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Research Article

Formulation and Evaluation of Niosomal Gel of Antifungal Luliconazole

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Abstract

Niosomes have potential applications in topical drug delivery system. Niosomes play an increasingly important role in drug delivery as they can reduce toxicity and modify pharmacokinetic and bio-availability. Topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. It can act as drug containing reservoirs and the modification of the vesicular compositions or surface properties can adjust the drug release rate and the affinity for the target site. Luliconazole is a potential prescription candidate drug for the treatment of topical fungal infections. However, it has water solubility and skin permeability limitations. To overcome these limitations, a niosomal gel of luliconazole was formulated using Span 60, cholesterol and chloroform to improve its bioavailability and to reduce its toxicity. Niosomes were analyzed by transmission electron microscopy (TEM) and Fourier transform infrared spectroscopy (FTIR) for morphological and spectral studies respectively. The formulations had ideal nanometric vesicle sizes, encapsulation efficiency (88.891% ± 0.0364%), Zeta potential (-40.1 mV), and storage instability was not observed. The sustained-release profile of niosomal gel was observed for up to 24 h. The highest R^2 value was 0.913; the Higuchi model was considered the best fit model for the niosomal formulations. Based on the results, it can be concluded that niosomal luliconazole may enhance the activity of luliconazole against *Candida albicans.*

Keywords: Luliconazole, Niosomes, Transdermal drug delivery, Antifungal drugs, Candida albicans

INTRODUCTION

Topical therapy in the form of vesicles delivery carrier is an attractive choice for treatment of superficial and cutaneous infections due to their advantages as better skin permeation and deposition, targeting the site of infection and alleviating the adverse effects by elimination the systemic absorption of the drug. Rationally developed drug delivery systems have the potential to deliver drugs at a predetermined rate and time, and this helps in improving drug efficacy by overcoming the existing limitations. Indeed, nonionic surfactant vesicles (niosomes) have demonstrated the ability to improve permeability and bioavailability of poorly water-soluble drugs and are promising for improvement of antifungal drug activity by enhancing the distribution of topical drugs[1,2]. Niosomes have generated considerable interest due to their chemical tolerance, high reliability, material's uniformity, low cost, easy storage of nonionic surfactants, and the availability of surfactants for their development[3-5]. Niosomes have a prolonged circulation period in the biological system and facilitate the absorption of entrapped drugs at the target area, while medication toxicity is reduced via a reduction in non-specific tissue uptake[6, 7]. Fungal skin infections are one of the most severe dermatological issues in the world. It has been reported that more than 150 million people develop severe fungal skin infections annually[8]. Fungal infections have a negative impact on the lives of patients in both developing and developed countries. Fungal diseases are present as a superficial infection on topical skin and mucous membrane infections to more serious, chronic infections in the internal organs of the body[9]. Superficial fungal diseases are common, with an approximate 20%-25% worldwide incidence, and correlate with regular habits, inadequate sanitation, and reduced health care efficiency. Superficial fungal diseases constitute the major reason for clinical consultations between patients and dermatologists[10-12]. Strategies for managing fungal infections include using systemic or topical antifungal drugs. The azole family, which includes imidazoles and triazoles, comprises a broad range of antifungal drugs which are an essential therapy for many fungal infections[13]. Additionally, most of the newly approved antifungal agents have primary shortcomings of unexpected toxicity associated with their continuous use, drug interactions, and physicochemical, biopharmaceutical, pharmacokinetics, and pharmacodynamic properties[14]. The hydrophobic nature of some antifungal drugs results in low oral bioavailability, limited water solubility, and narrow formulation approaches[14]. Luliconazole is one of the most commonly used azole antifungal drugs with a broad-spectrum activity. Luliconazole has a unique chemical structure and selectively inhibits fungal cytochrome P450 (CYP450) 14-a-demethylase enzyme. It disrupts the conversion of lanosterol to ergosterol, thus hinders the cell wall formation of fungi. It has a markedly poor aqueous solubility, which restricts its dermal accessibility[15]. Another significant barrier restricting the use of antifungal agents is toxicity and adverse drug reactions associated with systemic dosage forms[16-18]. Despite the existence of several conventional treatment formulations of antifungal pharmaceutical products, including tablets, creams, iv infusions and so on, they are limited by the above-mentioned constraints. Therefore, advanced novel drug

delivery technologies are urgently needed to address these concerns to improve treatment outcomes of anti-fungal therapy. Niosomes are known to improve the solubility, bioavailability, and stability of some poorly soluble drugs along with an ability to provide sustained release for prolonged drug action[19]. Surfactants contribute to the overall penetration enhancement of compounds primarily by adsorption at interfaces, by interacting with biological membranes and by alteration of the barrier function of the Subcutaneous, as a result of reversible lipid modification. Niosomal vesicles serve as a soluble matrix and often function as a local repository for prolonged release of drugs, permeation enhancers of dermally active compounds, or a rate-limiting membrane barrier to modulate systemic drug absorption via dermal drug delivery. This study therefore aimed to describe luliconazole's niosomal gel formulations with enhanced properties and increased retention time. The developed formulations of niosomal gel were optimized and evaluated for the entrapment efficiency, vesicle size, vesicle shape, in vitro drug release.

MATERIALS AND METHODS

Materials

Luliconazole was gifted by Prayosha Healthcare Pvt. Ltd., Ankleshwar, India. Span 40, Span 60, and Tween 60 were purchased from SD Fine Chemicals Ltd., Mumbai, India. Cholesterol was purchased from Across Organics, Mumbai, India. Carbopol934 was purchased from Himedia, Mumbai. Disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate were purchased from Fisher Scientific, Mumbai. Chloroform and methanol were purchased from Fisher Scientific, India. Deionization (DI) water from the Milli-Q purification system (Millipore Corp., USA) was used throughout the studies. All other chemicals and solvents were used without further purification and were of analytical grades.

Method

Preformulation study[20-22]

Solubility

Solubility study was conducted to determine the effect of different buffers on the drug. An excess amount of drug was dispersed in 5 ml of distilled water, methanol, acetone, phosphate buffer solution (pH 6.8 and 7.4), 0.1N HCl, in glass stoppered tubes respectively, all the glass tubes were closed with stopper and covered with cellophane membrane to avoid solvent loss. Tubes were kept in water bath shaker at 37°C for 24 hrs. As the samples attain equilibrium, they were subjected for centrifugation at 3000 RPM for about 5 minutes. After completion of centrifugation the samples get separated, then supernatant liquid is filtered through membrane filter and then analyzed by UV spectrophotometer at 293nm respectively.

Melting point determination

Melting point of luliconazole was determined by open capillary method.

Determination of partition coefficient

25 mg of luliconazole with aqueous phase and n-octanol was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated.

Determination of λmax

A solution of luliconazole containing the concentration 100µg/ml was prepared in methanol and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200- 400 nm.

Preparation of standard calibration curve of luliconazole

100mg of drug was accurately weighed and dissolved in 100ml methanol in 100 ml volumetric flask, to make (1000µg/ml) standard stock solution (1). Then 10 ml stock solution (1) was taken in another 100 ml volumetric flask to make (100µg/ml) standard stock solution (2), then again 2 to 20ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 20-200µg/ml with methanol. The absorbance of standard solution was determined using UV/VIS spectrophotometer (Shimadzu UV-1800) at 293nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

FTIR spectroscopy

For the identification of API, Fourier transform infrared spectroscopy was performed for different compounds. Fourier transform infrared spectroscopy is used to investigate any possible chemical interaction between drug and polymer. In FTIR spectroscopy, drug and polymer mixture in ratio (1:1) (each 10 mg) was mixed with 400 mg of potassium bromide (KBr) and compressed under very high hydraulic pressure in order to prepare the KBr pellets. Different peaks in FTIR spectrum of drug and polymer mixture were compared with FTIR spectra of pure drug and polymer in order to identify any shift caused due to chemical interaction between drug and polymer.

Preparation of niosomes

The adapted system of film hydration technique used in this research was based on studies performed with some slight modifications[1]. Accurately weighed amounts of nonionic surfactant (Span 60), cholesterol, and luliconazole at specified concentrations (Table 1) were dissolved in chloroform (5 ml) and poured into a round bottom flask (RBF). The solvent was evaporated under reduced pressure at a temperature of 55-65°C using a rotary evaporator till a thin lipid film formation was observed. The lipid film was kept overnight in a vacuum desiccator for the removal of traces of chloroform after which the formed film of lipid was hydrated using 5ml of phosphate buffer solution (PBS) (pH 7.4). This hydration procedure was performed for 1 h; meanwhile, the flask rotation was continued in the rotary evaporator at 55-65°C. The sonication of hydrated niosomes in a bath sonicator was conducted for 20 min. After that, niosomal dispersions were obtained containing both entrapped and free drug particles of varying sizes. The niosomes were left overnight at 4°C. To maintain sterility, the above-mentioned steps were performed under aseptic conditions.

Preparation of niosomal gel

Developed formulation was incorporated in to 1%w/w, 2%w/w carbopol 934 Table 2. Weigh quantity of carbopol 934 was dispersed in sufficient amount of niosomes formulation kept in dark overnight. This swelled carbopol 934 was then neutralized using sodium hydroxide i.e. adjusting pH 6.8 followed by agitation[23].

Table 1: **Different specified concentration of (Drug: Surfactant: Cholesterol)**

Formulation code	Ratio surfactant: cholesterol (Molar)	Drug (mg)
N1	1:0.1	10
N2	1:0.2	10
N3	1:0.3	10
N4	1:0.4	10
N5	1:0.5	10
N6	1:0.6	10
N7	1:0.7	10
N8	1:0.8	10
N9	1:1	10

Table 2: Different concentrations of carbopol 934 in preparation of gel

Sr. No	Concentration of carbopol 934
1	1%w/w
2	1.5%w/w
3	2%w/w

In-vitro evaluation of niosomes

Morphological characterization

Confirmation and visualization of the luliconazole niosome formulation was performed using optical microscopy at a 100× resolution. On a slide, a drop of niosomal suspension was carefully placed and covered with a cover slip. Fixation of the drop was performed after drying it at room temperature. The thin and dry niosomal film was observed under the microscope to ascertain the formation of vesicles. A digital camera was used to acquire microscopy images of the niosomes[24]. The morphology of the prepared luliconazole niosomes formulation was examined using a transmission electron microscope (TEM) (Hitachi H7500, Japan) at 100 kV to determine the specific sizes of particles. On a 300-mesh grid of copper coated with carbon, a drop of diluted niosome formulation was placed. For the niosomes to cohere with carbon substrate and for staining with 1% phosphotungstic acid, it was left to dry for 1 min. After complete drying, visualization and examination of the samples were conducted. Soft imaging software was used to visualize and document the electron diffraction pattern and TEM images[25].

Particle size and zeta potential determination

The Malvern Nano Zetasizer (Malvern Instruments, Malvern, U.K.) was used to measure the size distribution, average particle size, and Zeta potential of the prepared formulations[26]. An equivalent volume of PBS (pH 7.4) was used to dilute 100µl of the formulation for particle size and noisome diameter measurements. The measurement was conducted in triplicate. The Zeta potential was determined using electrophoretic light scattering and Laser Doppler velocimetry. The temperature of the system was maintained at 25^0C. Other parameters such as charge on the vesicles, and their mean Zeta potential and standard deviation values were directly measured. Zeta potential was investigated to understand the stability of vesicles and colloidal properties.

Entrapment efficiency

Dialysis was used to determine the entrapment efficiency of the final prepared niosomal formulation. To perform this process, a measured amount of niosomal suspension was collected in a dialysis tube, and the dialysis membrane was securely attached on one side of the dialysis tube. Further, the dialysis tube was suspended in 100ml PBS (pH 7.4) buffer along with 10% v/v methanol. The niosomal formulation was dialyzed for 24 h. After 24 h, the dialyzed niosomal suspension contained only the entrapped drug. From this niosomal suspension, 0.5 ml was collected, to which 5ml of chloroform was added. The volume of the solution was increased with the PBS (pH 7.4); the absorbance of the resulting solution was then measured at 293nm[27].

The entrapment efficiency is expressed as:

%EE= Total drug added-Supernatant free drug/ Total drug added×100

pH measurement

2.5g of gel was accurately weighed and dispersed in the 25ml of distilled water. The pH of the dispersion was measured by using a digital pH meter[28].

In vitro drug release studies of gels

In vitro permeation study was conducted to compare the permeation of the marketed formulation of luliconazole cream (Lulifin; 1% w/w in 20 g), niosomal gels, and controlled formulation. This was performed with Franz diffusion cell of capacity 60ml with Strat-MTM membranes (Millipore Temecula, MA, USA) using a dialysis membrane (molecular weight: 12 kDa; Sigma Aldrich) as a semi-permeable membrane. The gel was placed between the lower (receptor) and the donor compartments. PBS (pH 7.4) containing 10% v/v methanol was used to fill the diffusion Franz cell and maintained at a temperature of 37^0C±1^0C. The samples were continuously stirred at 50 rpm using a magnetic stirrer and withdrawn at a fixed time interval, and the drug percentage released was analyzed with UV Spectrophotometery at 293 nm. Here, the same volume of fresh buffer was used to replace the volume of aliquot[24]. The study was conducted in triplicate.

In vitro drug release kinetics

Several mathematical models were used to analyze the drug release kinetics of the final optimized formulations. These included Korsmeyer-Peppas, Higuchi, zero-order and first-order models. Furthermore, to obtain the best fit model, the correlation coefficient (R2) and root mean square error (RMSE) were calculated.

RESULTS AND DISCUSSIONS

The melting point of luliconazole (pure drug) was found to be 152ºC-156ºC. Luliconazole was freely soluble in N, N-dimethylformamide, soluble in acetonitrile and ethanol, sparingly soluble in ethanol. The partition coefficient of luliconazole was observed as 3.770±0.008 and it shows that the drug is lipophilic in nature. FTIR analysis of luliconazole and excipients mixture was conducted (Figure 1a and b). The analysis shows that peaks related to drug and excipients were observed in the FTIR spectrum indicating absence of interaction. The calibration curve of methoxsalen was found to be linear in the concentration range of 20-200 µg/ml at 293nm Figure 2. The results for the visualization of luliconazole gel formulation under natural light in transparent glass vials are shown in Figure 3. It was observed that the drug-loaded niosome gel was milky white in color. The

observation of the TEM image for morphology characterization of niosome formulations of luliconazole showed a slightly oblong shape with a smooth surface (Figure 4a and b). Additionally, the sizes of niosomes were similar to those in the DLS measurement. pH of niosomal gel was found to be 6.81±0.005 Table 3. The mean diameter of the vesicles was 505 nm. The size distribution estimation showed that the average dimeter of the niosomal gel was 505nm (Figure 5a). The polydispersity of some samples was observed after the DLLs analyses (polydispersity index ¼ 0.191). It was observed that the vesicular size reproducibility was good. The niosomal formulation had a Zeta potential (net charge) of -40.1mV (Figure 5b). From the above-mentioned outcome, it can be inferred that the niosomal formulations have an excellent stability. The zeta potential shows the extent of repulsion between similarly charged adjacent particles present in the dispersion, thus implying that drug loading will have an impact on the zeta potential. The results for the dialysis method to determine the efficiency of entrapment of different niosomal formulations at different cholesterol and surfactant ratios are shown in Table 4. The % entrapment efficiency was in the range of 53.637±0.1819% to (N6) 88.891% ± 0.0364% (N2). From Table 4, it is evident that the entrapment efficiency of the niosomal formulation increased when the ratio of cholesterol to drug was increased from 1% to 1.5%, the entrapment efficiency declined. Second, the elevated cholesterol to drug ratio might have caused a competition between cholesterol and the drug for space in the bilayer, thus displacing the drug as an amphiphilic compound. The fluctuating amount of surfactant impacted the entrapment efficiency of niosomes. Luliconazole content uniformity was determined against the blank sample using the Shimadzu UV/visible spectrophotometer at 293 nm. The calibration curve of luliconazole helped to determine the drug content. The obtained results were 92.707% ±0.002% for drug content in niosomal gel, and 78.725% ± 0.003% for the preparations already available in the market Table 5. The dialysis study on the niosomal formulation and pure drug demonstrated that niosomal formulation exhibited sustained-release in a controlled manner as compared to immediate release for pure drug suspense (Figure 6). In vitro drug release from different drug formulations in PBS (pH 7.4) are shown in Figure 6 a. Maximum release of niosomal gel formulation was found to be 38.78%. The observations from the data depicted that in vitro drug release of niosomal formulation occurred for 24 h. It was noticed that the N2 formulation exhibited maximal drug release, i.e. 70.828% after 24 h at a surfactant to cholesterol ratio of 1:0.2. The release profile of the drug was affected by the amount of surfactant in niosomal formulation. With the increase in the surfactant ratio from 1:0.1 to 1:1 (cholesterol: surfactant), a reduction in drug release from the niosomal vesicles was observed; the reason for this may be attributed to the fact that the increased surfactant acted as a depot and further led to a reduction in the leakage of drug from niosomes to dissolution media. The sustained-release pattern was observed for niosomal gel (70.828±0.600) up to 24 hr. It was observed in the in vitro drug release kinetics that the luliconazole samples exhibited similar kinetic behavior at pH 7.4. The highest R2 value was 0.913, while the lowest R2 value was 0.6570. Thus, the Higuchi model was considered the best fit model for the niosomal formulations of luliconazole release at pH 7.4 Table 6.

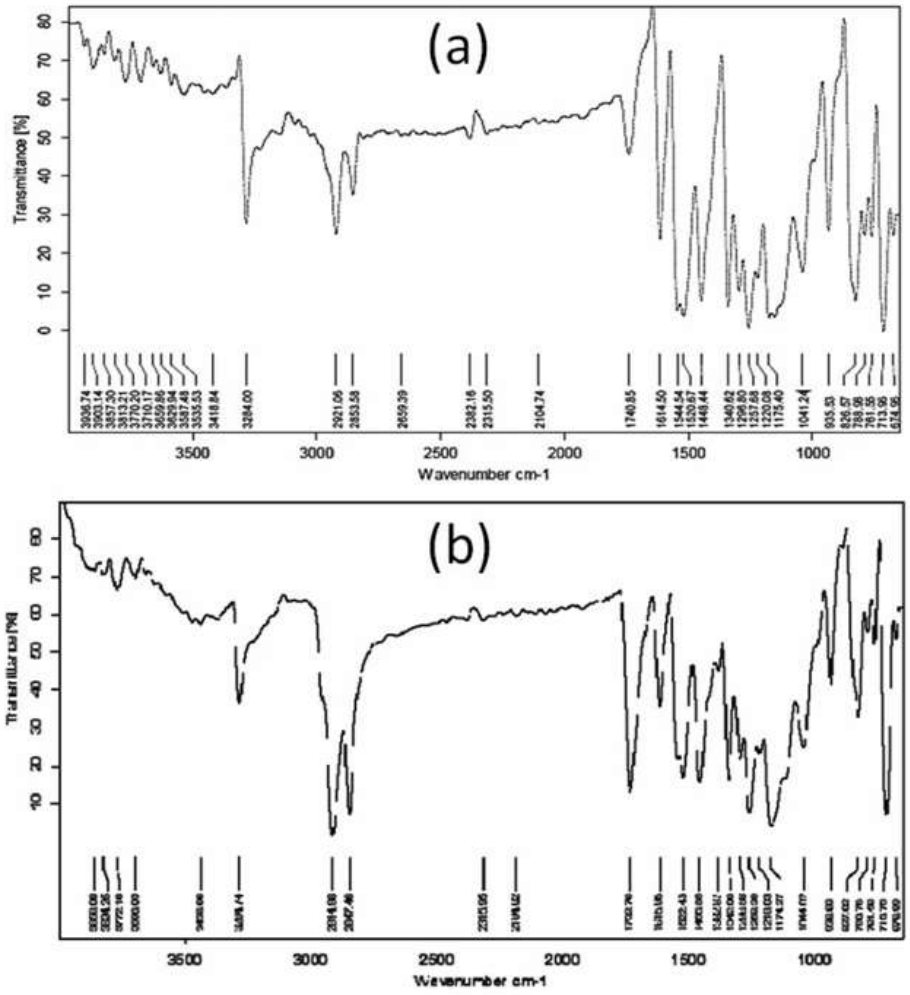


Figure 1: (a) FTIR spectrum of Luliconazole and; (b) FTIR spectrum of the physical mixture

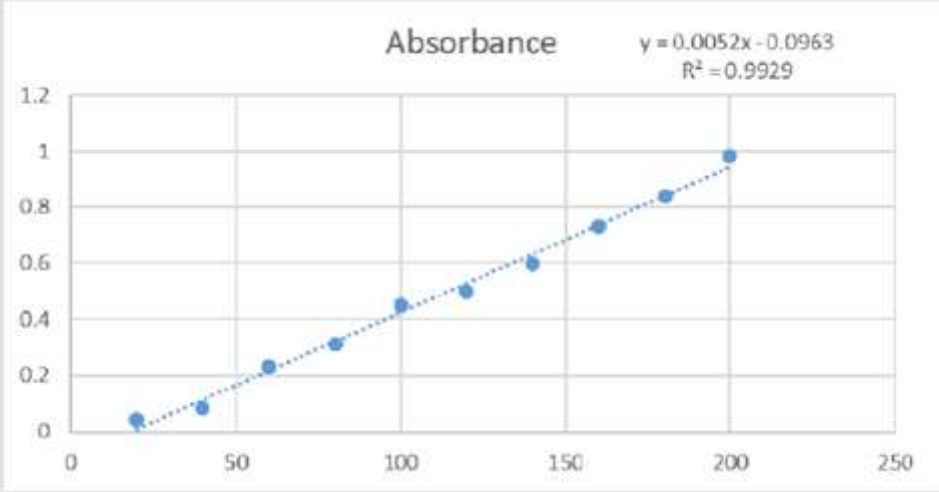
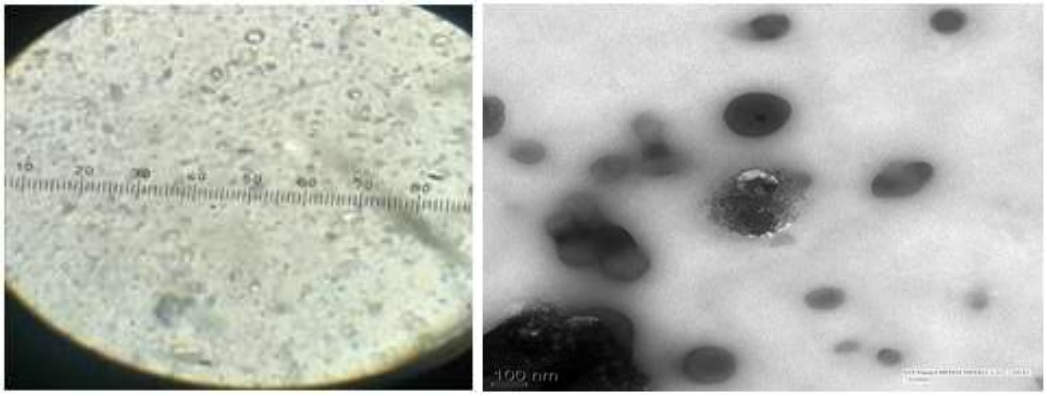


Figure 2: The calibration curve of luliconazole at 293nm

Figure 3: Visualization of luliconazole gel formulation under natural light in transparent glass vials

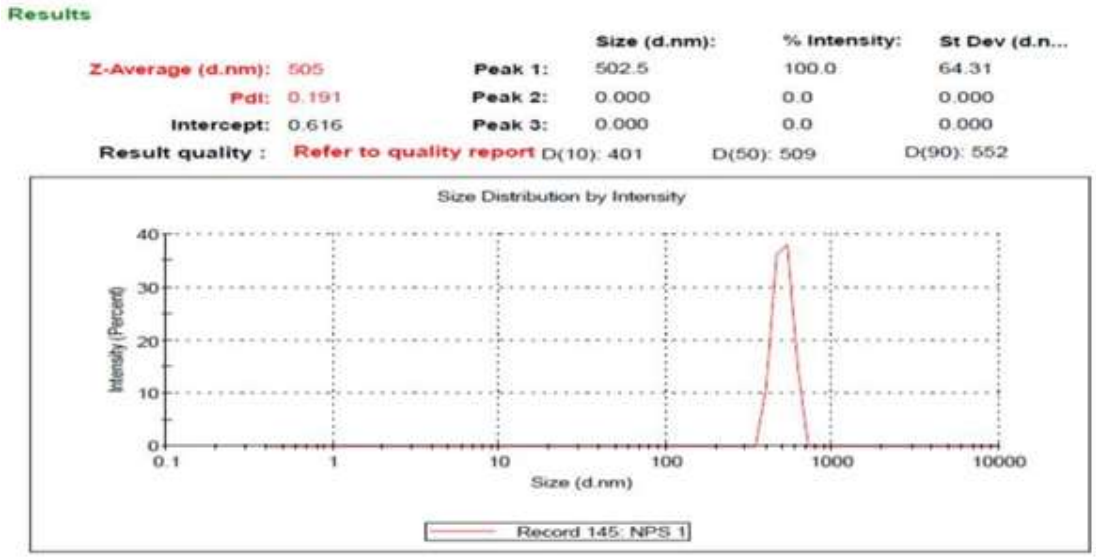


(a) **(b)**

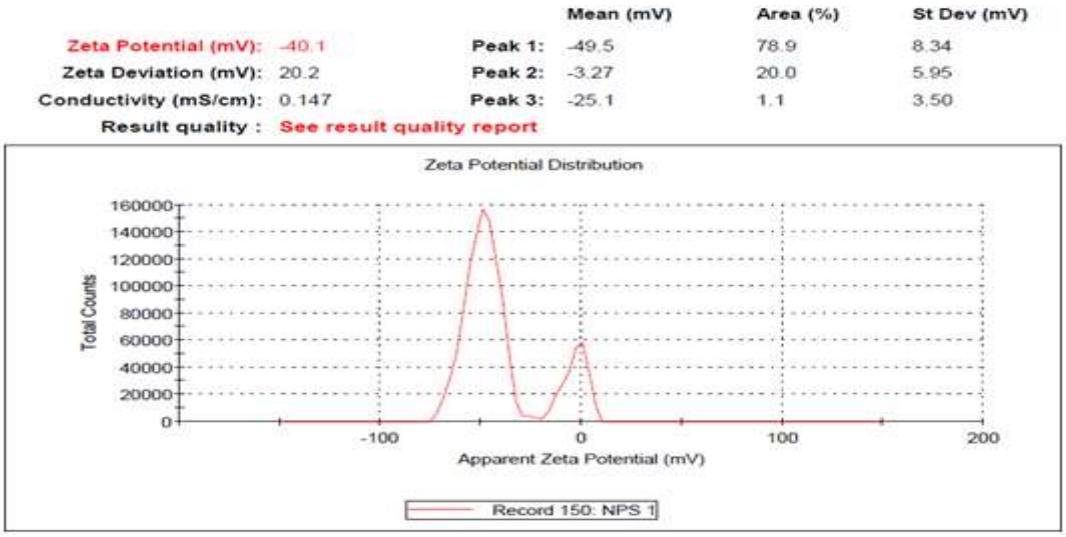
Figure 4: (a) Morphology of luliconazole gel niosomes determined by optical microscopy and; (b) Morphology of luliconazole gel niosomes determined by high-resolution transmission electron microscopy (HRTEM)

Table 3: pH study of niosomal gel

S. No.	Formulation	Reading 1	Reading 2	Reading 3	Mean±S.D
1	Niosomal Gel	6.81	6.82	6.82	6.81±0.005



(a)



(b)

Figure 5: (a) Particle size diameter; (b) Zeta potential for luliconazole gel formation

Table 4: Entrapment efficiency of formulation

Formulation code	Entrapment efficiency
N1	77.873±0.0456
N2	88.891±0.0364
N3	86.182±0.2778
N4	85.928±0.0735
N5	82.928±0.0364
N6	53.637±0.1819
N7	55.273±0.2778
N8	59.273±0.3637
N9	60.124±0.1691

Table 5: Percent drug content of niosomal gel formulation and marketed formulation

S. No.	Formulation	%Drug content of niosomal gel (Mean ± S.D)	%Drug content of marketed preparation (Mean ± S.D)
1		92.707±0.002	78.725±0.003

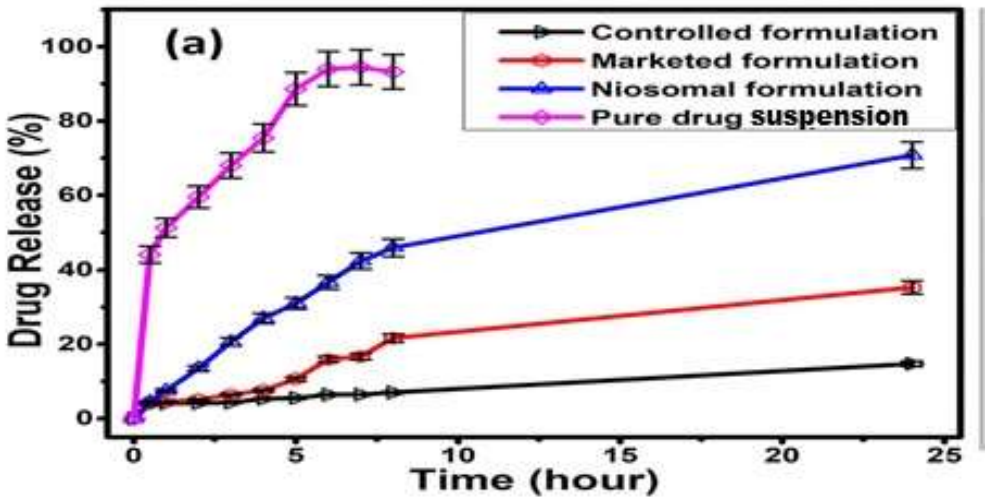


Figure 6: Comparative in vitro drug release study of the niosomal formulation, pure drug suspension, marketed formulation and controlled formulation in Phosphate buffer saline pH 7.4

Table 6: Release kinetics data from different models

Model	R^2	K0
Zero-order	0.677	21.26
First-order	0.844	1.901
Higuchi	0.913	1.853
Korsmeyer-Peppas	0.6570	0.6578

CONCLUSION

Luliconazole is a topical antifungal drug with lower bioavailability owing to its poor aqueous solubility. Dermal bioavailability of luliconazole can be improved by enhancing its aqueous solubility. In this study, luliconazole was formulated as niosomal gel to improve drug release and encapsulation. The results demonstrated that the niosomal topical gel formulations of luliconazole prolonged permeation of drug through the skin. The results of the current study reveal that niosomal gel formulation may be a better choice for the delivery of a wide variety of formulations for transdermal administration and other topical agents compared to the already existing similar commercial dosage forms.

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