RESEARCH PAPER

Topical Delivery Enhancement Of Luliconazole Via Liposomal Gel: Design, Characterization And For Skin Fungal Infection

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Abstract

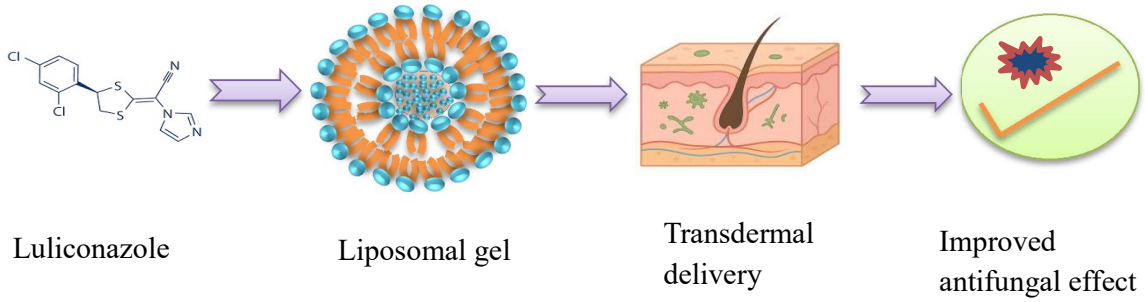
Background: The imidazole antifungal drug luliconazole is used to treat fungal infections, but it has a poor skin penetration rate and is quickly removed from the body.

Materials and Procedures: Luliconazole liposomes were created via thin-film hydration and added to carbopol gel. For lipid ratio, cholesterol content, and hydration time, nine formulations (F1–F9) were created and refined. Studies were conducted in comparison with marketed formulation.

Results: When compared to commercially available gel, the prepared liposomal gel displayed consistent drug content, nanosized vesicles, and prolonged drug release. The efficiency of entrapment reached 82.3%. Longer, slower release was confirmed by Franz diffusion studies.

Conclusion: Long-lasting therapeutic effects, enhanced skin retention, decreased dosage frequency, and patient compliance are all provided by liposomal gel of luliconazole.

Keywords: Topical Antifungal, Liposomal Gel, Luliconazole, and Thin Film Hydration Technique.



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Introduction

Fungal infections of the skin and mucous membranes, such as dermatophytosis, candidiasis, and pityriasis versicolor, are prevalent worldwide and present persistent therapeutic challenges1. These infections often lead to significant patient discomfort, prolonged treatment durations, and high rates of recurrence, thereby imposing a considerable burden on public health and healthcare systems2.

Luliconazole, an imidazole-class antifungal agent, has gained recognition for its potent and broad-spectrum activity against dermatophytes, Candida species, and Malassezia. Despite its clinical efficacy, conventional topical formulations of Luliconazole are frequently limited by inadequate skin penetration, rapid drug clearance, and suboptimal retention at the site of infection, which can compromise therapeutic outcomes3,4.

To address these limitations, innovative drug delivery approaches are being explored. Among them, liposomal drug delivery systems have emerged as promising carriers for topical antifungal therapy. Liposomes are biocompatible vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. Their structural resemblance to biological membranes facilitates enhanced drug

penetration through the stratum corneum, sustained drug release, and improved localization at the target site5,6.
The present study focuses on the design and optimization of a liposomal gel formulation of Luliconazole, aiming to enhance its therapeutic efficacy, skin retention, and overall effectiveness. The optimized liposomal gel is evaluated and compared with a conventional marketed formulation in terms of physicochemical properties, drug release behavior, antifungal activity, and skin permeation.
This research endeavors to demonstrate the potential advantages of liposomal drug delivery for topical antifungal treatment and to contribute to the development of more effective therapies for fungal infections.

Materials
Luliconazole was obtained from Optimus Drugs Pvt. Ltd. (India). Soya lecithin was purchased from Hi Media Laboratories Pvt. Ltd., Mumbai. Cholesterol was procured from Research Lab Fine Chem Industries and Thomas Baker (India). Chloroform, methanol, and other solvents were purchased from S.D. Fine-Chem Ltd., Mumbai. Ethanol was obtained from Qualigens Fine Chemicals. All other reagents and chemicals were of laboratory grade quality.

Drug Profile7,8
Luliconazole belongs to the imidazole class of antifungal agents and is applied topically to cure superficial fungal infections like tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum and Epidermophyton floccosum. It is most often made into a 1% cream and administered daily for 1–2 weeks. Luliconazole inhibits lanosterol 14α-demethylase, disrupting the formation of ergosterol and impairing integrity in the cell membrane of the fungus, resulting in cell death. It exhibits potent in vitro and in vivo efficacy against dermatophytes and certain Candida and Malassezia species. The drug has low systemic absorption, an excellent safety profile, and is well tolerated with only mild local side effects.

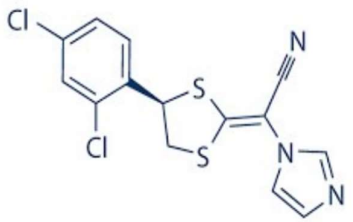


Figure 1: Structure of Luliconazole

Methods
Preformulation Studies Of Drug And Excipients:
Pre-formulation studies are the first step in the development of dosage forms of a drug substance. Pre-formulation studies refer to the early-stage research conducted to investigate the physical, chemical, and mechanical properties of a drug substance alone and when combined with excipients before it is formulated into a dosage form. These studies aim to gather essential data about the drug's stability, solubility, permeability, and compatibility with excipients.

Organoleptic Properties:9
The organoleptic studies like general appearance like nature, color, odor, etc. were performed by visual observation. The sample of drug was observed for colour, state.

Solubility Analysis: 10
One of the most important preformulation characteristics of a molecule is its solubility in different solvents. The Biopharmaceutics Classification System (BCS), which serves as a foundation for designing drug delivery systems, is primarily based on the solubility and permeability properties of the drug.

Procedure:
Drug solubility was determined using the shake-flask method. An excess amount of the drug was added to a measured volume of various solvents, including distilled water, ethanol, methanol, and phosphate buffers (pH 7.4), in separate stoppered flasks to prepare saturated solutions. These mixtures were shaken intermittently to facilitate equilibrium between dissolved and undissolved drug particles. After 24 hours, the solutions were filtered, and a measured volume of each filtrate was collected, appropriately diluted with the corresponding solvent, and analyzed for drug content using UV-Visible spectrophotometry.

Calibration Curve of Luliconazole: 11
- UV Spectroscopy (Determination of λ max) for Luliconazole
  The drug was diluted from the standard stock solution, and the resulting samples were scanned in the spectral range from 400 nm to 200 nm. Luliconazole exhibited its maximum absorbance at 296 nm.
- Preparation of standard stock solution:
  Standard stock solution was prepared by transferring 10mg of Luliconazole into 10ml volumetric flask and it was dissolved with methanol. Working standard solution was prepared by taking 2.5ml of stock solution into a 25ml volumetric flask.

The volume was made up to mark to produce 100µg/ml solution with methanol and distilled water. From the above working solution 0.2ml, 0.4ml, 0.6ml, 0.8ml & 1.0ml, were pipetted and transferred to 5 individual 10 ml volumetric flask and finally the volume was made up to the mark with diluent. Solutions were scanned from 200-400 nm UV range by using UV-Visible double beam spectrophotometer.

Compatability Studies: [12,13]

Compatibility studies are generally the final phase in preformulation profiling. Their primary goal is to detect any physical or chemical interactions between the pure drug and the excipients chosen for formulation development. Several experimental techniques, such as FTIR (Fourier Transform Infrared Spectroscopy) and DSC (Differential Scanning Calorimetry), are commonly employed to carry out these studies.

Fourier Transform infrared spectroscopy (FTIR): [14]

The Fourier Transform Infrared (FTIR) analysis of luliconazole and its excipients was performed using the Thermo Fisher Nicolet iS50 spectrometer equipped with an Attenuated Total Reflectance (ATR) accessory. The instrument was calibrated, and the ATR crystal was cleaned before sample placement. Finely ground solid or liquid samples were applied to the crystal with uniform pressure. Spectral data were acquired using OMNIC software, with appropriate parameters set for resolution and range. The obtained spectra were analyzed for characteristic peaks, compared with reference spectra, and assessed for purity and compatibility. The ATR crystal was cleaned after each measurement to prevent cross-contamination. The spectrum was recorded in the 4000–400 cm−1 range.

Experimental Design

Experimental design is a structured process used to plan and conduct experiments, enabling researchers to collect data that accurately tests hypotheses or explores cause-and-effect relationships. It involves deciding how participants or units are assigned to different conditions, what variables are manipulated, and how outcomes are measured, ensuring the research results are unbiased and reliable.

Independent variables: Soya lecithin, Cholesterol, Hydration time

Dependent variables: Entrapment efficiency, Particle size, In-vitro drug release

The preparation of liposomes was optimized using a full factorial design. Soya lecithin concentration (A), cholesterol concentration (B), and hydration time (C) were chosen as independent variables and each was evaluated at two levels (−1 for low and +1 for high). These formulation and process parameters were evaluated for their impact on entrapment efficiency (EE), particle size (VS), and in vitro drug release (DR). The JMP software version 13 was used for experimental design and analysis which resulted in 9 experimental runs. The experimental matrix containing coded and actual factor levels and measured responses can be found in Table 1. The experimental results were evaluated using analysis of variance (ANOVA) to assess the significance of each factor, their interactions and which was the most impactful on the chosen responses.

Table1: Experimental plan for 2x3 full factorial design in terms of actual and coded values.

Factors / Independent variables	Levels		Responses/ Dependent Variables	Constrains
	-1	+1		
Soya lecithin	100	300	Entrapment efficiency	Maximum
Cholesterol	50	150	Vesicle size	Minimum
Hydration Time	30	90	In-vitro drug release	Maximum

Preparation Of Liposomes:[15]

Liposomes were prepared employing thin film hydration technique. A lipid phase was prepared by dissolving accurately weighed quantities of the drug, PC and CHOL in the chloroform in 250 ml round bottom flask. The solvent mixture was removed from the lipid phase by rotary evaporation at 50-60°C (Buchi RE 121 Rotavapour, Buchi Laboratories AG, Flawil/Sheiz, Switzerland), to obtain a thin film of lipids on the wall of the flask. Subsequently, the flask was kept overnight under vacuum to ensure the complete removal of residual solvent. The dry lipid film was hydrated with saline solution at a temperature of 60±2°C. The dispersion was left undisturbed at room temperature for 2-3 hours to allow complete swelling of the lipid film and hence to obtain vesicular suspension.

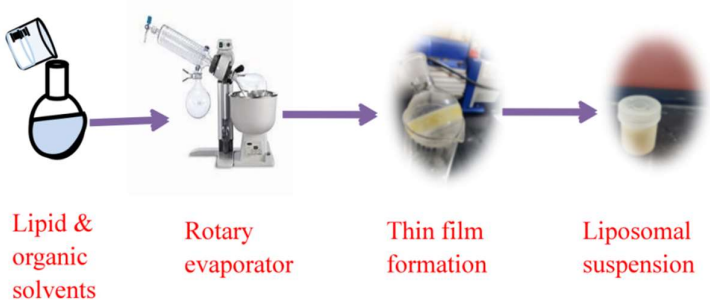


Figure2: Preparation liposomes by rotary evaporator

Table2: Composition of liposomes

Formulation code	Drug (Luliconazole)(mg)	Soya Lecithin(mg)	Cholesterol(mg)	Hydration Time(min)
F1	100	300	50	30
F2	100	100	50	60
F3	100	200	150	60
F4	100	200	50	90
F5	100	100	100	90
F6	100	100	150	30
F7	100	200	100	30
F8	100	300	100	60
F9	100	300	150	90

Preparation Of Liposomal Gel: [16]

Preparation of 1% Carbopol Gel:

Carbopol resin 1gm was dispersed in distilled water 88 gm in which glycerol 10 gm was previously added. The mixture was stirred until thickening occurred and then neutralized by drop wise addition TEA until transparent gel appeared.

Incorporation of liposome in 1% Carbopol gel:

Liposome containing drug was mixed in to 1% Carbopol gel by an electrical mixer 25rpm/2 min, with the concentration of liposome in hydrogel being 2.5% (w/w liposome suspension / total)

Characterization Of Luliconazole Liposome:

Determination Of Particle Size: [17]

The particle size of liposome is generally taken by zeta sizer instrument. This instrument containing Malvern PCS software. Before taking the result of sample solution the sample must be diluted with distilled water. The distilled water not interferes with result. Then after dilution the result were taken. The particle size must be required in nano range some time it goes to micron range if multilamellar vesicle are present. This software was taken the average particle size of liposome. The particle size of sample solution was determined by using light scattering technique and by transmission electron microscope. If the particle size of liposome increases then decrease the uptake and bioavailability of drug. The particle size is most important, the particle size of liposome in nano range are having more effective drug delivery as compare to micron range. The one advantage of large particle size liposome is having more area to fill more drug but it has very slow-release pattern. Various method is used for administration of particle size of liposome such as SEM, TEM.

Determination of entrapment efficiency: [18]

Luliconazole associated with liposome was separated from unentrapped drug using centrifugation method . Liposomes were centrifuged at 20000 rpm for 1 hr at controlled temperature of 4 C. Supernatant containing unentrapped Luliconazole was withdrawn and measured UV spectrophotometrically at 296 nm against phosphate buffer saline (pH 7.4). The amount of Luliconazole entrapped in liposome was determined as follow

Entrapment efficiency =drug entrapped ÷Total drug× 100

The entrapment efficiency was obtained by repeating the experiment in triplicate and the values were expressed as mean standard deviation.

In-vitro drug release: [19]

In vitro release studies were performed using modified Franz diffusion cell. Dialysis membrane (HiMedia molecular weight 5000) was placed between receptor and donor compartments. Luliconazole liposomal suspension was placed in the donor compartment and the receptor compartment was filled with phosphate buffer, pH 7.4 (18 ml). The diffusion cells were maintained at 37±0.5o C with stirring at 200rpm throughout the experiment. At fixed time intervals, 1ml of aliquots were withdrawn from receiver compartment through side tube and analyzed by UV-Visible Spectrophotometer at 296nm.

Determination of zeta potential: [20]

The zeta potential of liposome was taken in zeta sizer instrument having Malvern software. The analysis of sample was carried out at 25oc with the angle of detection 90o. The ideal zeta potential value must be required in range between +30 to -30mV. These ranges prevent the aggregation of liposomal particle.

Scanning Electron Microscope (SEM):
Surface morphology (roundness, smoothness, and formation of aggregates) and shape of lipsomes is carried out by scanning electron microscopy (SEM) size of the nanoparticle, shape and surface of the liposomes determined by Scanning electron microscope (SEM). In this method of determination liposomes are first diluted with ultra-pure water (1/5), and then a drop of the diluted liposomes was then directly deposited on a polished aluminum sample holder. Samples were dried in vacuum. The morphology of nanoparticles was observed at 15 kV using a scanning electron microscope

Evaluation Tests Of Optimized Formulation
Measurement Of Ph
The exact amount of Luliconazole gels was weighed in a 25ml volumetric flask and then volume was made up with double distilled water to 25 ml. The pH of the gel was measured using a digital pH meter by getting it in contact to equilibrate it for 1 min. pH evaluation was carried out in triplicate for all formulations.

Viscosity study
The viscosity measurements of the gels were determined at 25□C using a Brookfield Viscometer. All viscosity measurements were performed in triplicate.

Homogeneity
After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Spreadability
A sample of 0.5g of each formula was pressed between two slides (divided into squares of 5mm sides) and left for about 5 min where no more spreading was expected. Diameters of spreaded circles were measured and were taken as comparative values for spreadability. The results obtained are average of three determinations.

Release kinetics
Release kinetics models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio studies is always desirable. In this regard, the use of in-vitro drug dissolution data to predict in vivo bio-performance can be considered as rational development of controlled release formulations. Data obtained from the in vitro release studies were fitted to various model dependent kinetic equations such as zero order, first order, higuchi model, and korsmeyer- peppas model.

Zero- order model
$Qt = Q0 + Kt$
First order model
$Log\ C = log\ C0 - Kt/2.303$
Higuchi model
$Q = KH*t1/2$
Korsmeyer- peppas model
$Q/Q0 = Ktn$

Where, K0 to KH were release rate constant, Q/Q0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For fickian (diffusion controlled) $n \leq 0.5$; for non-fickian (anomalous) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.o; for super case transport II, $n > 1.040$. Based on the slop and the R2 value obtained from the above models the mechanism of drug release was decided.

Stability test
The stability of a pharmaceutical formulation refers to its ability to maintain physical, chemical, therapeutic, and toxicological properties within specified limits throughout its shelf life when stored in a defined container. According to ICH guidelines, short-term (accelerated) stability studies are conducted under specific storage conditions and timeframes.
For this study, accelerated testing was carried out at $40 \pm 2°C$ / $75 \pm 5\%$ RH for a period of three months. The optimized Luliconazole-loaded liposomal gel formulations were stored in amber-colored, screw-capped glass bottles and subjected to stability testing. During the study period, samples were evaluated at regular intervals for drug content, pH, and in-vitro drug release to monitor any potential changes in formulation characteristics.

Results And Disscussion
Pre-Formulation Studies

Organoleptic Properties

SL NO	PROPERTIES	INFERENCE
1.	Colour	White
2.	Odour	Odourless
3.	Taste	Tasteless

Solubility Studies Of Luliconazole

Solvents	Solubility
Water	Insoluble
Methanol	Soluble
Acetone	Soluble
Phosphate buffer 7.4	Soluble
Ethanol	Soluble

UV Spectroscopy (Determination of λ max) for Luliconazole

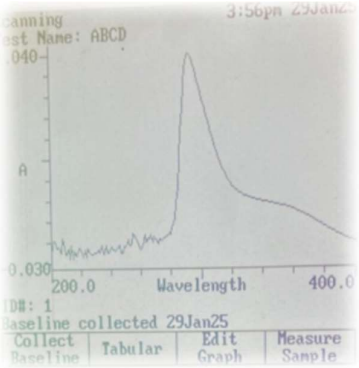
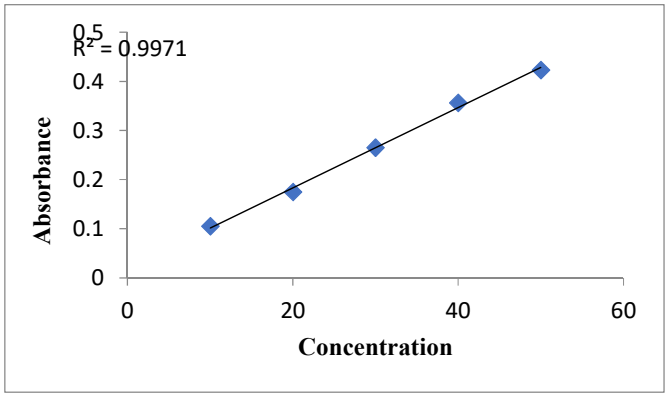


Figure 3: UV Spectrum of Luliconazole

Calibration curve of luliconazole with methanol

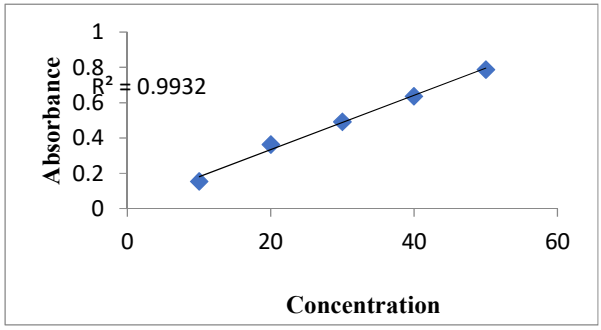
Concentration (µg/ml)	Absorbance
10	0.125
20	0.254
30	0.367
40	0.469
50	0.576



Lulicanazole + methanol

Calibration curve of luliconazole with phosphate buffer pH7.4

Concentration (µg/ml)	Absorbance
10	0.156
20	0.365
30	0.493
40	0.638
50	0.789



Luliconazole+ Phosphate buffer pH7.4

Table 3: Parameters for calibration curve in pH 7.4phosphate buffer solution & Methanol

Sl no	Parameter	Values in buffer pH7.4	Values in Methanol
1.	Absorbance maximum (λmax)	296nm	296nm
2.	Slope	0.993	0.997

Compatibility studies

In order to formulate a successful dosage form, it should be stable. So, compatibility study was conducted between drug and excipients to assess any compatibility issues which will affect the physiochemical properties of the dosage form.

Fourier-transform infrared spectroscopy (FTIR):

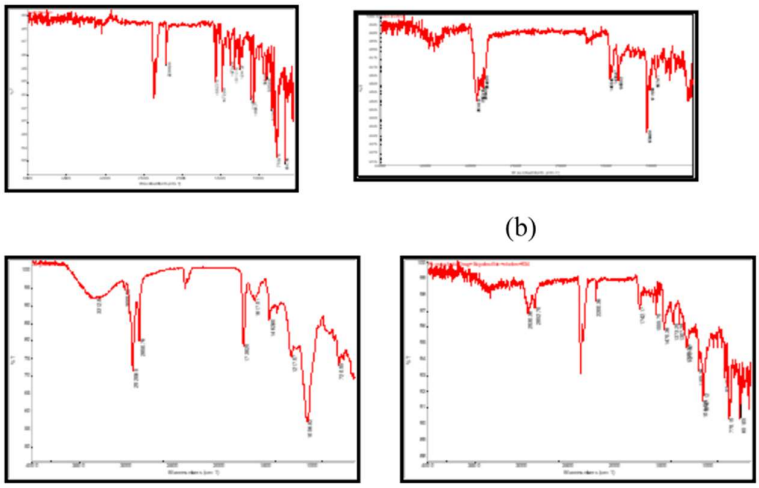


Figure4: Infrared spectrum of pure drug Luliconazole, Cholesterol, Carbopol, Soya lecithin and Physical mixture

Statistical experimental design:

2x3 full factorial design was used to investigate the impact of selected variables and their interactions in resulting in the maximum %EE, maximum PS and maximum In-vitro drug release. A total of 9 experimental trails were projected and their observed responses were given in Table4. The %EE of experimental formulations was the amount of drug entrapped, was ranged between66.2% to 82.3%. PS which will be identified in the range between 137.3nm to 221.5nm and In-vitro drug release, was ranged between 89.61% to 98.51% fit model and ANOVA were used to look at all of the experiment results for specific responses.

Table 4: The results of predicted experimental runs are observed

Formulation code	Factor 1 Soya Lecithin (mg)	Factor 2 Cholesterol (mg)	Factor 3 Hydration time (min)	Response 1 EE (%)	Response 2 PS (nm)	Response3 In-vitro drug release (%)
F1	300	50	30	66.2±0.32	181.9±4.39	93.65±0.61
F2	100	50	60	68.6±0.26	137.3±3.76	93.15±0.41
F3	200	150	60	70.2±0.63	152.7±3.16	89.61±0.81
F4	200	50	90	69.7±0.83	166±2.61	97.95±0.53
F5	100	100	90	73.4±0.21	198.4±3.81	93.65±0.87
F6	100	150	30	74.6±0.48	221.5±1.88	95.86±0.77
F7	200	100	30	77.3±0.71	176.4±1.87	94.83±0.87
F8	300	100	60	82.3±0.38	149±2.16	98.51±0.63
F9	300	150	90	71.3±0.27	149.8±0.99	92.8±0.54

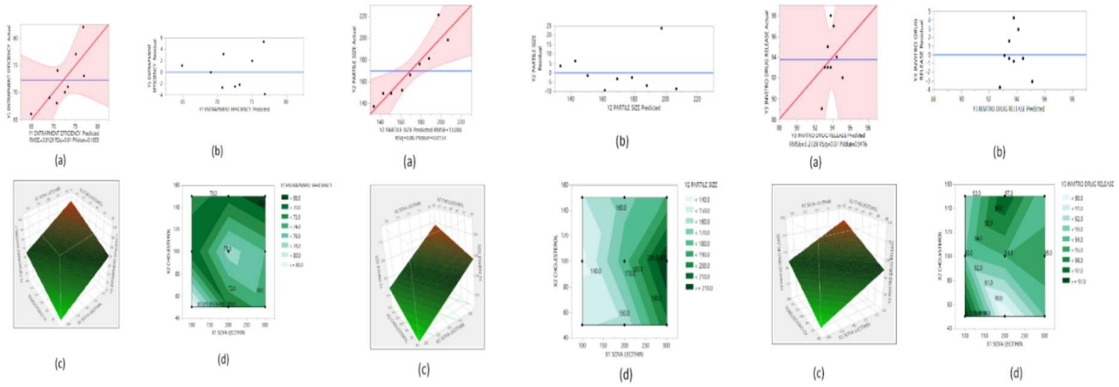


Figure 5: (a) Actual by predicted plot (b) Residual by predicted plot (c) Response surface plot (d) Contour plot of Response 1 Entrapment efficiency, Response2 particle size and response 3 In-vitro drug release

Evaluation Of Luliconazole Loaded Liposomes

Entrapment Efficiency:

The entrapment efficiency (EE) of the liposome formulations ranged from 66.2% to 82.3%. The highest EE was observed in F8, which might be attributed to the optimal combination of lipid and surfactant concentrations. The data shows that formulations with higher concentrations of soya lecithin (F8) had superior EE, indicating that cholesterol facilitates the incorporation of the drug into the hydrophobic core of the liposomes. An increasing trend in EE was observed as the lipid concentration in the formulations increased. This could be due to the enhanced viscosity of the medium, which may prevent drug diffusion from the liposome matrix into the external phase, thereby increasing the amount of drug encapsulated within the liposomes. Table 16 showed the percentage entrapment efficiency of all batches of Luliconazole loaded liposome.

Table5: Entrapment efficiency of liposomes

Formulation	Entrapment efficiency (%)
F1	66.2±0.3
F2	68.6±0.2
F3	70.2±0.63
F4	69.7±0.8
F5	73.4±0.21
F6	74.6±0.4
F7	77.3±0.71
F8	82.3±0.3
F9	71.3±0.2

In-vitro drug release

Drug release studies are required for predicting the reproducibility of the rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the liposomes drug release performance. The drug releases from the Luliconazole loaded liposome were studied by subjected to in-vitro drug release study for a period of 0-8hrs. The order of in-vitro drug release data was found to be highest for F8 formulation. The cumulative percent of drug release in 8hrs was noted. The drug release of Luliconazole loaded liposome was found to be 98.51% in 8hrs. Luliconazole loaded liposome formulation demonstrated substantially faster drug release until the end of 4hrs followed by sustained release.

Table6: In-vitro drug release for F1-F9 Formulation

Time in hrs	% cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.27	18.81	19.63	25.36	12.27	23.72	25.36	22.9	14.72
2	31.93	29.45	31.93	43.64	22.92	33.57	40.11	27.84	23.74
3	40.14	35.71	40.14	51.05	30.3	50.79	47.36	33.6	32.76
4	47.55	42.17	47.55	62.56	41.79	57.89	58.21	48.36	44.26
5	58.24	56.12	56.32	69.18	59.84	71.05	70.55	66.41	54.12
6	73.03	67.64	62.66	83.85	78.67	80.13	75.42	78.61	66.46
7	87.75	80.8	80.53	91.12	88.63	90.03	88.71	90.96	80.44
8	93.65	93.15	89.61	97.95	93.65	95.86	94.53	98.51	92.8

Particle size

The prepared Luliconazole loaded liposomes were tested for particle size, as shown in (Figure 16).The particle size ranged from (195.59nm). From the results of particle size, it was found that all prepared Luliconazole loaded liposomes have a particle size less than 200nm, and as such are effective for local and topical applications. From the obtained results it was found that liposomes prepared with a higher concentration of Lipid and cholesterol have a larger particle size.

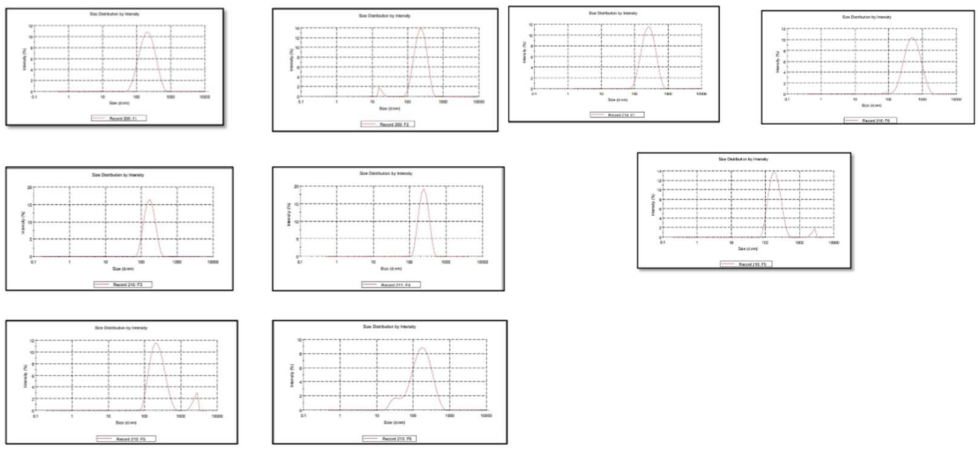


Figure 6: Particle size of the formulation F1-F9

Surface Morphology By Sem:

The surface morphology of Luliconazole loaded liposome was determined by using SEM.

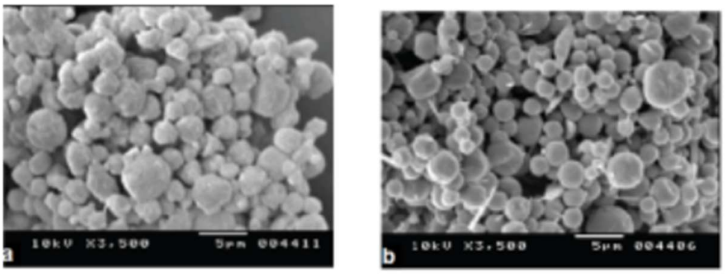


Figure 7: SEM images of Luliconazole loaded Liposomes

Evaluation of Topical Liposomal Gel

1. Visual Appearance

The formulation were white, odour less, semi solid in consistency and smooth in apperance

2. PH

Across all formulations, the pH ranged from 5.9 to 6.8. The F8 formulation in particular had measured pH of 6.8

3. Drug Content

The solutions were analyzed for drug content spectrophotometrically at 296nm. All the formulation batch exhibited fairly uniform drug content. The drug content of all formulations was in the range of 82 to 98%.

Table 7: Percentage Drug Content of Liposomal Gel

Slno	Formulations	% Drug content
1	F1	82.57 ± 0.26 %
2	F2	84.29 ± 0.28 %
3	F3	85.19 ± 0.30 %
4	F4	87.61 ± 0.22 %
5	F5	80.94 ± 0.24 %
6	F6	90.1 ± 0.32 %
7	F7	92.60 ± 0.28 %
8	F8	98.8 ± 0.34 %
9	F9	94.78 ± 0.38 %

4. Viscosity

Viscosity of the formulations were found to be measured by Brookfield viscometer at spindle no. 61.in10,20,30,60,100,rpm. The all gel formulation's viscosity ranged from 625- 17223cps. The formulations' viscosity declined on increasing the shear rate as depicted in the graph.

Table 8: Viscosity of Liposomal gel

Slno	RPM	Viscosity								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10	10192	13241	13250	13980	16020	17080	16890	15800	14850
2	20	5110	5204	5650	5900	5880	10200	5820	5700	5600
3	30	2623	2830	3100	3190	3280	2960	1880	3100	3000
4	60	1407	1324	1350	1980	2180	1950	1200	2000	1900
5	80	1013	1100	1249	1350	940	1050	1320	1200	1250
6	100	625	800	910	950	650	780	940	880	740

5. In-vitro drug release

Drug release studies are required for predicting the reproducibility of the rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the liposomes drug release performance. The drug releases from the Luliconazole loaded liposome were studied by subjected to in-vitro drug release study for a period of 0-8hrs. The order of in-vitro drug release data was found to be highest for F8 formulation. The cumulative percent of drug release in 8hrs was noted. The drug release of Luliconazole loaded liposome was found to be 98.51% in 8hrs. Luliconazole loaded liposome formulation demonstrated substantially faster drug release until the end of 4hrs followed by sustained release.

Table 9: In-vitro drug release for Liposomal gel

Time in hrs	% cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.81	12.27	10.63	13.9	13.09	11.45	15.45	14.72	10.63
2	13.93	16.37	17.19	22.92	18.83	23.73	22.1	25.37	20.46
3	26.53	31.21	33.57	34.4	31.12	33.58	31.93	40.13	31.94
4	35.29	40.97	39.34	48.35	41.79	46.71	42.6	44.27	41.79
5	48.47	51.65	46.75	54.13	54.93	59.85	55.74	59.04	54.93
6	55.12	59.07	55.79	66.46	64.81	72.19	68.89	73.02	63.99
7	73.32	79.59	64.86	77.99	75.55	79.63	77.91	78.82	76.09
8	89.86	86.23	81.94	87.89	85.42	87.08	85.36	92	86.24

6. Drug release kinetics:

In order to predict and correlate the in-vitro drug release from Luliconazole loaded liposome gel, it is necessary to fit into a suitable mathematical model. Investigation for the drug release from the cubosome hydrogel was done by different kinetic equations (Zero order, First order, Higuchi's equation, Hixon Crowell and Korsmeyer-Peppas). The drug release was followed by fitting the data to Higuchi release kinetics and the release mechanism was follows non-Fickian transport.

Formulation	Zero order kinetics	First order kinetics	Higuchi plot	Kors-peppas
F8	0.9906	0.9492	0.9212	0.9361

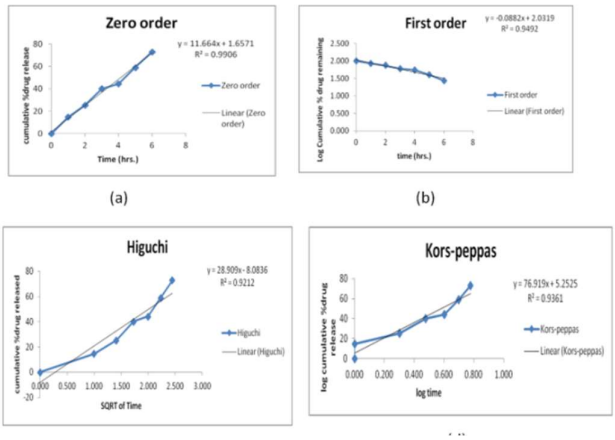


Figure8: Graph showing (a) zero order (b) First order (c) Higuchi (d) Kors-peppas

7. Stability Study of Liposomal Gel:

The stability of the Luliconazole-loaded liposomal gel was evaluated under two storage conditions: 4 ± 2°C and 25 ± 2°C / 60% RH for a period of three months. During the study period, the formulation was assessed for pH, drug content, and in-vitro drug release. The results indicated no significant variations in any of the evaluated parameters, suggesting that the physicochemical properties of the gel remained consistent. Thus, the Luliconazole-loaded liposomal gel demonstrated good stability under the tested conditions throughout the study duration.

Table10: Stability studies for Luliconazole loaded liposomal gel

Months	4 C±2 C			25 C/ 60%RH		
	pH	Drug content (%)	%CDR	pH	Drug content (%)	% CDR
Initial	6.52±0.39	95.8±0.83	92.01±0.3	6.52±0.39	95.8±0.83	92.01±0.3
1	6.51±0.37	95.1±0.79	91.8±0.10	6.32±0.17	94.7±0.39	91.6±0.15
2	6.50±0.35	94.7±0.76	91.5±0.14	6.28±0.21	94.3±0.51	91.3±0.23
3	6.47±0.32	94.5±0.79	91.3±0.16	6.25±0.23	94.1±0.14	91.1±0.18

Comparative Studies With Marketed Formulation

To assess differences on drug content as well as drug release qualitatively, the prepared liposomal gel formulation was compared with a marketed gel formulation. Drug content analysis was performed by taking 1g of each gel, dissolving, filtering, and quantifying through a validated analytical method. Both formulations appeared to have comparable drug content

which demonstrates that the drug loading was accurate in the prepared liposomal gel. In vitro drug release studies were performed in a Franz diffusion cell consisting of a dialysis membrane. The receptor compartment containing phosphate buffer (pH 7.4) was the release medium. Samples were taken and analyzed spectrophotometrically. The liposomal gel showed slower and more sustained drug release compared to the marketed gel, which was faster acting. The slower release profile of the liposomal gel may prolong therapeutic effect, reduce dosing frequency, and sustain drug delivery, which aligns with the behavior of lipid-based drug delivery systems.

Drug content:

Formulation	Drug content (%)
Liposomal gel	98.5
Marketed gel	99.3

In-vitro drug release:

Time(hrs)	Liposomal gel (%)	Marketed gel (%)
0	0	0
1	14.72	23.72
2	25.37	28.66
3	40.13	34.42
4	44.27	48.36
5	59.04	67.24
6	73.02	78.76
7	78.82	90.3
8	82.97	97.77

Conclusion

Formulation stability was confirmed via FTIR analyses for the excipients used with luliconazole. Through the application of a 3×2 full factorial design, 9 liposomal formulations (F1–F9) were created and tailored for soya lecithin, cholesterol, and drug concentration with the aim of achieving high entrapment efficiency, uniform particle size, and favorable zeta potential. The optimized liposome was 195.59 nm and under SEM displayed a distinctive phase structure, and was successfully incorporated into a gel which met the pH, viscosity, and spreadability requirements for topical use. In vitro testing confirmed that the liposomal gel released luliconazole in a sustained manner and adhered to the Higuchi release model. In comparison with a marketed gel, evaluation showed that while the drug content was similar, the release from the liposomal gel was slower and more prolonged, highlighting its potential for extending the therapeutic effect, reducing dosing frequency, and improving patient compliance in the treatment of fungal infections.

Summary

The study developed a topical liposomal gel of Luliconazole with enhanced entrapment efficiency, nanosized vesicles, and sustained release properties. Compared with marketed gel, the formulation showed prolonged release and improved therapeutic potential. This delivery system may improve management of fungal skin infections by reducing recurrence and dosing frequency.

Abbreviations

FTIR: Fourier Transform Infrared Spectroscopy
UV: Ultraviolet
SEM: Scanning Electron Microscope
TEM: Transmission Electron Microscope
ANOVA: Analysis of Variance
RH: Relative Humidity
EE: Entrapment Efficiency
PS: Particle Size
CDR: Cumulative Drug Release

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