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Research Article

Development and Evaluation of Luliconazole Niosomal Transdermal Drug Delivery System

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ABSTRACT

According to earlier research, using niosomes as drug carriers, particularly for antifungal drugs, produces greater results than using alternative carriers. Niosomes has the capacity to encapsulate both hydrophilic and hydrophobic pharmaceuticals, as well as their prolonged stability in circulation.

This work aimed to prepare and evaluate luliconazole niosomal gel for antifungal activity. In this study, niosomes containing luliconazole were prepared by thin film hydration technique using non-ionic surfactant (Span 60 and Tween 80) and cholesterol at different concentrations. The prepared formulations were evaluated for optical microscopy, drug entrapment efficiency, drug content, *in-vitro* drug release study, and stability studies. The ratio 2:1 of span 60 and cholesterol showed better results. Hence it was optimized as the final vesicle formulation. The FTIR study concluded there was no interaction between Luliconazole and any of the excipients. The niosomes gel was evaluated for various parameters of all the formulations. The 1% Carbopol 934 gel shows the best and most promising results. The niosomal gel formulation could be a useful dosage form to increase efficacy by the transdermal route. The potential of a secure and efficient therapy for difficult clinical applications is made possible by the development of niosomes with target specificity. Therefore, niosomes gel may be considered the best vesicular carrier for the effective delivery of luliconazole through the skin.

INTRODUCTION

Transdermal drug delivery has gained popularity as an alternative to hypodermic injections and the conventional oral medication delivery mode of administration. In particular, transdermal drug delivery outperforms oral drug delivery in several ways, not the least of which is the avoidance of first-pass metabolism, which results in abrupt drug metabolism and decreased bioavailability. Self-administration and low cost are features of transdermal medication delivery systems. The few medications that may be altered for transdermal distribution are a downside of this method of administration. Over the past several decades, advances in technology and discoveries in the field of drug delivery have enabled the successful manufacture of drugs with adequate molecular weights or delivery methods for efficient transdermal drug delivery.[1] Transdermal drug delivery systems (TDDS) are dosage forms created to spread an amount of medication across a patient's skin that is therapeutically effective. It is necessary to take into account the complete morphological, biophysical, and physicochemical characteristics of the skin to transfer medicinal substances through the skin of humans for systemic effects. Transdermal administration offers a competitive advantage over injectables and oral methods by improving patient compliance and avoiding first-pass metabolism. Transdermal delivery allows for continuous infusion of medications with brief biological half-lives and avoids pulsed entrance into the systemic circulation, frequently resulting in unfavorable side effects. This led to the emergence of

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numerous novel drug delivery methods, including TDDS and controlled release systems. Transdermal drug administration has many benefits, including limiting hepatic first-pass metabolism, improving therapeutic effectiveness, and maintaining a constant plasma level of the drug.[2] Topical and transdermal are phrases that are frequently misunderstood, interchanged, and have unclear definitions. This results from the fact that all drugs applied to the skin are, by definition, topical (applied to the top of the skin). However, the phrase "Topical Medication" often refers to drugs that are applied to the skin and have a local impact due to passive diffusion into the skin. Contrarily, transdermal medications are those that are applied to the skin but use technology, skin penetration enhancing substances, or both to increase the amount of drug that can penetrate the skin barrier, frequently to the point where the drug can enter the bloodstream and have an impact elsewhere besides the area of application.[3] On the other hand, innovative drug delivery systems are designed to deliver drugs to the desired location at a rate and volume that are controlled by the body's requirements. Maintaining medication release or maintaining an efficient therapeutic concentration with fewer adverse effects is the key driver behind the development of innovative delivery methods. By increasing cell penetrability and lipid smoothness, niosomal structures are highly effective at delivering chemicals both in terms of quantity and depth. The current study aims to describe niosomes containing luliconazole and phospholipids as vesicle-shaping agents and to observe their effects at the targeted region for a prolonged drug delivery system. Niosomes' beneficial skin penetrating properties and topical dosage form healing effects have been researched as part of the related investigations. These results have an impact on the design of transdermal drug delivery systems, which could lead to the future development of novel drug delivery vehicles.[4] Luliconazole is an antifungal drug used to treat skin problems. Luliconazole is indicated for the treatment of topical fungal infections caused by *Epidermophyton floccosum*, *Trichophyton rubrum*, and specifically, tinea pedis, cruris, and corporis. Luliconazole drug molecule has better pharmacokinetic properties in the skin. Luliconazole has strong in vitro antifungal activity.[5] Luliconazole niosome gel was developed to address the issues of stability.

Due to their enormous benefits, which support the expansion of the pharmaceutical sector, niosomes are now attracting the pharmaceutical industry's attention.

Materials and Methods

Materials

All the commercially available excipients and solvents such as span 60, tween 80, cholesterol, chloroform, carbopol 934, poloxamer 407, propylene glycol, glycerol, methanol, sodium chloride, potassium phosphate (Monobasic), sodium phosphate (dibasic), triethanolamine was purchased from Research- Lab Fine Chem Industries, Mumbai. Drug luliconazole was gift sample by Precise Chemipharma Pvt. L

Instrumentation

UV-vis spectrophotometry is done by Shimadzu 1800 Software: UV-Probe. The fourier transform infra-red (FTIR) spectra were carried out on a shimadzu IR Affinity-ISCE. TEM is done by Carl Zeis's model supra-5. To determine viscosity Brookfield viscometer DV2T-E95 model is used. EQ610 digital pH meter is used to check the pH of the gel.

UV-visible Spectrophotometry

Preparation of standard stock solution of luliconazole (in Methanol and PBS pH 7.4). Luliconazole 10 mg was accurately weighed and transferred to a 100 mL volumetric flask. It was dissolved and diluted up to the mark with Solvent to obtain 100 µg/mL as standard stock solution. Spectrophotometric scanning and determination of λ_{max} of the drug were done. From the standard stock solution, 1-mL was pipetted out and diluted up to 10 mL using methanol and it was scanned between wavelengths 200 to 400 nm. For the Plotting of the calibration curve of Luliconazole from the standard stock solution, a series of dilutions was made by pipetting out 0.2, 0.4, 0.6, 0.8,1.0 and 1.2 mL of standard stock solution and diluting up to 10 mL by methanol to obtain 2, 4, 6, 8,10 and 12 ppm solution, respectively. Absorbance was measured at 296 nm by using UV-vis spectrophotometer. This experiment was performed in triplicate and a calibration curve was plotted to check the linearity.

FTIR Spectroscopy

The IR spectrum of pure drug and excipients along with the mixture of drug and excipients, were recorded by FTIR and the compatibility of drug and excipients was checked by comparing the spectra.

Formulation of Niosomal Suspension

By Thin Film Hydration Method[6]

Niosomes were prepared by a thin film hydration method using a lipid mixture consisting of surfactants and chloroform, at different specified ratios as given in surfactant, chloroform, and drug were accurately weighed and dissolved in 7 mL of chloroform. The lipid mixture was then transferred to a 100 mL round bottom flask, and the solvent was evaporated under reduced pressure at a temperature of 55 to 65°C, using a rotary flash evaporator until a thin lipid film formed. The formed film was hydrated with 10 mL of Phosphate buffer saline pH 7.4. The hydration was continued for 1-hour, while the flask was kept rotating at room temperature in the rotary evaporator. The hydrated niosomes were sonicated for 20 minutes using a bath sonicator to obtain niosomal

Table 1: Formulations of luliconazole niosomal dispersion

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

dispersion containing both free and entrapped drugs of varying sizes. Formulation of Luliconazole niosomal dispersion listed in Table 1.

Characterization of Niosomes

Visual Appearance

A visual inspection was performed to ensure that niosomal dispersion was there. Placing the niosomal dispersion in clear containers also allowed for the inspection of turbidity, flocculation, and sedimentation.

Optical Microscopy[7]

Niosome suspension was diluted and dropped onto a glass slide. A cover slip was placed over the diluted niosome suspension, and an ordinary optical microscope was used to evaluate the average vesicle size and shape using a precalibrated ocular eyepiece micrometer.

Zeta Potential[8]

The niosomal formulation's polydispersity index and zeta potential were measured using a Malvern Zetasizer Nano ZS. The polydispersity index of niosomes was used to evaluate the size distribution of the delivery mechanism.

Vesicle Morphology[9]

The niosomal vesicle morphology was studied using transmission electron microscopy (TEM).

Entrapment Efficiency[10]

The free drug was separated from the entrapped drug in niosomes by ultracentrifugation at 4°C for 30 minutes. The supernatant containing free drug was collected and analyzed by UV spectrophotometer. Percent drug entrapment was calculated by using the following formula.

PDE = Total Amount of Drug – Free Amount of Drug/ Total Amount of Drug ×100.

Formulation of Niosomal Gel

By Dispersion Method[11]

A Niosome formulation was chosen for incorporation into gel bases made with different Carbopol 934 concentrations. Formulation of luliconazole niosomal gel listed in Table 2. Carbopol 934 was measured and sprinkled on the distilled water while continuously stirred. It remained for two hours, being soaked and hydrated. Following the addition of the needed amount of the best niosome formulation, additional chemicals, including propylene glycol and glycerol were added and equally distributed while being continuously stirred. Triethanolamine (TEA) was used to neutralize the gel's pH, and distilled water was used to adjust the final weight. To release trapped air the gel was sonicated for 30 minutes on a bath sonicator and left undisturbed overnight.

Table 2: Formulation of niosomal gel

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

By Cold Method [12]

A niosome formulation was chosen for incorporation into gel bases made with different Poloxamer 407 concentrations. Formulation of luliconazole niosomal gel listed in Table 2 Poloxamer 407 was measured and sprinkled on the distilled water while continuously stirring. It remained for 24 hours in the refrigerator, being soaked. Following the addition of the needed amount of the best niosome formulation with continuous stirring and dispersed uniformly. Triethanolamine (TEA) was used to neutralize the gel's pH, and distilled water was used to adjust the final weight. To release trapped air the gel was sonicated for 30 minutes on a bath sonicator and left undisturbed overnight.

Evaluation of Niosomal Gel

Physical Appearance[13]

The prepared gels were examined for clarity, color, homogeneity, and the presence of foreign particles and fibers.

pH[14]

The gel formulation's pH was determined using a digital pH meter. The electrode is first calibratedwith pH 4.0 and pH 7.0 solution, and then the readings were recorded on a pH meter.

Viscosity[14]

The prepared gel was subjected to viscosity studies using a Brookfield Viscometer with spindle LV- 3(63). The study was carried out at gradual increments of rpm. As carbopol gels exhibit non-Newtonian flow, expression of viscosity with one single value is impossible, as the viscosity decreases with increased rpm.

Spreadability[15]

The spreadability of the formulation was determined using the spreadability apparatus. A total of 1-gm of gel was placed on a glass slide which was fixed on a wooden block placed on the second slide above the first.

The thread was passed over the pulley whose one terminal was attached to the slide while another was tied with weight. The time required to separate the two slides i.e., the time in which the upper slide slips overthe lower slide is noted and taken as a measure of spreadability. The experiments were done in triplicate.The following formula is used to calculate the spreadability:

$$S = m (1/t)$$

Where S is the Spreadability

m is the weight tied to the upper slide (g)l is the length of the glass slide (cm)

t is the time taken to separate the slide from each other (s)

Homogeneity[12]

The prepared niosomal gel formulation was checked for the presence of any floccules or sediment by visual inspection.

Extrudability[11]

Niosomal gel was filled in collapsible aluminum tubes of 10 gm and sealed. A collapsible tube was placed between two slides on which a weight of 500 gm was placed. The amount of gel extruded was noted and weighed.

%Drug Content[9]

The drug content of the prepared gel was carried out by dissolving an accurately weighed quantity of gel equivalent to 10 mg of the drug in a 100 mL volumetric flask and the volume was made up to 100 mL with methanol. The content was filtered through Whatman filter paper 5 mL of the above solution was taken intoa 25 mL volumetric flask and the volume was made up to mark with methanol. The content of luliconazole was determined at 296 nm against blank by using the Shimadzu UV-vis spectrophotometer. The drug content was determined from the calibration curve of luliconazole.

Grittiness

All the formulations were evaluated microscopically for the presence of particles if any no appreciable particulate matter was seen under the light microscope. Hence, the gel preparation fulfills the requirement of freedom from particular matter and grittiness as desired for any topical preparation.

In-vitro Diffusion Study [13]

An in-vitro diffusion study is also termed an in-vitro drug release study. This study is carried out by using a diffusion cell and diffusion membrane. Most popularly Franz diffusion cell is used to carry out the study. In this study, PBS of pH 7.4 is used and the diffusion membrane is soaked overnight in it. The standard procedure for diffusion study is carried out and the absorbance was determined by UV spectrophotometer at 299 nm.

Release Kinetics Study [11,14]

To study the release kinetics of luliconazole from the niosomal gels the data obtained from the *in-vitro* release study were analyzed using various kinetic models to describe the mechanism of drug release from the hydrogels.

Antifungal Activity [16]

The antifungal efficacy studies were carried out to ascertain the biological activity of niosomal formulation, in comparison with plain luliconazole niosomal gel, and marketed luliconazole gel against *Candida albicans* as the test microorganisms. This is determined by an agar diffusion test employing the 'Cup plate' technique. A layer of Sabouraud's dextrose agar media seeded with the test microorganisms was allowed to solidify in the petri dishes. Cups were made on the solidified agar layer with the help of a sterile borer. The niosomal gel solution (1% of the drug) is filled into one cup (i.e., hole) and the marketed gel solution (1% of the drug) is filled into the second cup (i.e., hole). After keeping the petri dishes at room temperature for 1-hour, the plates were incubated at 37°C for 48 hours. The zones of inhibition were measured around each cup.

Stability Studies [12]

The stability studies are under process and are carried out as per ICH guidelines. Optimized niosomal gel formulation was subjected to stability testing as per ICH guidelines. Gel was filled in clean, lacquered, collapsible aluminum tubes and various replicates were kept at 25 ± 2°C & 60 ± 5% RH relative humidity in a humidity chamber. Gel was assessed for change in appearance, pH, and %drug content at an interval of 30, 60, and 90 days.

Result and Discussion

Ultraviolet-Visible (UV-Vis) Spectrophotometry

The greatest peak in the UV-Vis spectrum analysis of luliconazole, which is regarded as the drug's maximum absorbance (max), was observed at 296 nm in methanol and 299 nm in PBS pH 7.4. Figure no. 01 shows UV absorption spectrum of luliconazole in methanol. Fig. 3 shows UV absorption spectrum of luliconazole in PBS pH 7.4.

The concentration from 2 to 10 ppm of luliconazole in methanol was selected for the calibration curve. Fig. 2 shows the calibration curve of luliconazole drug in methanol. The value of R^2 was found to be 0.9972, indicating the relation of drug concentration and absorbance was linear in the selected range.

The value of R^2 was found to be 0.998 indicating the

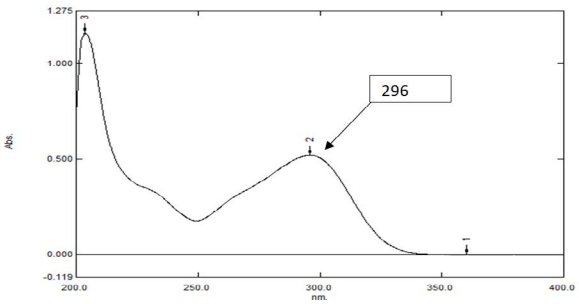

Fig. 1: UV absorption spectrum of Luliconazole in Methanol

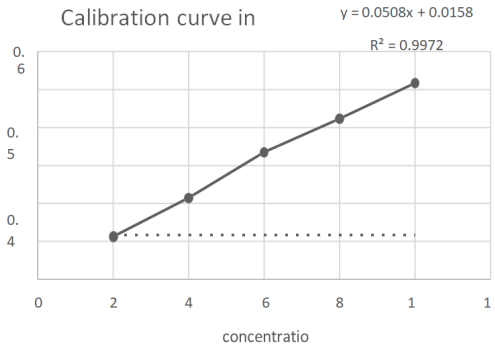

Fig. 2: Calibration Curve of Luliconazole in Methanol

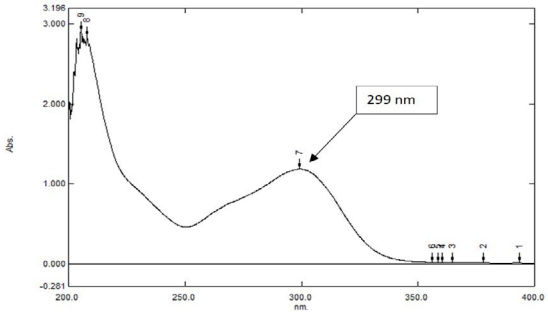

Fig. 3: UV absorption spectrum of Luliconazole in Phosphate buffer Solution pH 7.4

relation of drug concentration and absorbance was linear in the selected range. The absorbance of different concentrations of drug in phosphate buffer solution pH 7.4. Fig. 4 shows the calibration curve and linearity of luliconazole in phosphate buffer pH 7.4.

Drug-excipient Compatibility Study by Fourier Transform Infra-red (FTIR) Spectroscopy

Fig. 5 describes IR spectra of luliconazole drug and figure no.06 shows IR spectra of API and excipients used in luliconazole niosomal formulation. The IR spectrum of pure drug and excipients along with the mixture of drug and excipients were recorded by FTIR and the compatibility of drug and excipients was checked by comparing the spectra. The FTIR study concluded there was no interaction between drug luliconazole and any of the excipients.

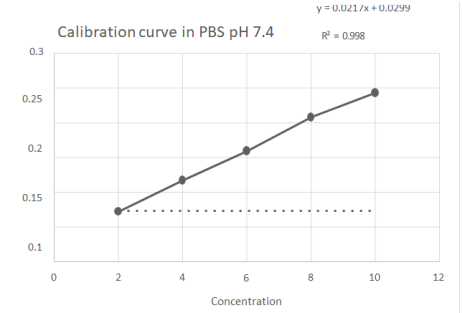

Fig. 4: Calibration curve and linearity of Luliconazole in Phosphate buffer solution pH 7.4

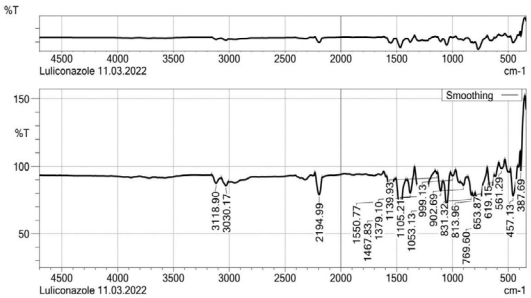

Fig. 5: IR spectra of luliconazole

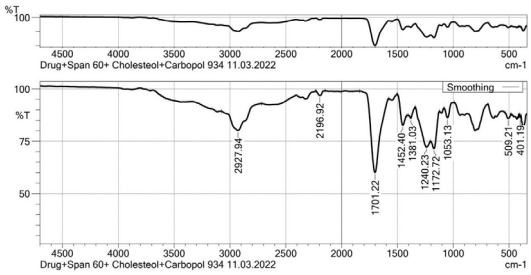

Fig. 6: IR Spectra of API and Excipients used in formulation

Entrapment Efficiency

Percentage drug Entrapment efficiency of luliconazole niosomal dispersion given in Fig. 7.

Zeta Potential Measurement

The zeta potential of the LS60III formulation was determined by using Zeta-sizer. The value of zeta potential was found to be -26.1 mV. This indicates good stability, thereby better shelf-life. The vesicle size, distribution, and zeta potential of the optimized formulation were determined by a third-party lab.

Optical Microscopy

Fig. 8 shows Transmission Electron microscopy (TEM) images of the LS60III Formulation shows the formation of Multilamellar Vesicles.

Viscosity and Spreadability

Table 3 contains luliconazole niosomal gel spreadability and viscosity parameters. LNG2 and LNG4 were found to have appropriate viscosity suitable for topical application. LNG2 was more viscous than other formulated gels and the viscosity of LNG3 was found a very low viscous.

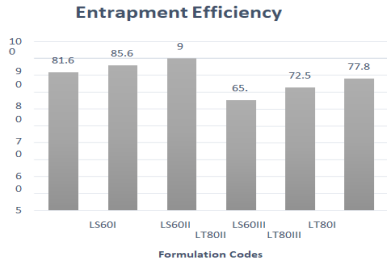

Fig. 7: Entrapment efficiency of luliconazole niosomal dispersion

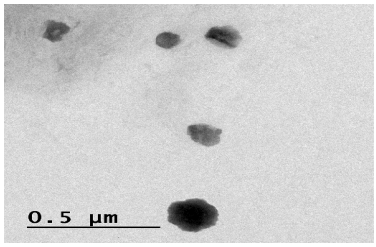

Fig. 8: Transmission electron microscope (TEM) image of LS60II

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

In comparison to LNG3 and LNG4, it was observed that LNG1 and LNG2 had better spreadability. Shorter separation times between two slides indicate more slip and better spreadability. The slides should separate with the least resistance possible; this suggests strong spreadability.

Drug Content Uniformity

Table 4 contains % drug content of luliconazole gel. Drug content uniformity of LNG2 shows better results.

In-vitro Diffusion Study

The amount of drug diffused through the membrane at a particular time interval is given in Table 5. In vitro drug release of niosomal gel in Fig. 9.

Drug Release Kinetic Modeling

To evaluate the drug's release mechanism from the niosomal gel, the *in-vitro* release data was integrated into several release kinetic models. Table 6 describes drug release in four different concentrations of luliconazole niosomal gel.

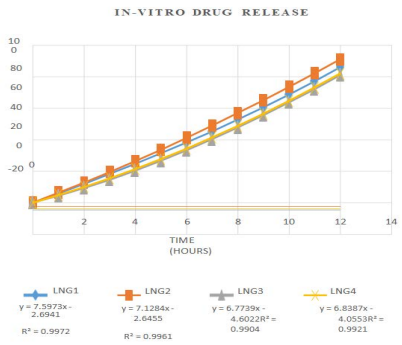

Fig. 9: *In-vitro* diffusion study of the niosomal gel formulation

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

The stability study of the niosomal gels was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. Samples were withdrawn periodically and tested for various evaluation parameters. The results of the stability study are tabulated in Table 7. There was not much more variation in the properties of the niosomal gel of LNG2 under stability study as the formulation retained all the properties when stored at specified.

Table 7: Stability study

Formulation	LNG2			
Storage condition	25 ± 2°C & 60 ± 5% RH			
Time interval (days)	0	30	60	90
Homogeneity	+ + +	+ + +	+ + +	+ + +
Grittiness	+ +	+ +	+ +	+ +
pH	4.53 ± 0.05	4.53 ± 0.05	4.52 ± 0.05	4.51 ± 0.05
Viscosity (cP)	49,260	49,260	49,260	49,260
Spreadability (g.cm/sec)	36.05	35.54	35.88	35.21
Extrudability (%)	97	9	97	97
Drug content uniformity (%)	89.75	88.90	87.05	85.12

+ + + Excellent, + + Good, + Satisfactory, - Poor, - - Fail

Conclusion

Recently, a novel vesicular drug delivery system has been used for the therapeutic effectiveness of transdermal drug delivery systems. According to the experiments that have been performed during the research, it was concluded that luliconazole niosomal gel was efficaciously formulated by utilizing luliconazole niosomes prepared by the thin film hydration method by using Span 60 and cholesterol in the ratio 2:1 and loaded in various proportions of carbopol 934. The average sizes of niosomes were found to be 0.5 µm and the zeta potential of niosomes was found to be -26.1mV which indicates that niosomes formulation is stable. The niosomes gel was evaluated for various parameters of all the formulations. The 1% Carbopol 934 gel shows the best and most promising results. The niosomal gel formulation could be a useful dosage form to increase efficacy by the transdermal route. Therefore, niosomes gel may be considered the best vesicular carrier for the effective delivery of luliconazole through the skin. The methodology applied for the preparation is simple and feasible for the lab and industrial scale.

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