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Development of a Novel Luliconazole SLN Gel for Enhanced Topical Antifungal Therapy

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ABSTRACT

Background: A common therapy for superficial fungal infections is luliconazole, a broad-spectrum imidazole antifungal medication. Its short skin retention period and restricted water solubility, however, limit its therapeutic effectiveness when applied using traditional topical formulations.

Objective: The goal of this study is to create and assess a new topical gel of luliconazole based on solid lipid nanoparticles (SLN) in order to improve skin penetration, extend retention, and offer controlled drug release.

Methods: Stearic acid was used as the lipid matrix and Poloxamer 188 as the surfactant in the hot homogenization followed by ultrasonication procedure to create miconazole-loaded SLNs. To create a topical gel, the optimized SLN dispersion was mixed with a Carbopol 934 gel basis. Particle size, zeta potential, drug entrapment effectiveness, pH, viscosity, and in vitro drug release were all evaluated for the formulation.

Keywords: Broad-spectrum, Solid lipid nanoparticles (SLN), Homogenization, Dispersion.

1. INTRODUCTION

Considering a high rate of mortality and morbidity, fungal infections are often defined by the gradual emergence of fungal species and create serious health issues in immunocompromised patients. Patients with hematologic, allogeneic, chronic leukopenia, and autologous graft diseases are much more likely to have it. Fungal infections typically cause the entire body to malfunction and cause the cellular system to become seriously fatal (1). It is known as subcutaneous mycosis and is brought on by a persistent fungal infection that affects the dermis and subcutaneous tissue (2).

One of the most significant tropical infection types, sporotrichosis is brought on by the increasing advent of the fungus Spoorthi schnecke. A medication should be highly effective in preventing the spread of any fungal infection without

having the potential to cause major damage (1,3). The only method to treat the increasing frequency of fungal infections is to make a clear and palliative decision for the patients. Despite this, there are several medications on the market that are often used as tropical medications to treat fungal infections of the skin and subcutaneous tissues. Pharmaceuticals come in a variety of forms, including gels, lotions, and creams. Patient compliance is a serious problem because of bioavailability hurdles or the drug's inaccessibility to the therapeutic location (4).

These days, solid lipid nanoparticles (SLNs) are a cutting-edge pharmaceutical new drug delivery system (NDDS). SLN was identified in 1991 and represents common colloidal carriers, including nanoparticles, liposome emulsions, and polymeric and micro-Enhancing drug penetration capability, a robust release profile, and targeted drug delivery with superior physical stability and minimal degradability are all linked to the contemporary SLN method (2,5).

The FDA has authorized luliconazole, a modern, broad-spectrum antifungal medication (USA). It excludes topical administration systems because of luliconazole's bioavailability barrier. In order to tailor drug penetration in fungal infections and provide high drug concentrations at the location of therapeutic action, cutaneous and subcutaneous encompassment is necessary. Nonetheless, luliconazole topical medications are widely available in markets with low skin permeability and short skin retention, and they significantly increase patient compliance (6).

Due to its high complexity in drug load capacity, restricted number of excipients, stability in drug stability, reduced toxicity, and ease of processing and scaling up, nanoformulation has experienced exponential expansion in the pharmaceutical industry in recent years. Due to their oddly diverse characteristics, SLNs are advantageous for topical medication administration due to their strong penetration capacity and potentiation of prolonged retention at the site of infection (5,7).

Nanoparticles with diameters ranging from 10 to 1000 nm show promise in increasing a drug's bioavailability. In the age of colloidal drug carrier systems, which produce an alternative particle in the field of NDDS, formulation hyphenated with SLN is a crucial concern (9).

2. Role of Selected Drug in Formulation of Topical Gel

The drug used in the formulation is based on their medical application-

a) Luliconazole

In topically applied products like creams or gels, miconazole, an imidazole antifungal drug, is frequently used to treat superficial yeast infections of the skin.

- Luliconazole is lodged in the lipid matrix of SLNs, where it stays stable and is progressively released into the layers of skin. By enabling targeted medication administration, this approach minimizes systemic absorption and related negative effects while optimizing antifungal activity at the infection site (6,10).
- Class: antifungal imidazole
- Mechanism of Action: By inhibiting the enzyme lanosterol 14α-demethylase, it prevents the creation of ergosterol, which is an essential part of fungal cell membranes.

Fig no.1 Luliconazole

b) Stearic Acid-

A common solid lipid matrix in the creation of solid lipid nanoparticles (SLNs) for topical medication administration is stearic acid, a long-chain saturated fatty acid (C18). Stearic acid is essential for the formation of the structural core of the nanoparticles in SLN-based topical gels, which are intended to encapsulate and transport active pharmaceutical ingredients (APIs) including antifungals, anti-inflammatory medicines, or other dermatological medications (11).

➢ It serves as the solid lipid matrix in SLN systems, which:

- Contains the medication.
- Regulates the release of drugs
- Increases the stability of drugs
- Increases the occlusive qualities and skin adhesion.

Fig no.2 Stearic acid

c) Carbopol 934

In pharmaceutical delivery systems, such as gels based on solid lipid nanoparticles (SLNs), Carbopol 934 is a made up, large-molecular-weight, cross-linked poly (acrylic acid) polymer that is frequently used as a gelling component and viscous enhancer. It is a white, light hygroscopic powder that, when neutralized with substances like sodium hydroxide or triethanolamine, swells in water to produce a clear, stable gel (8,12).

- Carbopol 934 is essential in formulations containing SLN because it transforms the nanoparticle suspension into a semi-solid emulsion that may be applied topically.

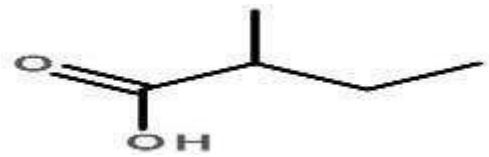

Fig no.3 Carbopol 934

d) **Poloxamer 188**

Poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (PEO–PPO–PEO) is the non-ionic triblock copolymer that makes up Poloxamer 188, sometimes referred to as Pluronic® F68. Because of its surfactant being used emulsion, and stabilizing qualities, it is frequently used in pharmaceutical formulations, especially in the creation of solid nanoparticles of lipids (SLNs) for topical drug administration (13).

- Poloxamer 188 is essential for preserving nanoparticle stability, regulating particle size, and improving the dispersing of lipid-based carriers in aqueous and gel matrices in SLN-based gel systems.

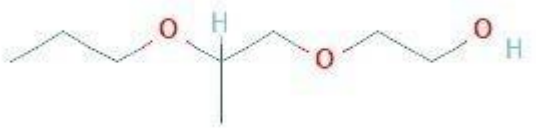

Fig no.4 Poloxamer 188

3. MATERIAL & METHOD

The selection of material in the formulation of gel is based on the therapeutic uses-

Formulation Table-

SLN code	**Luliconazole % (w/v)**	**Stearic acid % (w/v)**	**Poloxamer 188 % (w/v)**
F1	1	0.5	1
F2	1	0.7	1
F3	1	1	1
F4	1	2	1
F5	1	1	0.5

F6	1	1	0.7
F7	1	1	1.5
F8	1	1	2

Table no.1: Formulation Table of Gel

➢ **Procedure for Making Topical Gel (Methodology)**

- Preparation of lipid Phase (Melt stearic acid & Dissolve in luliconazole (e.g., 1% w/w) in the molten lipid phase ensuring uniform mixing).

Fig no.5 Melting & Dissolving Luliconazole

- Preparation of Aqueous Phase (Dissolve Poloxamer 188 in purified water in 70–75°C).

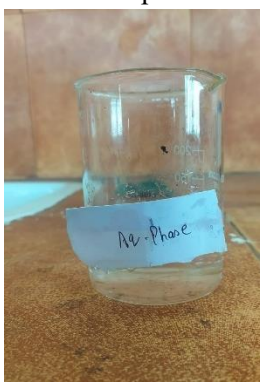

Fig no.6 Preparation of Aq Phase

- While continuously swirling at a high speed, gradually add the heated aqueous surfactant solution to the molten lipid-drug combination.

Fig no.7 Stirring

- While stirring constantly, let the Nano emulsion cool to room temperature.

Fig no.8 Colling

- On the other side, for avoiding lumps, gradually add Carbopol 934 (0.5–1% w/w) to filtered water while stirring gently & adjust the pH to ~ 6.5–7.0.

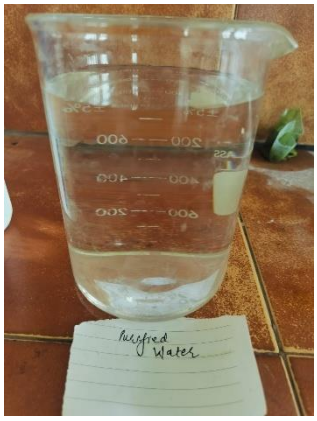

Fig no.9 Adjust pH

- To create a homogeneous and consistent SLN gel, gradually swirl the cooled SLN dispersion into the Carbopol gel base.

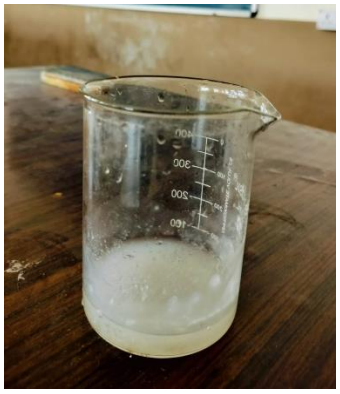

Fig no.10 Final Product

4. EVALUATION

a) Determination of the entrapment efficiency-

By measuring the free mass of the medication in the gel solution's diffused phase following centrifugation, the percentage EE of several gel batches was calculated. To guarantee adequate drug extraction in ethanol, 1g of gel was diffused with ethanol and vortexes for 5 minutes. The resulting mixture was then centrifuged for 60 minutes at 4 °C and 15,000 rpm. After centrifuging the combination, the supernatant was collected and permitted to be analyzed quantitatively using spectrophotometry at 299 nm (15) The following equation yielded the EE percentage:

EE % = W (Added drug) −W (free drug) / W (Added drug) x 100

Where, $W_{(initial\ drug)}$ is mass of drug added initially, $W_{(free\ drug)}$ is mass of free drug detected in supernatant after centrifugation.

b) Spreadability

The gel's spreadability was assessed using a modified version of the procedure that was described. To put it briefly, 500 mg of the improved formulation were placed in the middle of the acrylic plate, with a second plate positioned concentrically above it. diameter of the circle where the principal breadth of the gel spread is measured. For a few minutes, a weight of around 500 g was placed on the plate above. Gel spreadability is calculated based on the diameter increases brought about by gel dispersion and the measured diameter of the dispersed gel (13,16).

c) In-vitro drug release and kinetics study

Using the dialysis bag technique, in-vitro drug release profiling techniques were used to assess the drug release and kinetics profiling of the improved formulation (SLN G3) gel. A precisely weighed 1g gel sample was applied to a cellulose dialysis membrane. After being knotted with thread, the membrane was put into the flask with the 50 ml of ethanol and phosphate buffer solution. At 37 °C, the container is put on a magnetic stirrer and continuously stirred at 50 rpm (14,17).

d) Fourier transform infrared spectroscopy

The Win-IR, Bio-Rad FTS spectrophotometer is used to perform the SLN G3 spectrum analysis. After being mixed with potassium bromide, each sample is examined using a spectrophotometer between 4000 and 400 cm (18).

e) **Scanning Electron Microscopy**

With minor adjustments, the standard methodology is used to analyze the morphological examination of SLN G3 by SEM. A little SLN gel sample was put on a glass stub and vacuum-dried. Following that, the sample was placed in a stub and placed inside a gold-palladium-coated SEM chamber. The sample was then examined under a microscope at an accelerating voltage of 10 kV (15,18).

5. RESULT

a) Organoleptic Testing-

S.no	Parameters	Result
01	Color	Milky, Creamy
02	Odor	Characteristics
03	Consistency	Gel
04	pH	6.12±0.255

Table no.2: Organoleptic Testing

Fig no.11 Physical appearance

b) Evaluation of Entrapment Efficiency of SLN

Luliconazole was described using spectroscopy and physicochemistry. The % EE of luliconazole was calculated following the successful production of several batches of nanoparticles. Spectrophotometric evaluation of the percentage of EE at 299 nm. According to the data, SLN F6 and SLN F1 had the greatest and lowest percentages of EE of luliconazole-loaded SLN, respectively, at 92.13%±0.975 and 53.78%±1.052 w/w (19).

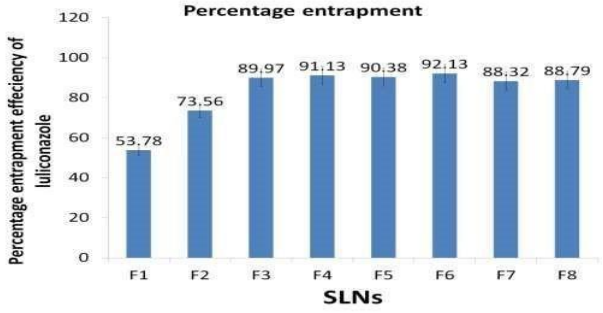

Fig no.12 Entrapment Efficiency of SLN

c) Optical microscopy

Luliconazole SLN is efficiently localized with a homogeneous and uniform texture inside SLN dispersion, according to optical microscopy of the optimal formulation, SLN F6, defined with the aid of a digital light microscope that operates at 100x magnification and observation. It claims that only particles with a mean diameter greater than 2.5 µm may be readily seen when compared to the resolution power of microscopy.

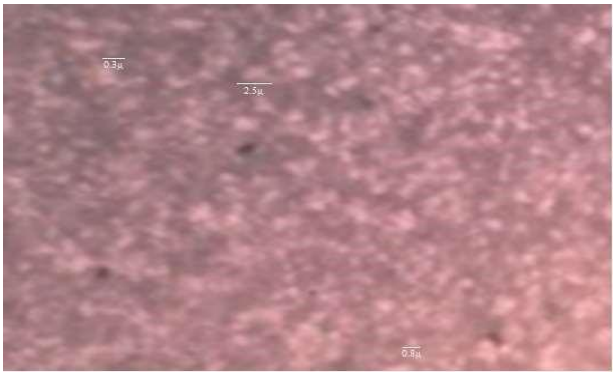

Fig no.13 Optical; Microscopy

d) Drug Excipients Comparability Studies by FTIR

To ascertain any potential interactions between the medication and its additives, FTIR analysis of SLN F6 was conducted. The primary absorption peaks of luliconazole are located at 2955.75 cm-1 for C-H stretching, 2523 & 2647 cm-1 for S-H stretching, 2201.52 cm-1 for C≡N stretching, 1556.90 cm-1 for C=N stretching, 1471.88 cm-1 for C=C aromatic ring stretching, and 720.33 and 1101.29 cm-1 for C-Cl stretching, according to the spectrum data (20,21).

Characteristics Peaks	**Reported (cm^{-1})**	**Observed(cm^{-1})**
C-H stretch	2850 – 3000	2955.75 2914.97 2848.05
C≡N Stretch	2100 – 2400	2201.52
C=C alkene stretch	1650 – 2000	1698.03
C=C Aromatic stretch	1450 – 1650	1463.82
C-Cl stretch	550 – 850	609.29

Table no.3: **Drug Excipients Comparability**

e) In-vivo Drug Release Kinetic Study-

To compare release profiles and predict release mechanisms, statistical models are frequently employed. Using the dialysis bag approach, the drug's in-vitro release profile was monitored for 24 hours in a buffer system that had been constructed. As shown, the percentage of luliconazole desolation from SLN increases with time (6,22).

Sr. no.	Time in hours	Percentage release drug of G3	Percentage drug release of control gel
1	0	0	0
2	0.25	7.375±0.153	1.923± 0.011
3	0.5	14.002±0.185	2.052± 0.155
4	1	22.064±0.102	3.042± 0.158
5	2	32.289±0.173	3.182± 0.162

Table no.4: In-vivo Drug Release Kinetic

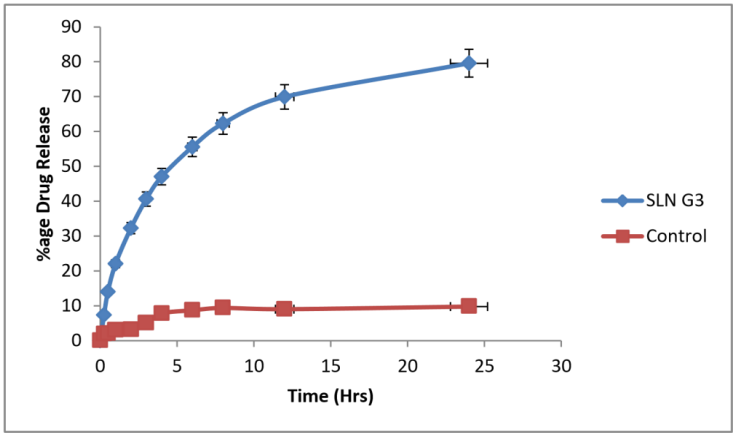

Fig no.14 In-vivo Drug Release Kinetic

6. DISCUSSION

An innovative and effective method of enhancing the medication's therapeutic efficacy in the treatment of superficial fungal infections is the formulation of liconazole into a topical gel based on solid lipid nanoparticles (SLN). Since liconazole is a lipophilic antifungal drug, its limited water solubility may restrict its skin penetration and absorption when applied topically (20,23). By improving solubility, drug retention in the skin, and regulated drug release, luliconazole's integration into SLNs overcomes these drawbacks (4,9,15).

Fig no.15 Final Product

7. CONCLUSION

Topical drug delivery systems are designed to deliver a therapeutic amount of medication to the right location in the body and to produce and maintain the intended effect for a long time. To improve skin penetration and controlled drug release at the targeted site, we have developed solid lipid nanoparticles (SLN) loaded with luliconazole for use in topical gel of carbopol 934 with a good skin retention duration. Following patient usage, the produced gel's physicochemical properties were assessed in accordance with normal operating procedures. There is no chemical interaction between luliconazole and excipients, even according to spectroscopic research. Microscopic analysis of the gel using optical and scanning electron microscopy revealed a homogeneous distribution of SLN with excellent drug release kinetics (24,25).

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