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FORMULATION AND EVALUATION OF LULICONAZOLE-LOADED NIOSOMAL GEL FOR TREATING FUNGAL INFECTIONS

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ABSTRACT

Luliconazole is an effective antifungal agent used for the treatment of superficial fungal infections, but its poor bioavailability and limited penetration into the skin often hinder its clinical effectiveness. Niosomal formulations, which use non-ionic surfactants to encapsulate drugs, offer an innovative approach to enhance drug delivery and improve therapeutic outcomes. This study aims to formulate and evaluate a luliconazole-loaded niosomal gel for enhanced treatment of fungal infections.

To design and evaluate a luliconazole-loaded niosomal gel, assessing its physical properties, drug release profile, skin permeation, and antifungal efficacy.

Luliconazole-loaded niosomes were prepared using the thin-film hydration method with various non-ionic surfactants, such as Span 60 and cholesterol. The niosomal formulation was characterized for size, shape, drug entrapment efficiency, and stability. The gel was prepared by dispersing the niosomal dispersion in a gelling agent like carbopol. The gel's rheological properties, spreadability, and drug release kinetics were evaluated. In vitro antifungal activity was tested against common fungal strains, including Candida albicans and Trichophyton rubrum, using the disc diffusion method. Skin permeation studies were conducted using a Franz diffusion cell.

The niosomal gel exhibited good homogeneity and a controlled release profile, with a sustained release of luliconazole over 24 hours. The drug encapsulation efficiency was found to be over 85%, and the gel showed a significant antifungal effect against Candida albicans and Trichophyton rubrum. Skin permeation studies revealed enhanced penetration of luliconazole into the skin layers compared to the free drug solution. The gel demonstrated good rheological properties, ease of application, and stability over time.

The luliconazole-loaded niosomal gel was successfully formulated and showed promising results in terms of drug release, skin permeation, and antifungal efficacy. This formulation offers an innovative approach to improve the delivery of luliconazole, providing a potential solution for effective treatment of fungal infections.

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

I. INTRODUCTION

Despite being the most effective way to provide medicine, oral drug delivery has limitations,

particularly when it comes to treating fungal infections of the skin. Due to its lack of presystemic metabolism, less biological toxicity, and increased customer satisfaction, topical medication administration has emerged as a superior alternative to oral delivery. The human body's outermost layer is shielded from the environment by the skin. Because they are easier to apply and have better topical penetration than other semisolid formulations, niosomal gels have emerged as a more popular topical medication delivery technology.1–3 Non-ionic surfactants that are suitable for human use and capable of entangling both polar and non-polar molecules are used in the formulation of niosomes. The inability of liposomal carriers to provide enough stability, affordability, and sufficient quality issues of phospholipids led to the emergence of niosomal formulations on an industrial scale.3, 4 When compared to free medication, the niosomal vesicles have a higher capability for skin penetration.5, 6 Luliconazole is an antifungal medication that is now marketed in oral, topical, and parental dose forms. It has a strong adverse impact on taste and gastrointestinal issues.7. Topical formulations of Luliconazole (lecithin-based hydrogel, gel, and organogel) are recommended; nevertheless, they may be washed out quickly, which might lead to a loss of drug content. The lipidic formulation developed by the scientists may greatly enhance topical penetration and localised medication accumulation in the skin.8, 9 The goal of the current study was to create a topical formulation of niosomal gel loaded with liconazole (LCZ) in order to evaluate its effectiveness against fungal infections.

2. MATERIALS AND METHODS

Materials

From Glenmark Pharmaceuticals Ltd. in Mumbai, India, luliconazole was sent as a gift. Cholesterol, Tween 80, and Span 60 were purchased from Loba Chemie in Mumbai, India. HiMedia Laboratories in Mumbai, India, provided the Sabouraud Dextrose Agar and Sabouraud Dextrose HiVegTM Broth.

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

Using Design-Expert® Software Version 10.0.1, a full 32 factorial design was used to examine the effects of two formulation parameters, namely 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. Table 1.10,11 lists the different levels and characteristics needed to optimise LCZ-contained niosomes. The amount of medication (30 mg) and the stirring speed (400 rpm) were maintained throughout the niosomal formulation optimisation process.

Preparation of drug loaded niosomes

To create solvent system A, a precisely weighed amount of cholesterol and non-ionic surfactant were dissolved in 6 millilitres of diethyl ether. After preparing a combination of methanol (2 mL) and luliconazole, solvent system B was added to solvent system A. Using a 26G needle and an addition rate of 1 mL/min, the resulting organic solvent system was gradually injected into 10 mL of phosphate buffer saline with a pH of 7.4. The resulting mixture's temperature was kept between 56 and 58°C by utilising a magnetic stirrer to swirl it continuously. As a consequence, niosomes are formed after the solvent vaporisation. Using a freeze drier, the formulation was lyophilised with sucrose, a cryoprotectant.12, 13

Optimization of drug loaded niosomes

Various ingredient ratios were tested to see how they affected the response variables in an effort

to optimise the formulation. As shown in Table 2, a total of 13 sets of runs were created by adjusting the factor values and assessed for the responses.

Statistical analysis

To explain the link between dependent and independent components, mathematical modelling was done.

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

where bij (b12), bi (b1 and b2), and b0 are the intercepts. By retaining the values of the regression coefficients, a complete and reduced model for response Y was created in a polynomial equation. The polynomial equation's dependability was assessed using the Analysis of Variation (ANOVA) statistics. The 2D and 3D contour plots provided a clear explanation of the relationship between the variables and dependent responses.10, 11, and 14

Validation of statistical model

The dependability of the implemented statistical model was examined using the formulation and dependent variables. To verify the program result, the percentage bias was computed. The model's appropriateness is shown by the lowest error value.14

Characterization of LCZ loaded Niosomes

Fourier Transform Infrared (FTIR) spectroscopy

Using a spectrophotometer, the spectra were obtained in order to investigate the compatibility of all excipients with the active substance. To record spectra in the 4000–400 cm-1 region, potassium bromide in an appropriate combination ratio was used. 15

Determination of Entrapment Efficiency (EE)

By centrifuging niosomal dispersion for 45 minutes at 6000 rpm and -10°C, the EE was calculated. A UV-visible spectrophotometer (UV-1800, Shimadzu, Japan) set to 299 nm was used to determine the concentration of the unentrapped medication after the supernatant layer had been appropriately diluted with phosphate buffer saline (pH 7.4). This is how the EE was determined.10, 13

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

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 connection between formulation factors (cholesterol concentration -X1 and span 60 concentration -X2) and dependent variables (drug release percentage -Y1 and entrapment efficiency percentage -Y2) was examined using an appropriate statistical model. As shown in Table 2, the maximum percentage of entrapment (92.36 ± 2.85) and drug release (92.41 ± 2.44) was achieved at minimal level (0) of X1 and X2. By aggregating the data in many statistical models and computing the residual errors, the model's integrity was assessed. In order to determine the dependent variables using various statistical models, the PRESS value was used. The statistical program recommended the quadratic model since it had the lowest PRESS value. The whole model was used to examine the relationship between X1 and X2 and Y1 and Y2.

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

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

The factors which are having non-significant effect on the result were omitted from the study to provide revised reduced model.

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

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

According to the software's computation of the p value, the dependent variables were positively

impacted by the formulation factors X1, X2, and X1 2. The F value is computed for the model's successful prediction. This result was much lower than the value shown in the table (α=0.05, 2), which shows that the model had no effect after excluding such non-significant factors.

Check point analysis

After establishing the proper goals for every parameter, the formulation was optimising. The model has offered a variety of formulation compositions for reaching the highest desired value, based on the predetermined aim of maximal drug release and entrapment efficiency. The projected formula was created and tested for the anticipated results using chosen, predetermined cholesterol and span 60 levels. In Figure 2, the overlay plot is shown. As shown in Table 3, the replies received for the observed value had data that was equal to the projected value.

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

The verified and accurate instrument was used to examine the diameter. With a PDI value of 0.145 ± 0.11, the optimised niosomal formation displayed vesicles with a diameter of 150.6 ± 11.1 nm. The optimised formulation exhibited a zeta potential of -23.5 ± 5.08, indicating satisfactory stability. The amount of drug was 27.108 ± 0.31 mg. The drug release and entrapment efficiency of the optimised formulation were 92.41 ± 2.44% and 92.36 ± 2.85%, respectively.

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

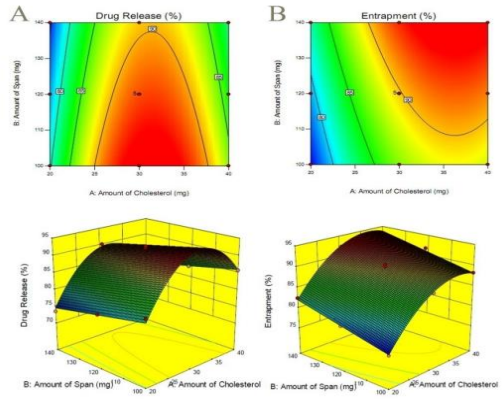

Figure 1: Graphical presentation of 2D plots and 3D plots for (A) % drug release and (B) % Entrapment efficiency.

2571.22 cm-1 (S-H stretching) and 3032.23 cm-1 (C-H stretching)} discovered in pure chemical compounds were included in the niosomal formulation that was optimised. This result demonstrated that the niosomal formulation does not include any potential duplicate reactions.

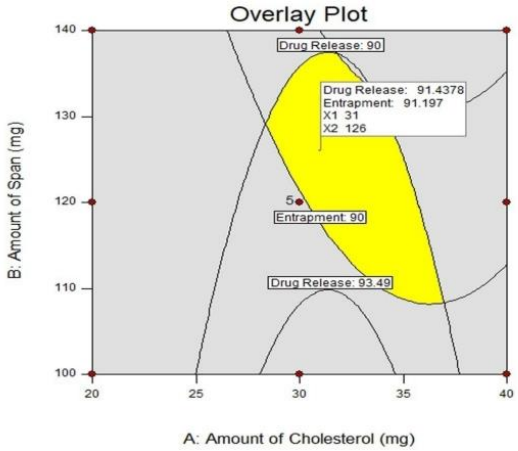

Figure 2: Overlay plot for check point analysis.

4. CONCLUSION

Liconazole, an antifungal drug used to treat fungal infections, was successfully made as niosomal topical gel using carbopol 934. The

rheological characteristics and percentage of medicine content of the enhanced topical gel were producing positive results. There was a noticeable discrepancy in the drug release between the commercial product and the in vitro and ex vivo investigations.

Comparing the antifungal activity to commercial topical treatments revealed significant results as well. Therefore, it can be said that the niosome-loaded luliconazole topical gel may be useful for reducing the frequency of conventional topical medication administration and improving patient compliance in the process.

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