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Luliconazole Niosomal Transdermal Drug Delivery System Development and Assessment

Divya [1],G.Rajani [2],Shilpadas [3],MD.Solaiman [4,]
Assistant professor [1,2,3,4],
Department of Pharmacy,
Samskruti College of Pharmacy,
Kondapur (V), Ghatkesar (M) Medchal Dist, Telangana, India.

ABSTRACT

Previous studies have shown that the use of niosomes as drug carriers yields better outcomes than other methods, especially when it comes to antifungal medications. Pharmaceuticals that are both hydrophilic and hydrophobic may be encapsulated in niosomes, which also prolongs their stability in circulation. The preparation and assessment of luliconazole niosomal gel for antifungal activity was the goal of this investigation. The present investigation included the preparation of luliconazole-containing niosomes by the thin-film hydration process, employing non-ionic surfactants (Span 60 and Tween 80) and cholesterol at varying concentrations. The produced formulations underwent evaluations for stability tests, in-vitro drug release investigations, drug content, drug entrapment efficiency, and optical microscopy. Better outcomes were shown when the ratio of cholesterol to span 60 was 2:1. It was thus refined to become the ultimate vesicle formulation. According to the results of the FTIR analysis, luliconazole and any of the excipients did not interact. The niosomes gel was assessed across all formulations for a number of criteria. The most favorable and encouraging outcomes are seen with the 1% Carbopol 934 gel. To improve transdermal effectiveness, the niosomal gel formulation may prove to be a helpful dose form.

Introduction

As an alternative to oral medicine administration and hypodermic injections, transdermal drug delivery has grown in favor. Transdermal medication administration specifically performs better than oral drug delivery in a number of areas, not the least of which is avoiding first-pass metabolism, which causes rapid drug metabolism and reduced bioavailability. Transdermal medicine delivery systems come with minimal costs and self-administration features. One drawback of this administration route is the limited number of drugs that may be modified for transdermal delivery. Technology advancements and developments in the area of drug delivery over the last several decades have made it possible to successfully create medications with suitable molecular weights or delivery systems for effective transdermal drug administration.[1] Therapeutically effective doses of medicine may be applied topically to a patient's skin using transdermal drug delivery devices (TDDS). For medicinal compounds to be transferred via human skin for systemic effects, consideration of the skin's whole morphological, biophysical, and physicochemical properties is required. Transdermal delivery increases patient compliance and prevents first-pass metabolism, giving it a competitive edge over injectables and oral techniques. Transdermal administration circumvents pulsed entry into the systemic circulation, which commonly has negative side effects, and enables continuous infusion of drugs with short biological half-lives. As a result, several cutting-edge drug delivery techniques, such as controlled release systems and TDDS, were developed. Among the numerous advantages of transdermal drug delivery are reduction of hepatic first-pass metabolism, enhancement of therapeutic efficacy, and maintenance of a stable drug plasma level.[2] The terms "topical" and "transdermal" are often used interchangeably, with ambiguous meanings. This arises from the fact that all medications given topically—that is, on the skin's surface—are topical by definition. On the other hand, medications administered topically that function locally via passive skin dispersion are sometimes referred to as "topicical medication." On the other hand, transdermal medications are applied topically, but they work by increasing the amount of drug that can pass through the skin barrier, often to the point where the drug enters the bloodstream and affects areas other than the skin. This is achieved through the use of technology,

substances that enhance skin penetration, or both.[3] However, cutting-edge drug delivery systems are made to administer medications to the intended spot at a volume and pace that are determined by the body's needs.
The fundamental motivation for the development of novel delivery techniques is the maintenance of pharmaceutical release or the maintenance of an effective therapeutic concentration with fewer side effects. Niosomal structures are very efficient in delivering drugs in terms of quantity and depth because they increase cell penetrability and lipid smoothness.

Materials and Methods

Materials

Research-Lab Fine Chem Industries, Mumbai is the source of all commercially available excipients and solvents, including tween 80, span 60, cholesterol, chloroform, carbopol 934, poloxamer 407, propylene glycol, glycerol, methanol, sodium chloride, potassium phosphate (monobasic), potassium phosphate (dibasic), and triethanolamine. Precise Chemipharma Pvt. L. sent a free sample of the medication luliconazole. Instrumentation Shimadzu 1800 is used for UV-vis spectrophotometry. UV-Probe is the software. Using a Shimadzu IR Affinity-ISCE, fourier transform infrared (FTIR) spectra were obtained. Carl Zeis's type supra-5 performs TEM. The Brookfield viscometer DV2T-E95 type is used to measure viscosity. The gel's pH is measured using a digital pH meter, the EQ610.

UV-perceptible Spectrophotometry

Making a luliconazole standard stock solution (pH 7.4) in methanol and PBS. After precisely weighing 10 mg of leviconazole, it was added to a 100 mL volumetric flask. It was dissolved and diluted with Solvent to a standard stock solution of 100 µg/mL Spectrophotometric scanning and the drug's λmax were determined. A 1-mL pipette was taken from the standard stock solution, diluted with 10 mL of methanol, and scanned between 200 and 400 nm in wavelength. Pipetting off 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 mL of the standard stock solution and diluting up to 10 mL by methanol yielded 2, 4, 6, 8, 10, and 12 ppm solution, respectively. This series of dilutions was done in order to plot the calibration curve of lumiconazole from the standard stock solution. The absorbance was measured using a UV-vis spectrophotometer at 296 nm. To ensure linearity, this experiment was run three times, and a calibration curve was created.

FTIR Spectroscopy

By comparing the FTIR spectra of the pure drug and excipients as well as the combination of drug and excipients, the compatibility of the drug and excipients was verified. Niosomal Suspension Formulation Using the Thin Film Hydration Method[6] Using a lipid combination of surfactants and chloroform in the various prescribed ratios as stated in the surfactant, chloroform, and drug were precisely weighed and dissolved in 7 mL of chloroform, niosomes were made using the thin film hydration technique. After that, the lipid mixture was put into a 100 mL round-bottom flask, and a rotary flash evaporator was used to evaporate the solvent at a temperature of 55 to 65°C while applying decreased pressure, until a thin lipid layer developed. Ten milliliters of phosphate buffer saline (pH 7.4) were used to hydrate the produced film. The flask was maintained spinning in the rotary evaporator at room temperature for the duration of the one-hour hydration. To create a niosomal dispersion containing pharmaceuticals that were both free and entrapped and had different sizes, the hydrated niosomes were subjected to a 20-minute sonication process using a bath sonicator. Luliconazole niosomal dispersion formulation is shown in Table 1.

Table 1: Liliconazole niosomal dispersion formulations

Formulation Code	*Drug (%)*	*Surfactant*	*Surfactant: Cholesterol Ratio (mg)*
LS60I	1	Span 60	1:1
LS60II	1	Span 60	1.5:1
LS60III	1	Span 60	2:1
LT80I	1	Tween 80	1:1
LT80II	1	Tween 80	1.5:1
LT80III	1	Tween 80	2:1

Characterization of Niosomes

Visual Appearance

To confirm the presence of niosomal dispersion, a visual examination was conducted. By putting the niosomal dispersion in transparent containers, turbidity, flocculation, and sedimentation could all be seen.

Lens Microscopy [7]

A glass slide was coated with diluted niosome solution. The diluted niosome solution was covered with a cover slip, and the average vesicle size and shape was assessed using an ocular eyepiece micrometer that had been previously calibrated under an ordinary optical microscope.

Zeta Potential [8]

Using a Malvern Zetasizer Nano ZS, the polydispersity index and zeta potential of the niosomal formulation were determined. The size distribution of the delivery mechanism was assessed using the niosome polydispersity index.

Cytoplasmic Morphology[9]

Transmission electron microscopy (TEM) was used to examine the morphology of niosomal vesicles.

Efficiency of Entrapment[10]

By using ultracentrifugation for 30 minutes at 4°C, the free drug was extracted from the drug that was entrapped in niosomes. A UV spectrophotometer was used to collect and evaluate the supernatant, which contained free drug. The following algorithm was used to determine the percentage of drug entrapment.

$$PDE = \text{Total Amount of Drug} - \text{Free Amount of Drug} / \text{Total Amount of Drug} \times 100.$$

Formulation of Niosomal Gel

By Dispersion Method[11]

To incorporate into gel bases prepared with varying amounts of Carbopol 934, a Niosome formulation was selected.

Liliconazole niosomal gel formulation shown in Table 2. Measured amounts of Carbopol 934 were added to the distilled water and mixed constantly. Soaked and moisturized, it stayed for two hours. Once the optimal niosome formulation had been added in the required quantity, further chemicals, such as propylene glycol and glycerol, were added and evenly dispersed while being constantly agitated. The pH of the gel was neutralized with triethanolamine

(TEA), and the final weight was adjusted using distilled water. The gel was sonicated for 30 minutes on a bath sonicator to liberate trapped air, and it was then left undisturbed for the whole night.

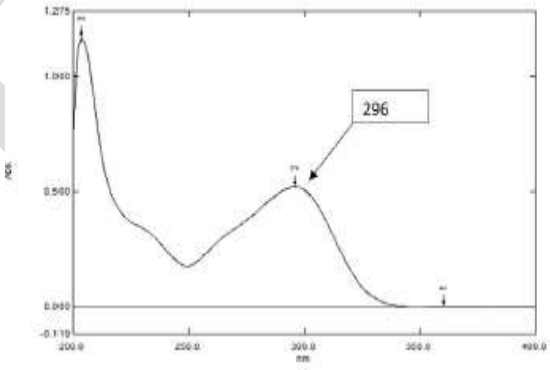
Table 2: Niosomal gel formulation

Formulation Codes	*Carbopol 934 (%)*	*Poloxamer 407 (%)*	*Propylene Glycol (%)*	*Glycerol (%)*
LNG1	0.5	----	10	30
LNG2	1.0	----	10	30
LNG3	----	20	10	30
LNG4	----	22	10	30

Result and Discussion

Ultraviolet-Visible (UV-Vis) Spectrophotometry

The maximum absorbance (max) of the medication, determined by observing the largest peak in the UV-Vis spectrum analysis of lumiconazole, was found to be 296 nm in methanol and 299 nm in PBS pH 7.4. The UV absorption spectra of luliconazole in methanol is shown in Figure No. 1. The UV absorption spectra of luliconazole in PBS pH 7.4 is seen in Figure 3. For the calibration curve, luliconazole concentrations in methanol ranging from 2 to 10 ppm were used. The luliconazole drug's calibration curve in methanol is shown in Figure 2. In the chosen range, the relationship between drug concentration and absorbance was linear, as shown by the value of R2 w as f ound t o b e 0.9972.



The R2 value as found to be 0.998 indicates that the

Fig. 1: UV absorption spectrum of Luliconazole in Methanol

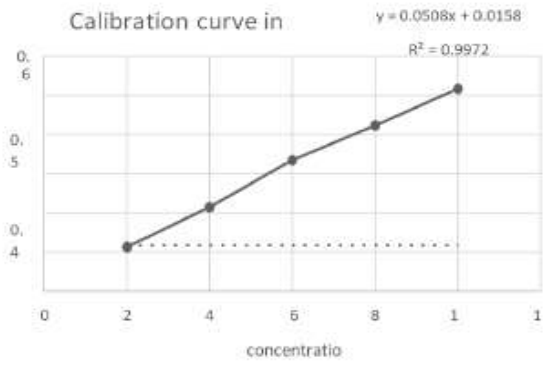


Fig. 2: Calibration Curve of Luliconazole in Methanol

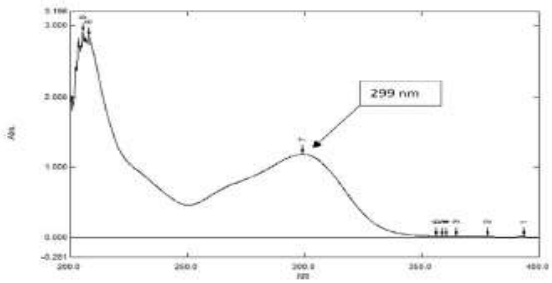


Fig. 3: The relationship between drug concentration and absorbance in the chosen range was linear in the ultraviolet absorption spectra of levidinezole in phosphate buffer solution pH 7.4. The drug's absorbance at various doses in a pH 7.4 phosphate buffer solution. The linearity and calibration curve of laconazole in phosphate buffer pH 7.4 are shown in Figure 4. Fourier Transform Infrared (FTIR) Spectroscopy: A Study of Drug-Excipient Compatibility
The luliconazole drug's IR spectra are described in Figure 5, and the IR spectra of the API and excipients employed in the luliconazole niosomal formulation are shown in Figure No. 6. FTIR was used to record the IR spectra of both the pure drug and excipients as well as the combination of drug and excipients. By comparing the spectra, the compatibility of the drug and excipients was verified. The FTIR analysis found that there was no interaction between any of the excipients and the medication luliconazole.

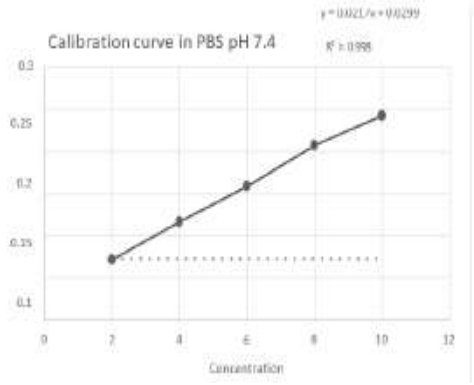


Fig. 4: Calibration curve and linearity of Luliconazole in Phosphate buffer solution pH 7.4

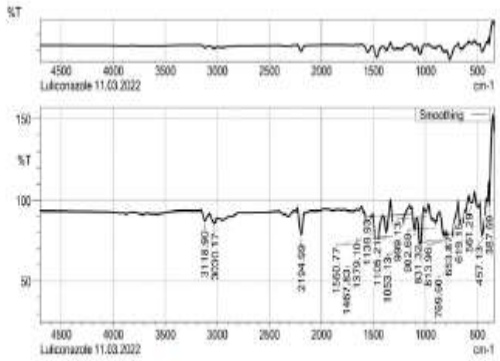
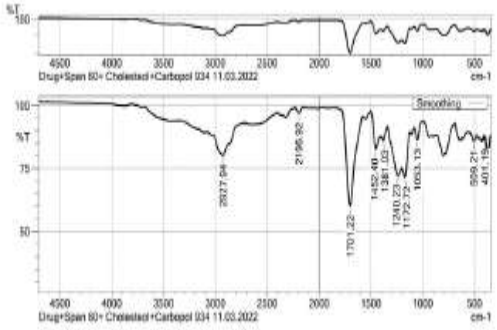


Fig. 5: IR spectra of luliconazole

Fig. 6: IR Spectra of API and Excipients used in formulation



Entrapment Efficiency

percentage of drugs Fig. 7 shows the entrapment efficacy of luliconazole niosomal dispersion.

Measurement of Zeta Potential

Using Zeta-sizer, the zeta potential of the LS60III formulation was determined. Zeta potential was determined to be -26.1 mV. This suggests improved stability and, thus, longer shelf life. A third-party lab determined the improved formulation's vesicle size, dispersion, and zeta potential.

Optical Microscopy

The development of multilamellar vesicles is shown by Transmission Electron Microscopy (TEM) pictures of the LS60III Formulation, as seen in Figure 8.

Spreadability and Viscosity

The viscosity and spreadability characteristics for luliconazole niosomal gel are shown in Table 3. It was discovered that LNG2 and LNG4 have the proper viscosity for topical application. Compared to other gel formulations, LNG2 had a higher viscosity, whereas LNG3 had a very low viscosity.

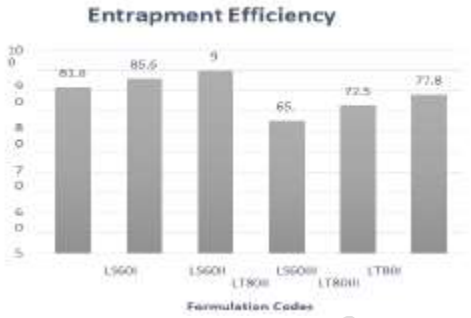


Fig. 7: Entrapment efficiency of luliconazole niosomal dispersion

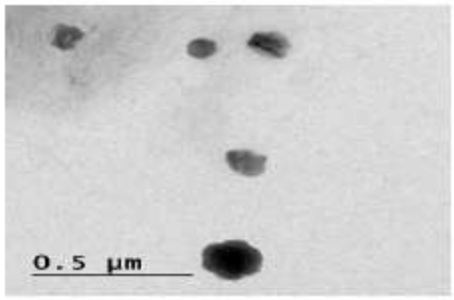


Fig. 8: Transmission electron microscope (TEM) image of LS60II

Table 3: Viscosity and spreadability

Formulation Codes	*Spreadability (g. cm/sec)*	*Viscosity (cP)*
LNG1	38.46	35,530
LNG2	35.71	49,260
LNG3	27.88	33,660
LNG4	23.73	41,740

Table 4: Drug content uniformity

Formulation codes	*Drug content uniformity (%)*
LNG1	85.86
LNG2	89.80
LNG3	79.76
LNG4	76.02

It was found that LNG1 and LNG2 had superior spreadability over LNG3 and LNG4. More slip and improved spreadability are shown by shorter periods between two slides. Strong spreadability is suggested by the slides should be able to separate with the least amount of resistance.

Uniformity of Drug Content

Table 4 lists the percentage of the medication in luliconazole gel. LNG2's consistent drug content yields superior outcomes.

Diffusion Study in Vivo

Table 5 shows how much medication diffused across the membrane at a certain period. Figure 9 shows the in vitro drug release of niosomal gel.

Medication Release Kinetic Simulation

The in-vitro release data was included into many release kinetic models in order to assess the drug's release mechanism from the niosomal gel. Table 6 lists the drug release for luliconazole niosomal gel at four distinct concentrations.

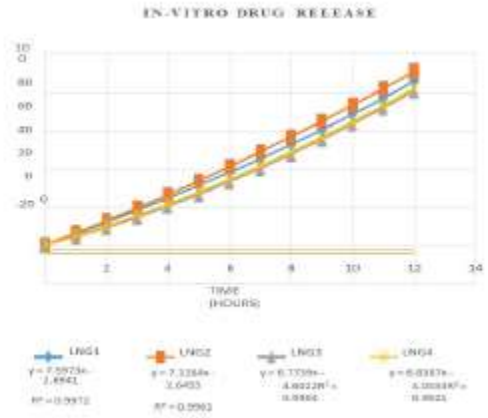


Fig. 9: *In-vitro* diffusion study of the niosomal gel formulation

Table 5: *In-vitro* diffusion study

Time (Hours)	*Drug diffused from the formulation (%)*			
	LNG1	*LNG2*	*LNG3*	*LNG4*
0	0	0	0	0
1	5.917051	6.285714	4.442396	4.81106
2	12.01843	12.75576	9.253456	9.990783
3	18.30415	19.41014	14.43318	15.53917
4	24.77419	26.43318	20.35023	21.45622
5	31.42857	33.64055	26.63594	27.74194
6	38.26728	41.21659	33.29032	34.39631
7	45.29032	48.97696	40.31336	41.41935
8	52.86636	56.92166	47.70507	48.81106
9	60.62673	65.05069	55.46544	56.57143
10	68.75576	73.54839	63.59447	64.70046
11	77.25346	82.23041	72.09217	73.19816
12	86.11982	91.09677	80.95853	82.06452

Table 6: Drug release kinetic modeling

Formulation kinetic models	*LNG1 (0.5%)*	*LNG2 (1%)*	*LNG3 (20%)*	*LNG4 (22%)*
Zero order model	0.9961	0.9972	0.9904	0.9921
First order model	0.7909	0.7845	0.8353	0.823
Higuchi model	0.8921	0.8954	0.8685	0.8749
Korsmeyer-Peppas model	0.8941	0.8895	0.9307	0.9207
Hixson-crewel model	0.8395	0.8386	0.8701	0.8613

Stability Study

In accordance with ICH recommendations, the niosomal gel stability investigation was carried out. According to ICH rules, freshly made formulations were separated into groups and stored under certain circumstances. Periodically, samples were taken out and subjected to tests for different assessment criteria. Table 7 presents a tabulation of the stability research findings. The formulation maintained all of its characteristics when kept at the designated temperature, therefore there was not much additional alteration in the niosomal gel of LNG2 during stability investigation.

Conclusion

Transdermal medication delivery systems have recently been tested for therapeutic efficacy using a unique vesicular drug delivery method. It was determined from the research's experiments that luliconazole niosomal gel was effectively made by employing luliconazole niosomes made by the thin film hydration method, which involved combining cholesterol and Span 60 in a 2:1 ratio and loading them with different amounts of carbopol 934. The mean dimensions of niosomes were determined to be 0.5 µm, and their zeta potential was discovered to be -26.1 mV, indicating a stable niosome formulation. The niosomes gel was assessed across all formulations for a number of criteria. The greatest and most encouraging results are obtained with the 1% Carbopol 934 gel. To improve transdermal effectiveness, the niosomal gel formulation may prove to be a helpful dose form. As a result, niosomes gel could be the ideal vesicular carrier for luliconazole's efficient skin distribution. The preparation process used in the lab and on an industrial scale is straightforward and workable.

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