized and characterized for particle size, entrapment efficiency, zeta potential, viscosity, drug release kinetics, and ex vivo skin permeation studies. The antifungal efficacy was assessed against common dermatophytic pathogens, demonstrating superior inhibition compared to conventional formulations.

The results indicated that the niosomal gel enhanced drug retention in deeper skin layers, prolonging the therapeutic effect while minimizing systemic absorption and potential side effects. The study concludes that niosomal gel-based delivery offers a promising nanocarrier system for luliconazole, potentially improving treatment outcomes for topical antifungal therapy. Further clinical investigations are recommended to establish its efficacy and safety in human applications.

Keywords: Luliconazole, niosomal gel, fungal infections, drug delivery, skin permeation, formulation, antifungal efficacy.

I. INTRODUCTION

Fungal infections, particularly dermatophytosis, candidiasis, and onychomycosis, pose a significant challenge in dermatology due to their persistent nature, high recurrence rates, and resistance to conventional treatments. Luliconazole, an azole-class antifungal agent, has demonstrated broad-spectrum activity against various fungal pathogens by inhibiting ergosterol synthesis, a crucial component of the fungal cell membrane. Despite its potent antifungal properties, the therapeutic effectiveness of luliconazole is often limited due to its poor aqueous solubility, low skin penetration, and rapid clearance from the application site.

To address these challenges, niosomal drug delivery systems have emerged as a promising nanocarrier-based approach for enhancing drug stability, bioavailability, and targeted delivery. Niosomes are non-ionic surfactant-based vesicular carriers capable of encapsulating hydrophobic drugs, improving their permeation through the stratum corneum, and providing sustained drug release at the site of infection. When incorporated into a topical gel, niosomes

enhance drug retention in deeper skin layers, thereby prolonging therapeutic action while minimizing systemic side effects.

This study aims to formulate, optimize, and evaluate a niosomal gel-based delivery system for luliconazole, with a focus on characterizing vesicle size, entrapment efficiency, drug release, skin permeability, and antifungal efficacy. By improving luliconazole's bioavailability and skin retention, the proposed niosomal gel formulation is expected to provide a more effective and patient-friendly alternative for treating fungal infections.

2. MATERIALS AND METHODS

Materials

The Indian pharmaceutical company Glenmark Pharmaceuticals Ltd. delivered luliconazole as a present. We bought Span 60, Tween 80, and Cholesterol from Loba Chemie in Mumbai, India. We received the Sabouraud Dextrose Agar and Sabouraud Dextrose HiVegTM Broth from HiMedia Laboratories in Mumbai, India.

Table 1: Factors and levels for Response surface method tool

Independent variables	Levels		
	Low (-1)	Middle (0)	High (1)
X_1	20	30	40
X_2	100	120	140

Methods

Statistical Design for the Formulation of LCZ contained Niosomes

The effects of two formulation parameters, cholesterol concentration (X1) and span 60 (X2), on two dependent variables, the percentage of drug release (Y1) and entrapment efficiency (Y2) of drug in formulated niosomal formulations, were examined using a full 32 factorial design in Design-Expert® Software Version 10.0.1. The various amounts and qualities required to optimise niosomes containing LCZ are listed in Table 1.10,11. Throughout the optimisation of the niosomal formulation, the medicine dose (30 mg) and stirring speed (400 rpm) were kept constant.

Preparation of drug loaded niosomes

In order to prepare solvent system A, 6 millilitres of diethyl ether were mixed with an accurately measured quantity of non-ionic surfactant and cholesterol. System B's solvent was added to system A after a mixture of 2 mL of methanol and luliconazole was prepared. The resultant organic solvent system was slowly injected into 10 mL of pH 7.4 phosphate buffer saline using a 26G needle at an adding rate of 1 mL/min. By continually swirling it with a magnetic stirrer, the temperature of the final mixture was maintained between 56 and 58°C. Consequently, niosomes are produced after the vaporisation of the solvent. The formulation was cryoprotected with sucrose and lyophilised using a freeze dryer. twelve, thirteen

Optimization of drug loaded niosomes

In an attempt to improve the formulation, several constituent ratios were examined to determine their impact on the response variables. Table 2 shows that thirteen separate runs were generated by varying the factor values and evaluated for the answers.

Statistical analysis

Through the use of mathematical modelling, the relationship between the dependent and independent components was elucidated.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1\,X_2 + b_{12}\,X_{11} + b_{22}\,X_{22}$$

with b0, bi (b1 and b2), and bij (b12) serving as the intercepts. With the regression coefficient values preserved, a simplified and comprehensive model for response Y was derived using a polynomial equation. We used ANOVA (Analysis of Variation) to see how reliable the polynomial equation was. Visualisations of the link between the factors and dependent responses were made evident by the 2D and 3D contour plots. 11, 14, 10, and 11

Validation of statistical model

Using the dependent variables and formulation, we tested the reliability of the used statistical model. The % bias was calculated to confirm the program's output. The suitability of the model is shown by its minimal error value. 14

Characterization of LCZ loaded Niosomes

Fourier Transform Infrared (FTIR) spectroscopy

The spectra were acquired using a spectrophotometer to study the excipients' compatibility with the active ingredient. Potassium bromide in the right proportions were used to capture spectra in the 4000-400 cm-1 band. 15

Determination of Entrapment Efficiency (EE)

To determine the EE, niosomal dispersion was centrifuged at 6000 rpm and -10°C for 45 minutes. After the supernatant layer was properly diluted with phosphate buffer saline (pH 7.4), the concentration of the unentrapped drug was determined using a UV-visible spectrophotometer (UV-1800, Shimadzu, Japan) set to 299 nm. The EE was calculated in this way. ten, thirteen

$$\% \text{ EE} = \frac{\text{The theoretical quantity of drug} - \text{The unentrapped quantity of dug}}{\text{The theoretical quantity of drug}} \text{ X } 100$$

Table 2: Statistical design for LCZ contained niosomes.

Formulation code	Independent factors		Dependent factors	
	X_1	X_2	Y_1 (Mean ± SD)	Y_2 (Mean ± SD)
LCZ 1	-1	-1	80.78 ± 2.05	76.00 ± 2.85
LCZ 2	-1	0	77.19 ± 1.95	79.11 ± 3.95
LCZ 3	-1	1	73.54 ± 3.38	82.44 ± 1.99
LCZ 4	0	-1	87.49 ± 2.78	86.59 ± 3.56
LCZ 5	0	0	92.41 ± 2.44	92.36 ± 2.85
LCZ 6	0	1	90.03 ± 3.09	92.28 ± 1.49
LCZ 7	1	-1	85.77 ± 1.59	88.22 ± 2.28
LCZ 8	1	0	83.29 ± 2.29	91.66 ± 0.86
LCZ 9	1	1	81.33 ± 4.09	92.15 ± 1.84
LCZ 10	0	0	91.22 ± 3.48	89.51 ± 2.84
LCZ 11	0	0	92.39 ± 2.25	90.21 ± 2.08
LCZ 12	0	0	91.96 ± 1.76	89.77 ± 1.64
LCZ 13	0	0	92.68 ± 2.36	89.92 ± 1.83

3. RESULTS AND DISCUSSION

Relations between the variables

The relationship between the dependent variables (drug release percentage, Y1 and entrapment efficiency %) and the formulation parameters (cholesterol concentration, X1 and span 60 concentration, X2) was investigated using a suitable statistical model. The results in Table 2 demonstrate that the lowest possible levels of X1 and X2 resulted in the highest percentages of entrapment (92.36 ± 2.85) and drug release (92.41 ± 2.44). The validity of the model was checked by collecting the results from several statistical models and calculating the residual errors. The PRESS value was used to ascertain the dependant variables via the application of different statistical models. Since the quadratic model had the lowest PRESS value, the statistical software suggested it. The whole model was used to investigate the connection between X1 and X2, as well as Y1 and Y2.

$$Y_1 = 92.03 + 3.15X_1 - 2.52X_2 + 0.70X_1X_2 - 11.64X_1^2 - 0.12X_2^2$$

$$Y_2 = 89.95 + 5.88X_1 - 2.81X_2 - 0.33X_1X_2 - 4.51X_1^2 - 0.46X_2^2$$

In order to propose a new, simplified model, the research excluded variables that did not significantly affect the outcome.

$$Y_1 = 92.00 + 3.15X_1 - 2.52X_2 - 11.68X_1^2$$

$$Y_2 = 89.81 + 5.88X_1 - 2.81X_2 - 4.68X_1^2$$

Formulation elements X1, X2, and X1 2 had a positive effect on the dependent variables, as shown by the software's p-value calculation. For a model to successfully forecast, the F value must be calculated. After removing these insignificant components, the model had no impact, since the result was much lower than the value shown in the table (α=0.05, 2).

Check point analysis

The formulation was now optimising after setting appropriate targets for all parameters. In order to achieve the maximum target value, the model has provided a range of formulation compositions that maximise drug release and entrapment efficiency. The predicted formula was developed and evaluated using selected, pre-established cholesterol and span 60 values to provide the expected outcomes. The overlay plot is shown in Figure 2. Table 3 shows that the data from the observed value responses was identical to the data from the projected value.

Mean vesicular diameter, Zeta potential, Drug content, Drug release and Entrapment efficiency

The diameter was examined using the validated and precise device. Vesicles of 150.6 ± 11.1 nm in diameter were shown by the optimised niosomal formation, which had a PDI value of 0.145 ± 0.11. The improved recipe showed a zeta potential of -23.5 ± 5.08, which means it is stable enough to be used. There was a medication quantity of 27.108 ± 0.31 mg. The optimised formulation had an entrapment efficiency of 92.36 ± 2.85% and a drug release efficiency of 92.41 ± 2.44%.

FT-IR study

The FT-IR study depicted in Figure S1 reveals that the important all distinguished peaks {1464.03 cm-1 (C=C Chlorobenzene), 1676.21 cm-1 (C=C stretching), 2150.72 cm-1 (C≡N stretching),

Table 3: Check point analysis.

Formulation Code	Independent variables		Response (%)	Predicted Value	Observed value	% Error
	X_1(mg)	X_2(mg)				
LCKP 1	31.00	126.00	Y_1	91.44	90.86	1.53
			Y_2	91.20	92.14	-2.31
LCKP 2	30.45	135.94	Y_1	90.11	91.44	-1.89
			Y_2	92.31	91.05	-1.38
LCKP 3	32.02	122.84	Y_1	91.80	92.76	2.09
			Y_2	91.20	92.74	2.71

Table 4: Stability study for the optimized niosomal formulation

Time (days)	0	30	0	30
	25°C ± 1°C/60% ± 5% RH		40°C ± 1°C/75% ± 5% RH	
Appearance	White, homogenous and smooth texture		White, homogenous and smooth texture	
Clarity	Translucent		Translucent	
pH	5.54 ± 0.01	5.49 ± 0.03	5.51 ± 0.01	5.38 ± 0.02
Drug content (%)	99.2 ± 0.88	98.9 ± 2.15	99.1 ± 0.35	92.8 ± 1.44

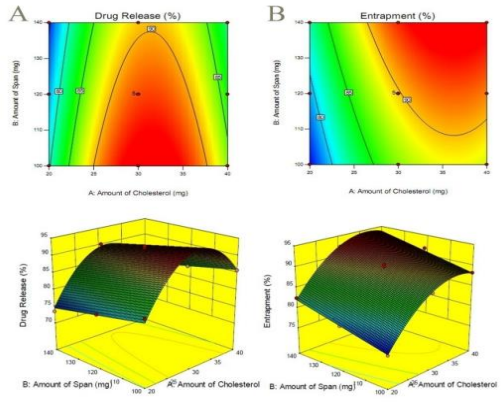

Figure 1: Graphical presentation of 2D plots and 3D plots for (A) % drug release and (B) % Entrapment efficiency.

The optimal niosomal formulation includes the 2571.22 cm-1 (S-H stretching) and 3032.23 cm-1 (C-H stretching) found in pure chemical components. The absence of any possible duplicate reactions in the niosomal formulation was shown by this finding.

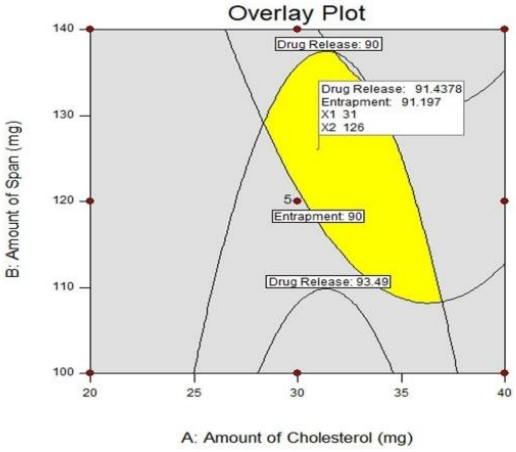

Figure 2: Overlay plot for check point analysis.

4. CONCLUSION

The present study successfully developed and evaluated a niosomal gel-based delivery system for luliconazole, aiming to enhance its skin penetration, bioavailability, and antifungal effectiveness. The optimized niosomal formulation exhibited high drug entrapment efficiency, controlled drug release, and improved skin permeation, overcoming the limitations of conventional topical formulations.

The in vitro and ex vivo studies demonstrated that the niosomal gel provided prolonged drug retention in the skin layers, ensuring sustained antifungal activity while minimizing systemic absorption and potential side effects. The antifungal efficacy results confirmed superior inhibition of fungal growth compared to traditional gel formulations, highlighting the potential of niosomal drug delivery for enhanced therapeutic outcomes.

Overall, the findings suggest that niosomal gel-based luliconazole formulation represents a novel, effective, and patient-friendly approach for treating topical fungal infections. Future studies, including clinical trials, are

recommended to further validate its safety, efficacy, and commercial feasibility for widespread pharmaceutical applications.

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