



Research Article

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Development and Characterization of Niosomal Gel for Topical Delivery of Luliconazole

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ABSTRACT

Luliconazole is a novel imidazole antibacterial candidate for treating fungal infections on the skin. Its current treatment is limited by extremely poor and sluggish skin absorption, necessitating long-term, repetitive dosing to cure the condition completely. Niosomes are becoming essential in medication delivery due to their potential to minimize toxicity and alter pharmacokinetics and bioavailability. Luliconazole niosomes were created utilizing a thin-film hydration process with varied ratios of non-ionic surfactants Span 40 and cholesterol to increase poor skin penetration and decrease adverse effects of topical traditional medication administration (CHO). The regular particle size of the Niosomal formulation was determined to be between 3 and 6.5 micrometers. The entrapment efficiency of the Niosomal formulation FN3 (1: 1) of cholesterol and Span 40 was excellent (88.56 percent). The Niosomal formulation was spherical using transmission electron microscopy (TEM). At (1: 1) cholesterol: Span 40 ratio, Niosomal formulation (FN3) showed a high proportion of drug release after 24 hours (79.87 percent). Furthermore, a chosen Niosomal formulation was employed to create a topical gel assessed in pH, viscosity, spreadability, and ex vivo research. In an ex vivo research, Niosomal gel outperformed regular topical gel in terms of skin permeability. These results showed that Niosomal gel has a high potential for use as a new, nanosized drug delivery medium for transdermal Luliconazole delivery.

Key words: *Luliconazole, Niosomes, Transdermal, Permeation, Niosomal gel*

INTRODUCTION

Fungal pathogens are one of the most common dermatological illnesses worldwide, with over 150 million people suffering from severe fungal infections that significantly affect their lives or are deadly, with a high frequency in developing and underdeveloped countries [1]. Even though fungal pathogens do not cause death, they are the leading source of morbidity and healthcare costs. Opportunistic fungal infections are common, 20–25 percent global frequency, and are linked to everyday activities, poor cleanliness, and inadequate care quality [2]. Despite the availability of an antifungal medicines variety, the incidence rate has not decreased. Antifungal medicines of the azole family, such as imidazole and triazoles, have a wide range and are effective in many fungal infections. Clinical investigations have shown that clinical manifestations commonly resolve in 2-4 weeks, although a complete clinical cure might take anywhere from 12-36 weeks based on the kind and location of infection [3]. Furthermore, present imidazole antifungal drugs have certain drawbacks, such as resistance. Numerous agents need prolonged therapy courses of up to quite a few weeks, leading to patient noncompliance with dose schedules and, ultimately, disease recurrence.

Luliconazole, an optically active R-enantiomer of Lanoconazole, was discovered as a novel imidazole molecule with greater patient compliance, higher effectiveness, and better tolerance due to continuous clinical research for

improved topical therapeutics for fungal infection [4]. A new imidazole antifungal is Luliconazole (–)-E-[(4R)-4-(2, 4-dichlorophenyl)-1,3-dithiolan-2-ylidene] (1H-imidazole- 1-yl) acetonitrile. Its R-enantiomer side chain as well as one chiral center distinguishes Luliconazole. Introducing an imidazole moiety to the compound's ketene dithioacetate structure improves its ability to attack filamentous fungi like dermatophytes while maintaining its wide antifungal activity. Luliconazole has been clinically evaluated for tinea pedis therapy, cruris, as well as corporis [5]. It has been demonstrated to have antifungal action contrary to dermatophytes and *Candida* in vitro. Luliconazole was first introduced in Japan in 2005 as a topical antifungal agent. It is now accessible as 1 percent creams and solutions for managing dermatophytosis, candidiasis, and Pityriasis Versicolor [6-8].

The application of a medicine to the skin for a localized impact is known as topical drug delivery. The human body's epidermis is among the most widely distributed and publicly accessible structures [9]. Dermal drug delivery has several benefits, including lengthier lengthy treatment, dosages versatility, lowered adverse reactions, unified plasma levels, patient volume compliance, etc., but it also has roughly drawbacks, including the potential for local irritation, erythema, itching, as well as low drug permeability inside the stratum corneum [10].

Dermal delivery using new drug delivery carriers has a lot of promise. Lipidic, along with nonlipidic vesicular systems such as liposome transfer, some ethosome, and Niosome, is employed to alleviate the difficulty related to the traditional topical formulation. Niosomes have numerous concentric bilayer membranes enclosing the aqueous phase in the center, mostly composed of non-ionic surfactants and cholesterol. Niosomes have been shown to increase the solubility, bioavailability, and durability of several poorly soluble medicines, as well as their potential to provide sustained pharmacological activity. Surfactants improve total chemical penetration largely by absorption at interfaces, interactions with biological membranes, and changes in the SC's barrier function as a consequence of reversible lipid alteration [11].

This aims research is to create a Luliconazole transdermal Niosomal gel with improved penetration and anti-inflammatory efficacy, as well as to increase patient compliance by giving sustained-release medicine. In vitro assessment, including synthesis and characterization of Luliconazole niosomes, in vitro release studies, and in vivo evaluation of the optimized Luliconazole Niosomal gel, are all part of the present research.

MATERIALS AND METHODS

Material

Glenmark Pharmaceuticals, based in Mumbai, donated Luliconazole. SD Fine Chemicals Ltd., Mumbai, was the source for Span 40. Sigma-Aldrich in Mumbai provided the cholesterol. Merck, Mumbai, provided Carbopol, Methyl Paraben, and Propyl Paraben. SD Fine Chemicals Ltd., Mumbai, provided the chloroform, methanol, glycerol, and triethanolamine. The rest of the material was of analytical quality.

Formulation of niosomes

The thin-film hydration process using several Niosomal formulations of Luliconazole was created thru varying the surfactant amounts (span 40) as well as surfactant cholesterol. Surfactant, cholesterol, and medication were dissolved in an 80:20 v/v combination of chloroform and methanol. The lipid mixture was then moved to a 250 mL round bottom flask, as well as the solvent was removed with a rotary flash evaporator underneath decreased pressure at 55-65°C until a thin lipid layer formed. 20 mL Phosphate buffer saline pH 7.4 was used to hydrate the produced film. The hydration was maintained for 1 hour while the flask in the rotary vacuum evaporator was continuously spinning at 55-65°C. The formed Niosomal dispersion was first sonicated in an ice bath using a probe sonicator (four cycles of 60 seconds each) to convert multilamellar vesicles into the desired size unilamellar vesicles and then 4,000 rpm centrifugation as well as 15 minutes in 4°C to cause the untrapped drug to settle as a pellet at the bottom of the centrifuge tube. The Niosomal dispersion (supernatant) was decanted and analyzed for vesicle size and percentage of drug entrapment (PDE), while the drug pellet was utilized to determine mass balance by measuring untrapped drug. The formulation process variables were tuned to obtain maximal drug entrapment while maintaining an acceptable size range [12-15].

Formulation of niosomes entrapped Luliconazole gel

The gel base was made by dissolving 0.8 percent w/w Carbopol 934 in filtered water and allowing it to swell for one hour. Then, with continuous homogenization, glycerin was applied to the dispersion. Triethanolamine was used to alter the pH. The determined volume of Luliconazole Niosomal preparation F4 was spun for 90 minutes at 4°C and 12,000 rpm in a cooling centrifuge as per mentioned in **Table 1**. The semisolid mass of niosomes using

an electric homogenizer was removed from the supernatant and combined with the 0.8 percent Carbopol gel basis [16, 17].

Evaluation of Luliconazole niosomes

Microscopy optical microscopy

An optical microscope was used to examine the manufactured niosomes. The Niosomal solution was put on a glass slide, and the development of niosomes was seen. For the first imaging of niosomes, photomicrographs acquired with an Olympus BX 40 microscopy (at 40) were employed [18-20].

Scanning electron microscopy

The vesicles' diameters were assessed using scanning electron microscopy (SEM) (HITACHI S-150). A tiny quantity of niosomes suspension was obtained on the specimen stub in a cover slip. Using a Hitachi vacuum evaporator, model HITACHI S 5 GB, it was covered with carbon and subsequently with gold vapor. The materials were analyzed and photographed using a scanning electron microscope operating at 15 kilovolts [21].

Zeta potential analysis

The colloidal characteristic of the Niosome was studied using zeta potential analysis to determine its stability. Aggregation is as described to the particle surface charge being shielded by ions in solution, lowering electrostatic repulsion. Analysis of particle electrophoretic mobility may be used to quantify vesicle surface charge, which is quantified as the Zeta potential. Malvern Zeta Analyzer was used in this work [22].

Entrapment efficiency

The free untrapped drug was extracted from the Luliconazole niosomes by cooling centrifugation at 5000 rpm for 30 minutes at 4°C with the cooling spinner (Union 32R, Korea). After that, the Niosomal pellets are rinsed in 10 mL PBS and centrifuged again. A 0.22 µm Millipore filter was used to filter the supernatant (Millipore, USA). A UV spectrophotometer was used to assess the quantity of free medicine in the supernatant by measuring absorbance at 295 nm. This procedure was performed three times to guarantee that all free drugs were eliminated. After centrifugation, the niosomes were lysed with n-propanol, and the absorbance at 295 nm was quantified to validate the percent drug entrapment (**Table 2**).

The percentage of drug entrapment

$$\text{Drug entrapment percentage} = \frac{\text{Total drug-drug in supernatant}}{\text{Total drug}} \times 100 \quad [23] \quad (1)$$

Drug content analysis

Through a breakdown of the niosomes with 50 percent n-propanol, the quantity of medication in the solution is determined. 1 mL of the Niosomal mixture was pipette out, 50 percent n-propanol was added, and the mixture was thoroughly agitated for complete vesicle lysis. The solution absorbance was determined at 295 nm in the UV-Visible Spectrophotometer after appropriate dilution with phosphate-buffered saline of pH 7.4 containing 10% Methanol. The excipients combination was employed as a control without the medication and was processed as the Niosomal solution. The medication content was determined [24].

In vitro release study

The experiment was conducted utilizing the membrane diffusion method. In this experiment, 10 mg of Niosomal preparation was put in a glass tube with a diameter of 2.5 cm and a total of 8 cm, which had previously been coated with a soaking osmotic cellulose membrane, which served as the donor compartment. The glass tube was put in a beaker with 100 mL of phosphate buffer saline (pH 6.5). The diffusion medium surface was barely touching the receptor compartment holding suspension. The medium was kept at 37 ± 0.50 C and mixed with a magnetic stirrer at a 100-rpm speed. 5 ml aliquots of media were removed at intervals of 0.5, 1, 2, 3 up to 24 hours and replaced with a new medium in the same amount. The obtained samples were examined with phosphate buffer (pH 6.5) as a blank at 295 nm in a double beam UV Visible spectrometer [25].

Table 1. Various concentrations of surfactants in which niosomes are prepared and Evaluation parameters of Luliconazole niosomes

Formulation	Cholesterol: surfactant ratio	Percentage Yield	Entrapment Efficiency	Particle size (nm)	Zeta potential (mV)
F1	1:1	35.76±0.67	51.15±0.87	160.32	-4.7
F2	1:3	44.12±1.12	59.48±1.36	132.61	-5.4
F3	1:4	61.32±1.32	71.55±0.82	123.67	-5.2
F4	2:4	78.96±0.98	86.23±0.85	110.65	-5.1

(Mean ± SD, n=3)

The Niosomal formulation stability studies

The capacity of vesicles to maintain the medication was evaluated by exposing the Niosomal gel to 3 dissimilar temperatures: refrigeration (4°C–8°C), the temperature of the room (25°C ± 2°C), as well as temperature of the oven (45°C ± 2°C). Niosomal gel compositions were kept in metal glass vials throughout the investigation. Over a month, samples were taken at various intervals, and pharmaceutical leaking from the formulations was evaluated for drug content to use a UV spectrophotometer [26].

*Evaluation of gel**Physicochemical evaluation of gel*

Homogeneity: After the gel had been cured in the container, all generated gels were visually inspected for homogeneity. They were examined for aggregate presence and appearance. **Grittiness:** All formulations were examined under a microscope for the existence of particles, if any were present [27].

pH measurements

A digital pH meter was used to determine the pH of the gel's compositions. The pH meter was calibrated before the measurements, and readings were collected by dropping the glass rod into the gel compositions [28].

Viscosity measurement

A Brookfield viscometer was utilized to regulate the viscosity of gel compositions. A 100-gram gel was placed in a beaker, and the sample's viscosity was evaluated by rotating spindle number 4 at 75 rpm [28].

Spreadability

Gels must have strong spreadability, which is an essential criterion. Spreadability is a phrase used to describe the region across which the gel disseminates when applied to the skin. A formulation's therapeutic effectiveness is also influenced by its spreading value. A specific apparatus was created to investigate the dispersibility of the formulations, and spreadability is measured by the time it takes for two slides to separate from a formulation when they are put between each other and subjected to a certain load. The spreadability advances as the time it takes to distinct two slides reduces. It is calculated using the formula below.

Spreadability (gcm/sec) = weight tied to the upper slide (20 grams) × length of glass slide (6cms) / time taken is seconds.

Content uniformity

The content of the drug-produced gel was determined by liquefying a precisely balanced amount of gel corresponding to 10 mg of the drug in a 100 ml volumetric flask and adding methanol to bring the volume up to 100 ml. Whitman filter paper No. 1 was used to filter the material. 41.5 mL of the aforementioned solution was moved to a 25 mL volumetric flask, and the volume was increased to the desired level with methanol. The content of Luliconazole was evaluated using a Shimadzu UV/visible spectrophotometer at 295 nm against a blank. The medication content was calculated using the Luliconazole calibration curve.

In vitro drug diffusion study

A glass cylinder with openings on both ends serves as the device. With the use of an adhesive, dialysis membranes bathed in distilled water (24 hours before usage) are attached to one end of the cylinder. The cell is submerged in a small beaker 100ml of PBS pH 7.4 with 10% v/v methanol (to retain sink condition), and a gel corresponding to 10 mg of Luliconazole is taken into the cell (donor compartment). The whole assembly was positioned such that the bottom end of the cell-containing gel lies just above the surface of the diffusion medium

(1.2 mm deep), and the medium was stirred at $37 \pm 0.5^\circ\text{C}$ using a magnetic stirrer. Periodically, aliquots (5 ml) are removed from the receptor compartment and substituted with the equivalent amount of new buffer. A UV visible spectrophotometer set at 295 nm was used to examine the samples. The tests were performed three times [28, 29].

Stability of final niosomal gel

The final formulation's stability was decided through placing it in a steady environment for 1 month at room temperature, kept in the fridge temperature, and 45°C , and measuring the content of the additional drug in the formulation at numerous intervals (1, 3, 7, 14, and 30 days); adjustments in the final formulation's content were calculated to use a UV spectrophotometer [27, 28].

RESULTS AND DISCUSSION

Evaluation of niosomal formulation

The particle size, shape, entrapment efficacy, and in vitro drug release profile of developed Niosomal formulations were evaluated.

Microscopy optical microscopy

Optical microscopy was utilized to regulate the shape and Niosomal formulations morphology. The spherical form of niosomes may plainly be seen in **Figure 1**.

Scanning electron microscopy

Figure 1 indicates SEM micrographs of Luliconazole-loaded niosomes formulation F4 at various magnifications. At 5000X magnification, SEM micrographs of a group and a single Luliconazole filled niosomes formulation (F4) were collected. The improved formulation's SEM image suggests that the vesicles were virtually spherical and homogeneous.

Table 1 indicated the Luliconazole niosomes' % value, the ability of the drug entrapment, particle size, and zeta potential.

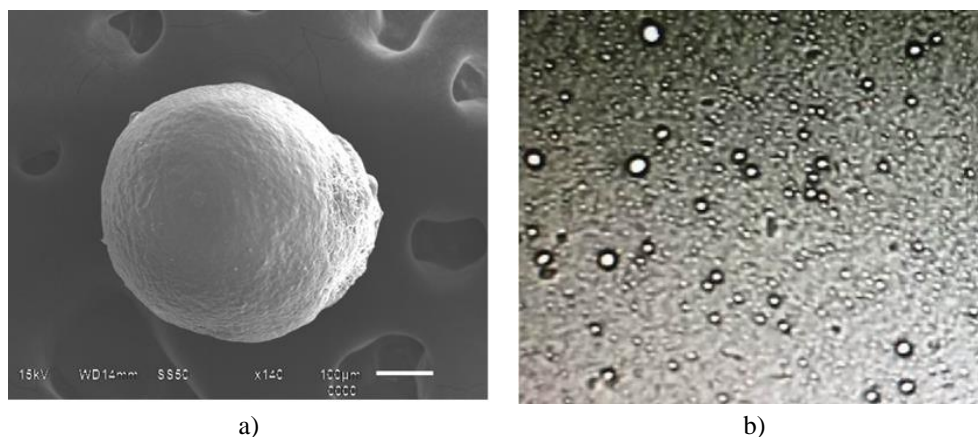


Figure 1. SEM of Luliconazole niosomes

Luliconazole niosomes had the greatest % yield value in F4. The percent yield fell when the polymer content was raised due to the sticky character of the material, which could not be purified. Luliconazole niosomes were determined to have the best trapping performance in formulation F4. Because of the polymer's poor solubility in the aqueous procedure, entrapment quality decreased as the polymer percentage was raised. The height of Luliconazole niosomes was reported to range from 100.1 nm to 190.56 nm (**Table 1 and Figure 2**).

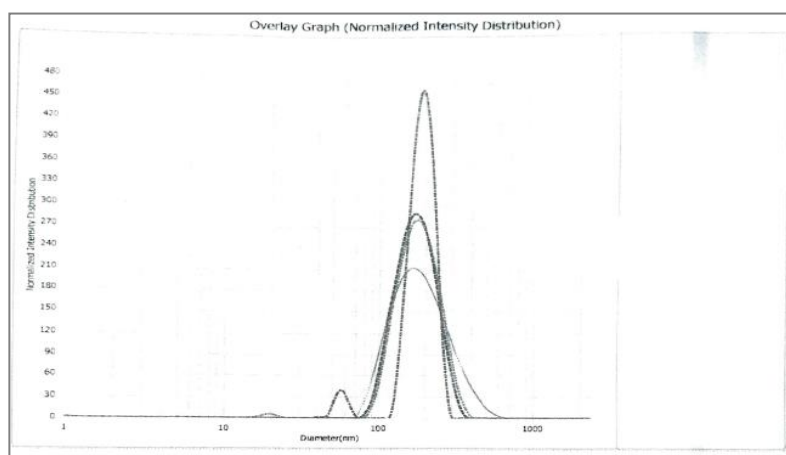


Figure 2. Particle size of luliconazole niosomes

Zeta potential analysis

The zeta potential is significant because its value may be linked to the stability of the colloidal dispersion. The zeta potential represents the repulsion degree amongst nearby, correspondingly charged particles in the dispersion. Malvern tools were used to assess the zeta potential for Niosomal diffusion. The surface charge of all Niosomal vesicles was shown to be negative using the zeta potential method (**Table 1**). The niosomes produced from Span 80, 60 provided negative zeta potential values greater than (-30 mV), suggesting stable systems.

The physical mixture's thermal activity was equivalent to a single medication, although less intense. The melting endothermic of the Micro sponge formulation was inhibited following niosomes, correlating to Luliconazole's partial security. In the Microsponge formulation, the medication's crystallinity altered drastically, suggesting that it was disseminated in the environment (**Figure 3**).

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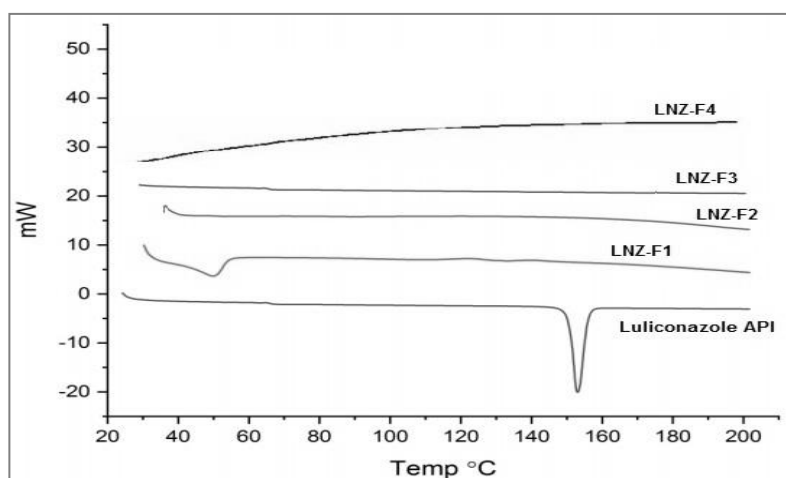


Figure 3. DSC thermograms of luliconazole and luliconazole niosomes

The drug sample's infrared spectrum was recorded (**Figure 4**), and spectral analysis was done. The acquired drug sample spectrum contained its hallmark IR absorption peaks at 1193–1062 cm^{-1} (C O bending), 1278–1215 cm^{-1} (C F stretch), and 1620–1507 cm^{-1} (C = C stretch), indicating its purity. The FTIR spectroscopic investigation indicated no new peaks or the lack of existing peaks, excluding any chemical interaction amid the material as well as the polymer utilized. Both of the Luliconazole trademark peaks are observed in the physical hybridization along with Microsponge composition continuity (**Figure 4**). The medication was shown to be compatible with a range of polymers and excipients and have excellent stability in all Niosomal formulations due to the IR spectroscopy data.

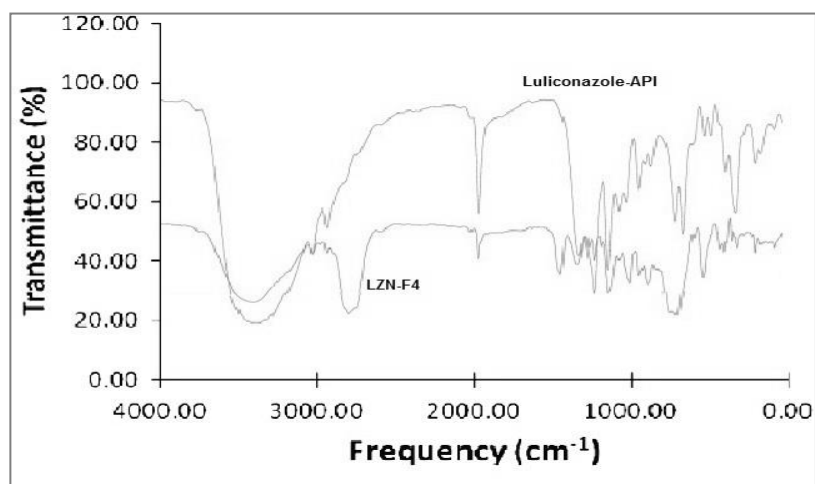


Figure 4. FTIR spectra of Luliconazole and Luliconazole Niosomes

Characterization of luliconazole niosomal gel

Table 2. Evaluation parameters of Luliconazole Niosomal gel formulations

Formulation	Viscosity (cp)	Mucoadhesive strength (dyne/cm ²)	pH	Drug content (%)	Percent release (%)
F1	36500± 2100	5.9±0.1	6.55± 0.2	88.24±2.84	77.19±3.42
F2	32250 ± 1400	5.7±0.8	6.11± 0.3	85.23±2.15	71.56±2.12
F3	28500 ± 2100	5.4±1.2	5.56± 0.4	94.02±1.65	67.54±6.40
F4	26400 ± 2400	5.1±0.1	5.22± 0.3	96.65±3.54	89.23±3.34

(Mean ± SD, n=3)

Physical properties

The physical features of the formed gel, such as transparency, homogeneity, texture, viscosity, pH, and spreadability, were investigated. According to the findings, all manufactured gels are clear, homogenous, lump-free, and smooth. All of the produced gels had a pH range of 5.22±0.3-6.55±0.2 and were within the normal range of skin pH. Spreadability values of 5.1±0.1 – 5.9±0.1 g.cm/s were found in both created nanogels, including the gelling ingredient carbopol-934, indicating that F4 spreads faster with a little level of shear stress than other formulas. All of the prepared gels had viscosities ranging from 36500±2100cp to 26400±2400cp. The drug concentration of all produced gels was found to be between 85.23±2.15 and 96.6±53.54%.

In vitro drug release

The produced nanogel's Luliconazole release was noticed. After 24 hours, Luliconazole Niosomal compositions F4 had the largest release, with an estimated 89.23±3.34%, whereas formulations F3 had the lowest release, with an estimated 67.54±6.40%. Both formulations were determined to have first order release kinetics during in vitro drug release studies. The release of drugs from across all five formulations is seen in **Figure 5**.

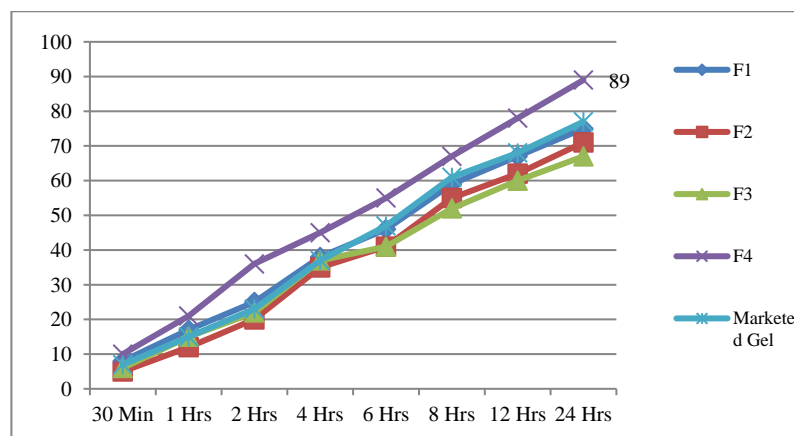


Figure 5. Comparison of percentage release of Marketed drugs and Niosomal Gel

Stability test

After six months of storage at 30°C ± 10°C and 40°C ± 10°C, stability tests demonstrated that all Luliconazole Niosomal Gels retain satisfactory physical features, with no substantial relation to drug purity, the release of drug pattern, viscosity, pH, or humidity [29].

CONCLUSION

Because the nanocarrier may infiltrate the medicine deeper into the skin layer than conventional topical semisolid preparations, the nano-based dosage form is appropriate for the successful treatment of fungal infections. Nanocarriers boost therapeutic effectiveness by channeling drugs deeper into the epidermal layers, allowing fungal infections to be eliminated. The proposed Luliconazole Niosomal gel might be an effective antifungal drug delivery system (DDS) for the successful treatment of infections by maintaining medication release and minimizing dosage frequency and SFI recurrence. Because recurrence of fungal infection is common in Candidiasis and Aspergillosis, Luliconazole Niosomal gel might be used as a DDS within the fungal infections treatment of the skin.

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