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DEVELOPMENT AND CHARACTERIZATION OF SOLID LIPID NANOPARTICLES CONTAINING ANTI-FUNGAL AGENT FOR TOPICAL DELIVERY

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ABSTRACT: Fungal infection is becoming more common all over the world. Oral therapy for fungal infections is linked with toxic effects, a long treatment period, and patient intolerance. In contrast, the link between topical therapy and superficial fungal infections is low drug solubility, skin irritability, and low permeability via the skin. Top topical therapy would aim to improve the penetration of poorly soluble drug and minimize side effects like irritation and rapid symptomatic relief from fungal diseases. In the present research, Luliconazole-loaded SLN was formulated to improve penetration via the stratum corneum and enhance therapeutic action. Solid lipid nanoparticles gel was prepared using the high shear homogenization method. The formulation contained excipients like stearic acid, glyceryl monostearate, Tween 80, carbapol 934, *etc*. Further, formulations were subjected to tests like Entrapment efficiency, drug content, viscosity, spreadability, gel consistency, and *in-vitro* release. Formulations were examined to be spherical, with the greatest drug entrapment potential. Particle size, SEM, *in-vivo*, FT-IR and stability studies were performed on the optimized formulation. The gel showed a bi-phasic release pattern which showed early burst release than a sustained release. The first burst release provides a rapid initiation of activity, whereas continuous release provides a long-lasting anti-fungal impact. A skin irritation study was carried out according to the guidelines given by OECD, and formulations were reported to be non-irritant and safe for topical use. The Luliconazole-Solid Lipid nanoparticles gel showed enhanced anti-fungal activity and stability. Hence, Lulliconazole-loaded solid lipid nanoparticles prove to be a promising carrier for drug delivery.

INTRODUCTION: Fungal infections are common in many areas of the natural environment. In humans, fungal infections arise when an invasive fungus takes over an area of the body that is too large for the immune system to handle.

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Fungal infections are classified as either superficial or invasive. Invasive fungal infections are infections that affect internal organs or other tissues and the agents that cause them to infiltrate the tissue or organ.

Superficial fungal infections impact up to 20%-25% of the world's population, causing interruptions in daily living, low quality of life, and higher healthcare expenditures. In clinical practice, the most common infectious disease among humans is superficial fungal diseases of the skin. Superficial fungal infections are skin surface, scalp,

and nail infections caused by Candida albicans or dermatophytes. Epidemiological research on fungal infections has shown that the fungi that cause superficial mycoses are widespread, affecting individuals of different ages. Dermatophytes (fungus) are the most common cause of infection, and they work by destroying keratin, which is a protein found on the outer layer of the skin. The infected body part determines how fungal infections are classified. Fungal infections in one area of the body may induce rashes in other areas that are unaffected. A fungal infection on the fingertips may cause a scratchy, bumpy rash on foot. This s usually caused by an allergic response to the fungus. They are not caused by touching the contaminated spot [1, 2].

Causes of fungal infections-Fungi may not belong to either the animals' or plants' kingdom. They are classified as their kingdom. Certain fungi cause most infections in humans. Fungi replicate by the spread of microscopic spores. These spores are often found in the air and soil, where they can be inhaled or come in contact with the body's surfaces like skin. As a result, fungal infections normally start in the lungs or on the skin's surface.

Types of fungal infections-Tinea pedis, also called athlete's foot, is a skin condition affecting the horny epidermal layers. Trichophyton rubrum, Trichophyton inter-digitale, and Epidermophyton floccosum are the organisms that cause tinea pedis. Tinea cruris-Tinea cruris, also called jock itch, is a form of ringworm. It's a fungal infecting the skin's, hair or nails' outer layers.

Tinea corporis-It is a dermatophytosis that affects layers of skin surface. Trichophyton or Microsporum are the most common causes of tinea corporis. Pinkish-to-red, round patches with elevated scaly border which are usually clear in the middle is the most common symptoms of the infection. Itchy rash is a common occurrence.

Treatment - Antifungal medications and moisture-prevention measures. Fungal infections are normally treated with antifungal medications, which are administered directly to the infected region. Creams, gels, lotions, and solutions are examples of topical medications. In addition to medication, people can use precautions such as adding powders or wearing open-toe shoes to keep the infected areas dry. Physicians use corticosteroids to treat such diseases to reduce inflammation and itching [3, 4].

Mechanism of antifungal drugs - In treating fungal infections, a systemic or topical antifungal drug is administered. Ergosterol is the primary component of fungal cell membranes. The currently available antifungals block the production of ergosterol, an important part of the fungal cell wall, inhibiting fungal growth and replication. This activity on various enzymes in the same pathway, on the other hand, can result in a variety of properties and degrees of efficacy. Azole antifungals - Azoles may be either imidazoles or triazoles. They are usually fungistatic, Except at high doses, where they may be fungicidal. The molecules are built around a pharmacophore that blocks fungal cytochrome P450 activity. Azole antifungals attach to the heme group in the target protein structure and inhibit lanosterol demethylation to ergosterol, changing the composition and function of the fungal membrane [5].

Delivery of anti-fungal drugs-Fungal infections is among the most common skin diseases. Antifungal medications are used to treat fungal infections. Antifungal drugs, both topical and oral, are used in treatment. Owing to the potential side effects of oral treatment, the topical approach is usually favored. Topical antifungal medications treat superficial fungus infections until the fungus has spread to a large area or has become resistant to the initial treatment [5, 6].

Transport through the skin- The molecules which enter the subcutaneous layer are through two different pathways, with hydrophilic molecules using the trans-cellular pathway and a lipophilic solute using inter-cellular lipids. Drug diffusing across the skin can also happen via appendages like hair shafts and sweat glands. The follicular route has resurfaced as one of the most common routes for nanoparticle entry, as well as a route for the most hydrophilic drugs and perhaps bigger molecules like polar steroids, which would not usually be able to go across the skin surface easily [6, 7]. Need for novel nanocarriers in topical drug delivery system Fungi affect the skin surface and subsequently infiltrate the subcutaneous layer in

superficial fungal infections, avoiding being shed from the skin surface through shedding.

Topical drug delivery is the application of medication-containing formulations on the skin surface to treat cutaneous or sub-cutaneous diseases directly and conditions such as acne or fungal infections by delivering the drug to the skin's surface or inside the skin. The topical route is said to be the most preferred method for local delivery of medicinal agents among the numerous routes of administration. Compared to the traditional oral method, the topical delivery approach has many benefits. Diffusion of the medication into the systemic circulation must be avoided or minimized in topical distribution. Topical delivery entails delivering drugs to various layers of the skin with minimal systemic absorption, and drug localization in the skin is critical [7, 8].

Advantages of topical DDS-Eliminates the need for first-pass metabolism. It is Convenient, simple to use. It avoids the drawbacks and also hazards associated with IV treatment. Avoids issues associated with conventional medication, such as the various circumstances of absorption, such as pH fluctuations, the presence of enzymes, stomach emptying time, and so on. Medication can be readily stopped anytime necessary. The availability of a greater application area than other options such as buccal or nasal cavities. Target the medicine to a certain spot, more specifically. It prevents gastrointestinal incompatibilities [9].

Lipid drug delivery systems-"Nanotechnology" was introduced by Novel laureate Richard P. Feynman 1959. Pharmaceutical formulations for oral, topical, parenteral, and pulmonary administration, solid lipid-based DDS are a well-established, well-proven, and commercially exploitable approach. Solid lipid nanoparticles (SLNs) are the most common, and they may be customized to have different benefits over liposomes and polymeric nanoparticles. Nano-lipid dispersions are good colloidal carriers because of their biodegradability and nontoxicity. These essential and unique features include a high surface to the mass ratio, far greater than that of other colloidal particles, and their ability to attach, adsorb or transport other compounds. Lipid nanoparticles display fascinating qualities at the nanoscale level that are helpful for therapeutic applications and are sought for medical reasons due to these intriguing and significant characteristics. The interaction between formulation properties and mode of administration, such as cutaneous, pulmonary, and parenteral routes, can affect how well lipid drug delivery systems function [8, 9].

Advantages of lipid-based nanocarriers are - The ability to increase pharmaceutical stability. Both lipophilic and hydrophilic substances can be incorporated. Manufacturing is generally simple to scale up and maintain sterile. The vast majority of lipids employed are bio-degradable, bio-compatible, and non-toxic. They are inherently low-cost than polymer or surfactant-based carrier due to their capability to monitor and target the drug release [8, 9].

Solid Lipid Nanoparticles: Solid-lipid nanoparticles are a new type of therapeutic carrier whose structure is composed of a solid matrix consisting of a lipid that is solid at both room and body temperatures and has a total mean particle size ranging from 50-1000 nanometers.

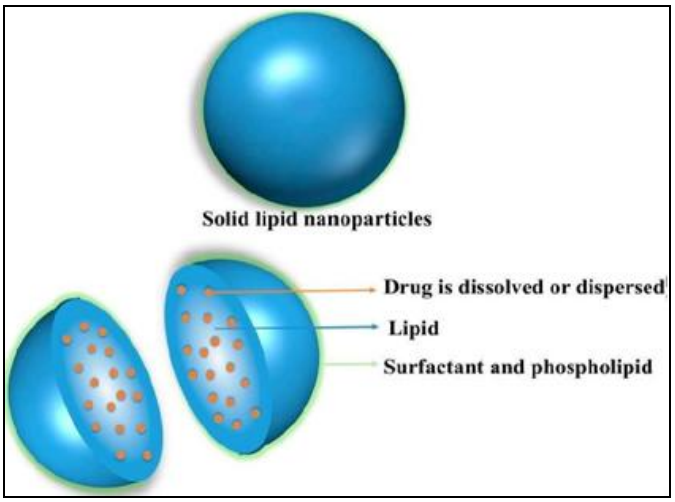


FIG. 1: SOLID LIPID NANOPARTICLES

Extremely purified triglycerides, complex glyceride mixtures, or waxes are commonly used in the preparation of SLNs. For regulated drug delivery, Solid Lipid nanoparticles were formed as an alternative to emulsions, liposomes and polymeric-nanoparticles.

There are three major models for integrating bioactive components into SLNs: model with a homogeneous matrix. A model with a drug-

enriched shell and a model with a drug-enriched center.

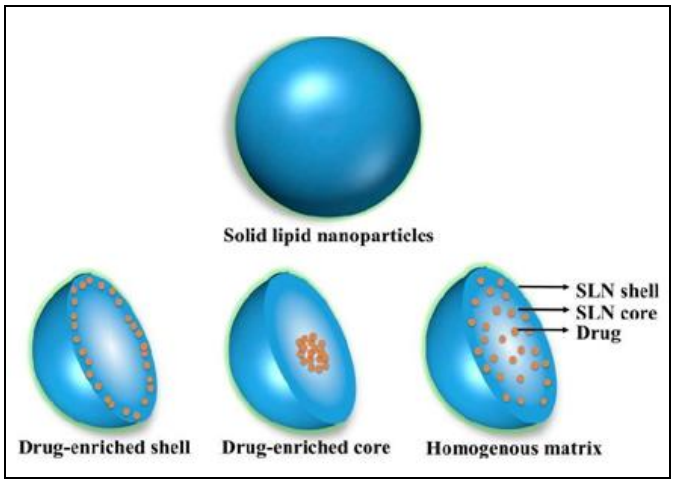


FIG. 2: TYPES OF SOLID LIPID NANOPARTICLES

SLNs are an alternate DDS to other colloidal carriers such as lipid emulsion, liposome and polymer-containing nanoparticles since they blend the benefits of these DDS while eliminating some of their drawbacks. Drugs administered *via* DDS have higher antifungal efficacy than their parent compounds administered via conventional methods. Solid lipid nanoparticles (SLNs) have received much attention over the last few years among DDS. Because of their chemical affinity for skin, they are particularly suitable for topical application. They have a moisturizing effect on the skin by occluding the pores, improving skin hydration. Since they are built on non-irritant and non-toxic lipids, they are ideal for use on impaired or inflamed skin [10].

Since, SLNs have a strong affinity for the stratum corneum, the encapsulated substance has a higher bioavailability to the skin. SLNs improve the penetration and transport of active substances, especially lipophilic agents, increasing their concentration in the skin. This allows for sustained release from these carriers, which are useful as it is required to supply the medication over a long period [11].

Drug Release Mechanism from Solid Lipid Nanoparticles: Higher drug release is achieved by having a larger surface area due to lower particle size in the nanometer range. Slow drug release can be accomplished when the drug is homogeneously distributed in the lipid matrix. It is determined by the type of SLN and drug entrapment model. Advantages of solid lipid nanoparticles-Enhanced skin penetration and/or permeation, Nature's biocompatibility and biodegradability, Accumulation and the formation of films that facilitate skin hydration, Output is simple and scalable, Drug solubility is increased, and skin deposition lasts longer (act as drug reservoir), In the case of dermal drug delivery, avoid systemic absorption and side effects. Specific follicular targeting is a possibility, and Good stability is maintained during the storage cycle [12]. Solid lipid nanoparticle-based gel - The ability of nanoparticles to cross many anatomical obstacles, the continuous release of their contents, and their nanometer-scale stability are all important factors in their use for drug delivery.

Lipids have been proposed as an alternative carrier to overcome the limitations of polymeric nanoparticles, especially for lipophilic pharmaceuticals. The formulation of Luliconazole as solid lipid nanoparticles also increases the drug's efficacy and exhibits a better therapeutic action [13, 1]. Luliconazole- It is an antifungal agent belonging to imidazole group, which has a broad spectrum antifungal activity and has been shown to be effective against a wide range of fungi, especially dermatophytes. Luliconazole belongs to BCS class II drug. Fungal infections include the epidermis, dermis, and deeper layers of skin, necessitating the customization of drug distribution to localize elevated drug concentrations at the epidermis and dermis layers.

However, industrial topical formulations are associated with lower drug permeation and shorter drug retention in the skin. Luliconazole has a lower aqueous solubility, which reduces dermal bioavailability. Furthermore, the drug's solubility in the lipid layer of the stratum corneum is a rate-limiting stage in permeation. To achieve successful topical therapy for different fungal infections, it is important to localize it in the dermal and epidermal layers of the skin. Solid lipid nanoparticles have been developed to improve drug delivery across the skin, allowing for drug retention and, in some cases, controlled release. The novel nano-sized drug carrier is critical in overcoming the shortcomings of traditional dosage types to increase effectiveness, and nanoparticles serve as ideal carriers for poorly soluble drugs. This study aims to

develop and evaluate a solid lipid nanoparticle of an antifungal medication for topical administration. The objectives of the intended work are: To study the compatibility of drugs and excipients. To formulate solid lipid nanoparticle of anti-fungal drug for topical delivery to improve the permeability and obtain sustained release. Solid lipid nanoparticles are evaluated for: Particle size, zeta potential, and PDI. Surface morphology. SLN gels are evaluated for drug content, entrapment efficiency, spreadability and viscosity, pH and appearance of the gel, *In-vitro* dissolution study, In-vivo study, and Stability studies.

Harshalgarse *et al.,* 2015 worked on A gel-based on stable lipid nanoparticles for topical antifungal agent delivery. This study aimed to create an SLN-based gel of bifonazole with a sustained release profile. Melt emulsification followed by ultrasonication was used to create bifonazole SLN. The particle size, surface morphology, entrapment performance, and drug release profiles of the formed SLN were all evaluated. Bifonazole SLN gels are prepared using a suitable gelling agent. Rheological parameters, *in-vitro* drug release, and permeation tests were carried out on the SLN-based gels. *In-vitro* antifungal studies revealed that an SLN-based drug was more effective in inhibiting the growth of Candida albicans and had a sustained release drug profile, implying that it could be used to treat topical fungal infections [13].

Shilpa N. Shrotriya *et al.,* 2017 worked on Silybin-loaded stable lipid nanoparticle-enhanced gel formulation and development for irritant contact dermatitis. The ultrasonic probe sonication method was used to prepare the SLN, which was then tested for particle size and entrapment performance. The SLN was mixed into a gel for effective topical application. *In-vitro* skin occlusion, skin irritability, *ex-vivo* diffusion, and drug deposition were performed on the SLN-gel, which was then compared to the SIL-plain gel. The *Ex-vivo* analysis of silybin SLN gel indicated prolonged percentage release of the drug, while the skin irritability study revealed no irritation [14]. Roohi Kesharwani *et al.,* 2016 worked on Etoricoxib Topical Gel Formulation and Evaluation Using Solid Lipid Nanoparticles. The aim was to create and test a topical gel-based on solid lipid nanoparticles (SLN) of the nonsteroidal anti-inflammatory medication etoricoxib for the treatment of arthritis that will reduce the gastrointestinal drawbacks associated with oral drug delivery administration. Melt emulsification and solidification at low temperatures is used to develop SLN. Particle size analysis, particle size distribution, zeta potential, SEM, DSC crystalline analysis and *in-vitro* release analysis were done for all the formulations. It was discovered that the formulations with high lipid content had greater entrapment than the other two formulations. The SLN-dispersion demonstrates the stability of the formulation. The *in-vitro* drug release rate of gel was determined using a modified Franz diffusion cell with a dialysis membrane and PO_4 buffer pH 7.4 as receptor media. The *in-vitro* drug release was compared to a carbopol gel and a hydroxyl propyl methyl cellulose (HPMC) gel. It was observed that the Etoricoxib-loaded SLN-based gel optimized formulation carbopol is ideal for topical use and exhibits significantly improved anti-inflammatory action [15].

MATERIALS: Luliconazole-Yarrow chemicals Pvt. Ltd, Stearic acid-Avra synthesis, Glyceryl monosterate- Yarrow Chem Pvt. Ltd, Tween 80-Himedia labs Pvt ltd, Carbopol 934-Avra synthesis, Glycerine-Avra synthesis and Triethanolamine-Avra synthesis.

METHODOLOGY: Pre-formulation studies: Preformulation studies are mainly carried out to identify the properties of active ingredients and excipients that may impact formulation, process design, and performance. The preliminary goal of the pre-formulation phase or research is to create the groundwork for introducing a new pharmacological entity into a pharmaceutical formulation so that it can be delivered correctly in the correct amount and perhaps most importantly at the correct target. The secondary goal of the pre-formulation research is to offer extended formulation stability by properly designing and safeguarding therapeutic components from environmental conditions and assessing the prepared formulation's performance [16]. Melting point estimation: The identification of the drug and its pure form is tested using Thiele's tube equipment, which involves first placing the powdered material in a pre-heated one-end sealed capillary tube and tapping it up to 2-3 mm. The

capillary tube is attached to the thermometer with a thread clamped on the iron stand immersed in the bath of liquid paraffin in the tube above the tripod stand and gently heats the tube to maintain a uniform temperature. Take note of the beginning and finish points of the melting of the drug. The melting point of the drug is correctly determined by taking the average of three readings.

Fourier Transform-Infrared (FT-IR) Spectrophotoscopy estimation: Luliconazole FT-IR spectra were performed using a Jasco Fourier transform infrared (FT-IR) spectrophotometer (FT-IR JASCO 460 Plus Digisun Ltd.), Using KBr, each sample was coarsely ground and triturated by mortar and pestle. The blank was first run with KBr, then the triturated samples in dry powder form were compacted into a disc, placed in a holder, and then scanned between 400 and 4000cm^{-1}. The particular peaks were documented [17].

Solubility studies-Luliconazole's solubility in lipids such as stearic acid, compritol 888 and glycerly monostearate was carriedout. For solid lipid screening, Luliconazole was added to 10mg solid lipid in a test tube at 700C. Solubility of drug in molten lipid was visually assessed by confirming the absence of drug crystals. If the increased drug concentration was soluble, more drugs were added until saturation was achieved. A solid lipid that can solubilize a high concentration of a drug with a low concentration of lipid was selected [18].

Preparation of Solid Lipid Nanoparticle Dispersion: Luliconazole-loaded SLNs was prepared using the hot homogenization and sonication approach. To achieve a clear melted solution, the lipid was melted at around 750C (100C over the lipid's melting point), and the drug was added. An aqueous phase was created by dissolving surfactant in 10 ml of double-distilled water and heating it to the same temperature as the oil phase. The heated aqueous phase was introduced drop by drop to the oil phase, and homogenization was conducted for 5 minutes at 8000 rpm at 750C. Hot oil in water emulsion was prepared, and the mixture was sonicated for 5 minutes at 60% power using sonicator. Allowing heated nano-dispersion to cool to room temperature yielded Luliconazole-loaded SLNs [19].

Preparation of Solid Lipid Nanoparticle-Based Gel: Solid Lipid NP gel was prepared by weighing the required quantity of Carbopol 934 and dispersed in an appropriate quantity of distilled water to get an aqueous dispersion. Allow the dispersion to hydrate for 4 to 5 hours. Glycerol was added to the dispersion along with a sufficient quantity of Luliconazole SLN dispersion and an overhead stirrer set at 1200 rpm (IKA Ultra turrax, Remi world), and triethanolamine was added in to the resulting dispersion. The stirring was maintained until the carbopol was distributed. To eliminate entrapped air and the gel was left to stand overnight [20].

Formulation Studies:

TABLE 1: FORMULATION TABLE

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Luliconazole (mg)	20	20	20	20	20	20	20	20
Stearic acid (mg)	200	400	600	800	-	-	-	-
Glyceryl monostearate (mg)	-	-	-	-	200	400	600	800
Tween 80 (ml)	1	1	1	1	1	1	1	1
Carbopol 934 (mg)	300	300	300	300	300	300	300	300
Glyceryl (ml)	1	1	1	1	1	1	1	1
Distilled water (ml)	10	10	10	10	10	10	10	10

Evaluation Studies:

Characterization of Luliconazole Loaded Sln Dispersion:

- ✓ **Particle size:** The Malvern Master sizer 2000 MU was used to determine the mean particle size analysis, Zeta potential and PDI of SLN for size distribution [21].
- ✓ **Scanning Electron Microscopy:** SEM examination was performed to understand the morphology of SLN further. The samples to carry out SEM were prepared by lightly dusting the SLN powder over a double adhesive tape that was adhered to an aluminium stub. SEM was also carried out for the pure drug to compare with the SLN dispersion.

The samples were studied using a scanning electron microscope at an acceleration voltage of 30kV.24

- ✓ **Drug Content:** DC of Luliconazole nanoparticles was done by taking equivalent to 10mg accurately weighed the product and dissolved in a suitable solvent in which entire particles goes into solutions. Shake it to dissolve Luliconazole and filter through a membrane filter with the pore size of 0.45µm. Assay of these formulations were carried out by pipetting aliquot of 1ml and diluting up to 10ml through 7.4 pH PO_4 buffer measured at 298nm by UV Spectrophotometer and calculated using the Formula 2 below. Drug content is determined for all the batches of the nanoparticles [22].

- ✓ **Entrapment Efficiency:** Equivalent weight of 10mg from each preparation of nanoparticles were taken thrice and dispersed by sonicating in the 1ml of methanol for 10 min and centrifuged at 10000 rpm for 20 min, the polymer quantity was separated and by pipetting the supernatant portion, further was determined spectro-photometrically measured at 298 nm against 7.4 pH PO_4 buffer and using Equation 4 calculated [23].

Evaluation of Solid Lipid Nanoparticle-Based Gel: The current work emphasizes the development of new DDS for the treatment of fungal infections which infect the skin surface. In order to overcome drawback of the current dosage form, which is the permeability of the skin subcutaneous layer and obtain a sustained release, the formulation of Luliconazole-loaded solid-lipid nanoparticle would be an appropriate topical delivery for the treatment of fungal diseases. The Luliconazole SLN was synthesized, characterized, and then incorporated into carbapol gel before being assessed for *in-vitro* and *in- vivo* study.

Physical Appearance and pH Measurement: The formed gel's texture, homogeneity, and clarity were assessed. It was also checked to see whether there were any foreign components. The pH of formulation was done using a digital pH meter, and then pH^- values were recorded. The pH measurement was carried out in triplicates [24].

Spreadability: The spreadability of the gel was determined by spreading the gel in a circle of 2 cm in diameter pre-marked on a glass plate, followed by the use of a second glass plate. Weight was placed on the second plate for 5mins. The diameter of the circle after the gel was dispersed was then measured. The increase in the diameter indicates the gel spreadability [24].

Determination of Viscosity: A Brookfield viscometer was used to determine the gel formulations' viscosity.

A. Spindle Selection: Spindle T 95 was used to test all gels' viscosity.

B. Container Sample size: The viscosity was measured by putting 50 grams of gel in a 100 ml beaker.

C. Spindle Immersion: The T-bar spindle (T95) was positioned perpendicular to the centre, not making contact with the container's base.

D. Viscosity Measurement: The viscosity of the gels was measured using the T-bar spindle (T95). The T- bar spindle was moved up and down, providing viscosities at various points along the path. The torque measurement was significantly greater than 10%. The viscosity of gels was determined by taking an average of three measurements in one minute.

Drug Excipient Compatibility Studies:

FT-IR Studies: FTIR spectra were performed using a Jasco Fourier transforms infrared (FTIR) spectrophotometer (Jasco FTIR-401, Japan). Using KBr, the pure drug and the selected polymer are coarsely ground and triturated by mortar and pestle. The blank is first run with KBr, then the triturated samples in dry powder form are compacted into a disc, placed in the holder, and scanned between 400 and 4000cm^{-1}. The particular peaks are documented and compared with the FT-IR of the pure drug [22].

***In-vitro* Studies:** The *In-vitro* drug release was carried out for all the preparations. FDC containing cellophane membrane was used. The donor compartment was full with 1ml of the formulation and the receptor compartment consisted of phosphate buffer pH 7.4 at room temperature beneath slow magnetic stirring. At normal time

intervals, 1ml of aliquot was withdrawn from the receptor chamber throughout the sampling port and immediately replaced with a freshly prepared buffer solution of the same volume. Aliquot was diluted; absorbance was determined by UV-|Spectrometer at 298 nm [23].

***In-vivo* Studies-Skin Irritation Study:** Skin irritation of Anti-fungal agent loaded solid lipid nanoparticle gel was evaluated by carrying out a skin-irritation test on new gel and white rabbits and Wistar albino rats [24]. For seven days prior to the start of the trial, these rats were allowed to adapt to the conditions. Hours before the experiment, the animal's dorsal surface was rendered hairless without injuring the skin surface. The animals were divided into three groups-3 for test and 1 for control.

The formulation was applied topically on the hairless skin area (6cm2) daily for 7 days and observed for 14 days. They were returned to their designated cages after 24, 48, and 72 hours and examined. Dermal responses such as erythema and swelling were noted at the applied areas.

The mean of erythemal and edema scores was recorded based on their degree of severity produced by applying all formulations: Absence of erythema or edema-0, Presence of slight edema or erythema-1, Presence of moderate erythema or edema-2 and Presence of severe erythema or edema-3.

Stability Studies: Stability testing of a product was carried out to evaluate the drug and formulation stability. This study was performed for the final optimized formulation. Accordingly, the ICH Q1A (R2) standards were followed for the accelerated stability of the topical gel. To test the stability of topical SLN-gel, two-month stability research was conducted at 25°C±2°C during which the formulation was sealed in a glass vial and stored. After two months, appearance, pH and drug content uniformity were assessed.

Statistical Analysis: Statistical analysis for this study was performed using a software-GraphPad prism (version 9). All the data are expressed in terms of mean ± standard deviation, and data was analyzed using ANOVA to find the p-value and if the data provided is statistically significant.

RESULTS AND DISCUSSION:

Pre-formulation Studies: It is a method of improving drug delivery by determining the physic-chemical parameters that may influence the performance of the drug delivery system. It provides decisive information on the drug's nature and an outline of drugs in combination with various pharmaceutical excipients for drug design. Following that, the research plays an active role in a drug's credentials and validity.

* - All the procedures were performed in triplicates and found as mean ± S.D.

Authentication of Luliconazole by melting point:

TABLE 2: LITERATURE AND OBSERVED VALUE OF MELTING POINT OF LULICONAZOLE

Literature value	Observed value *
150-152°C	151°C±0.1°C

A melting point reading is obtained when a material melts in a specific range at a temperature defined in 1-atmosphere standard pressure. The melting point of Luliconazole was reported to be 1510C±0.10C. The experimental value was found to be within the reported value, indicating the drug's purity.

Authentication of Luliconazole by UV-Spectroscopy Method: UV spectroscopy is used to determine a substance's quantitative composition, identify contaminants and understand the structural properties of organic molecules. The estimation was done in pH 7.4 phosphate buffer.

(A) Estimation of Absorption maxima (λ_{max}): UV-Spectrum of Luliconazole was scanned between the range 200 to 400 nm in pH 7.4 PO_4 buffer.

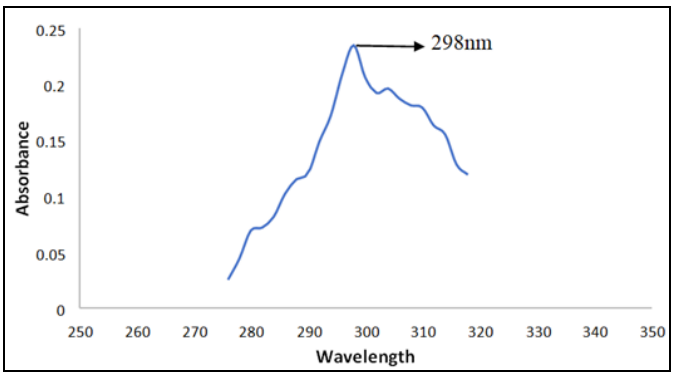


FIG. 3: UV-SPECTRUM OF LULICONAZOLE

The maximum point peak is observed as shown in **Fig. 3,** indicating λmax of 298nm and was found to be similar to that of the literature value.

(B) Standard calibration curve of Luliconazole in pH-7.4 phosphate buffer:

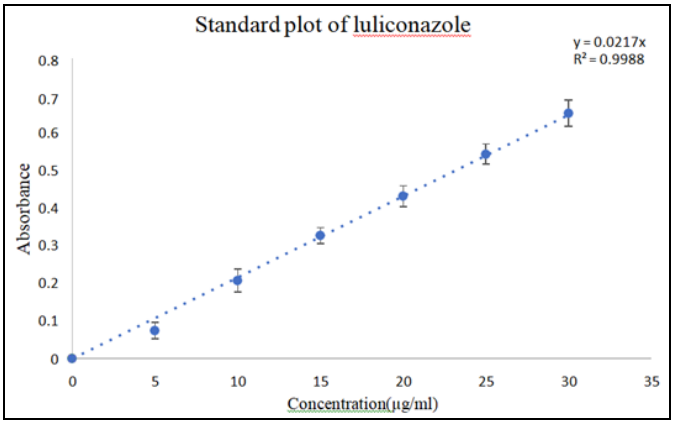


FIG. 4: STANDARD CALIBRATION CURVE OF LULICONAZOLE IN PH 7.4 PO4 BUFFER AT 298NM

The above table shows the absorbance values of Luliconazole calculated at 298nm concerning the linear concentration range of 5-30 µg/ml of the drug in pH 7.4 phosphate buffer and **Fig. 3** & **4** shows linear standard curve with slope 0.0217 and regression coefficient value of 0.9988.

Fourier Transform Infrared (FT-IR) Spectroscopy Method: The FTIR spectrum of the pure drug was recorded by FT-IR spectrophotometer shown in **Fig. 5** and compared with the standard functional group's frequencies in the literature shown in **Table 2.**

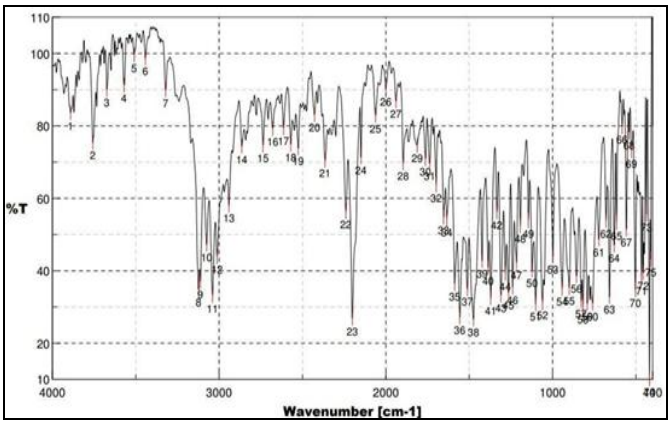


FIG. 5: INFRARED SPECTRUM OF LULICONAZOLE

TABLE 2: LITERATURE AND IDENTIFIED EXPERIMENTAL FT- IR FREQUENCIES OF LULICONAZOLE

Class of functional compounds	Literature range Frequencies (cm^{-1})	Identified Experimental range Frequencies (cm^{-})
C-H Stretching (alkene)	2925-3114	3074.94
S-H Stretching (thiol)	2527	2526.29
C≡N Stretching (nitrile)	2240	2239.91
C=N stretching	1634	1634
C-Cl Stretching (halo)	1100	1060.66
O-H Stretching	3440	3442.31
C=C aromatic stretching	1557	1557.24

The FT-IR studies have been involved in the studies to identify the drug, determine the structure, study the complex molecules, and perform conformational analysis.

The characteristic peak of Luliconazole was found to appear at 3074.94 (due to C-H Stretching), 2526.29(due to S-H stretching), 2239(due to C≡N Stretching), 1634 (due to C=N stretching), 1060 (due to C-Cl stretching), 3442.31(due to O-H stretching) and 1557.24 (due to C=C aromatic stretching).

Solubility Studies: Solid lipids like stearic acid, glyceryl monostearate, and compritol 888 were selected to study the solubility of Luliconazole in these lipids as shown in **Table 3** and **Fig. 6.**

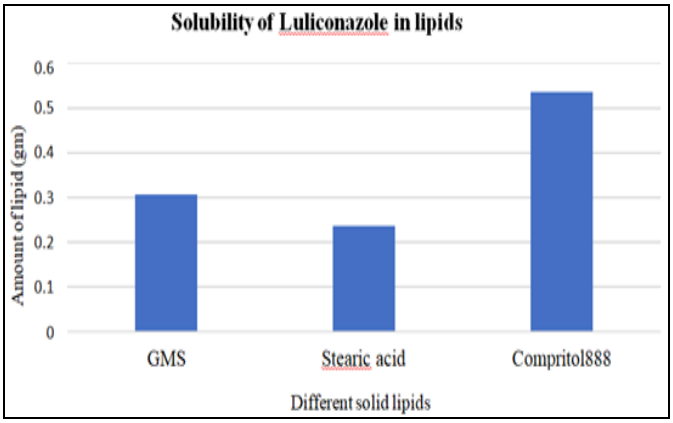


FIG. 6: SOLUBILITY STUDIES OF LULICONAZOLE

The lipids used in the formulation of SLNs were chosen based on their solubility. Luliconazole was shown to be soluble in a variety of solid lipids.

The final lipid was chosen based on the lowest quantity of lipid necessary to solubilize the given amount of drug. This retains the drug-to-lipid ratio at a low concentration, resulting in a smaller particle size. Glyceryl monostearate and stearic acid were selected for further evaluation.

TABLE 3: SOLUBILITY STUDIES OF LULICONAZOLE IN SOLID LIPIDS

Sl. no.	Solid lipid	Trial 1	Trial 2	Trial 3	Solubility
1	Glyceryl monostearate	0.29	0.36	0.27	0.30g/ml
2	Stearic acid	0.19	0.2	0.32	0.23g/ml
3	Compritol 888	0.71	0.4	0.5	0.53mg/ml

The pure drug was then characterized for melting point, UV-Spectroscopy, and FT-IR studies. The formulations of solid lipid nanoparticles, were initiated with the selection of lipids by carrying out solubility study. Lipids such as stearic acid and glyceryl monostearate were chosen since a minimal amount of lipids was required to solubilize the drug. Tween 80 was selected as a surfactant and was maintained at a constant concentration throughout the study. The SLN based gel was prepared using carbapol 934 and other excipients like glycerol and triethanolamine were added to enhance the formulation's characteristics. The high shear homogenization method was used to obtain Luliconazole SLN dispersion. The formulations were created utilizing a selection of excipients at varied concentrations. The selected polymer was subjected to drug excipient compatibility study through FT-IR and no significant interactions were found between the drug and the polymer.

Preparation of SLN Dispersion: The lipid selected was stearic acid and glyceryl monostearate according to the solubility studies of various lipids. Both lipids varied in different concentrations in the range of 200-400mg for the formulation. The particular concentration of lipid was melted above its melting point, and the drug was added to form a clear mixture; this is the oil phase. The aqueous phase was prepared by dissolving the selected surfactant, *i.e.*, tween 80 in the required quantity of distilled water under the same temperature as the oil phase. The aqueous phase is incorporated into the oil-phase dropwise under magnetic stirring while maintaining the temperature constant. This solution was homogenized for 5 min under 8000 rpm and then sonicated for 5 min. This nano-dispersion was allowed to cool to room temperature for yielding nanoparticles. In order to prepare the SLN gel, weighed quantity of SLN dispersion was added to the already prepared gel and stirred under magnetic stirring along with glycerol. Once the dispersion was equally distributed in the gel medium, then stored in a refrigerator overnight to remove entrapped air.

Evaluation Studies:

Scanning Electron Microscopy: It was utilized to learn more about the particle size and morphology of the SLN dispersion. Furthermore, no evidence of drug precipitation was seen, suggesting that the generated dispersion is stable. SEM was carried out for the pure drug to compare it with SLN dispersion.

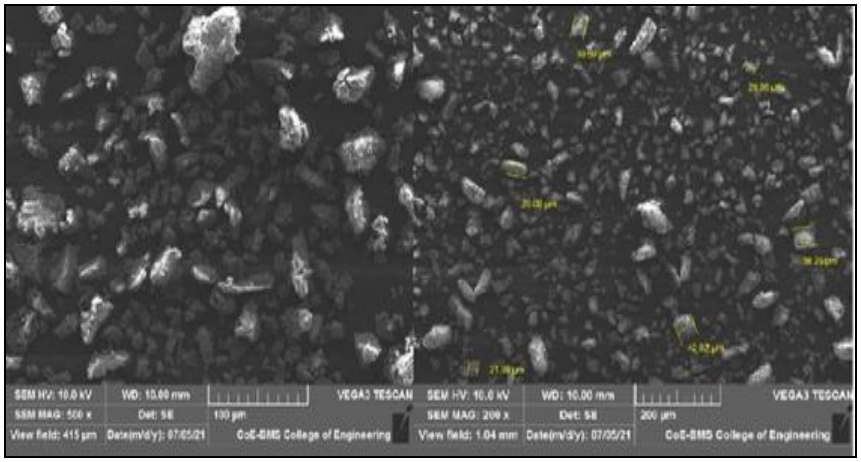


FIG. 7: SEM IMAGE OF LULICONAZOLE

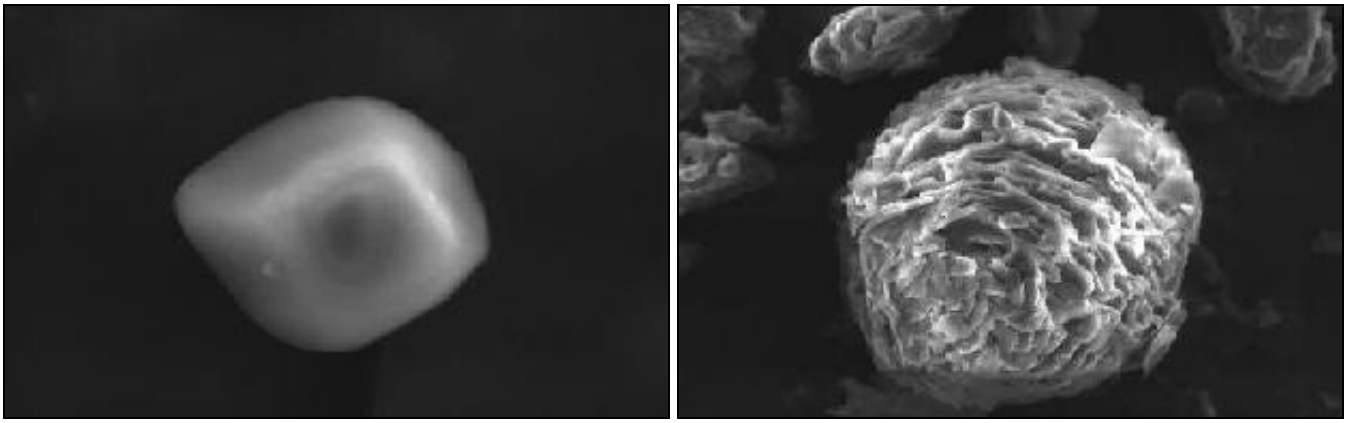
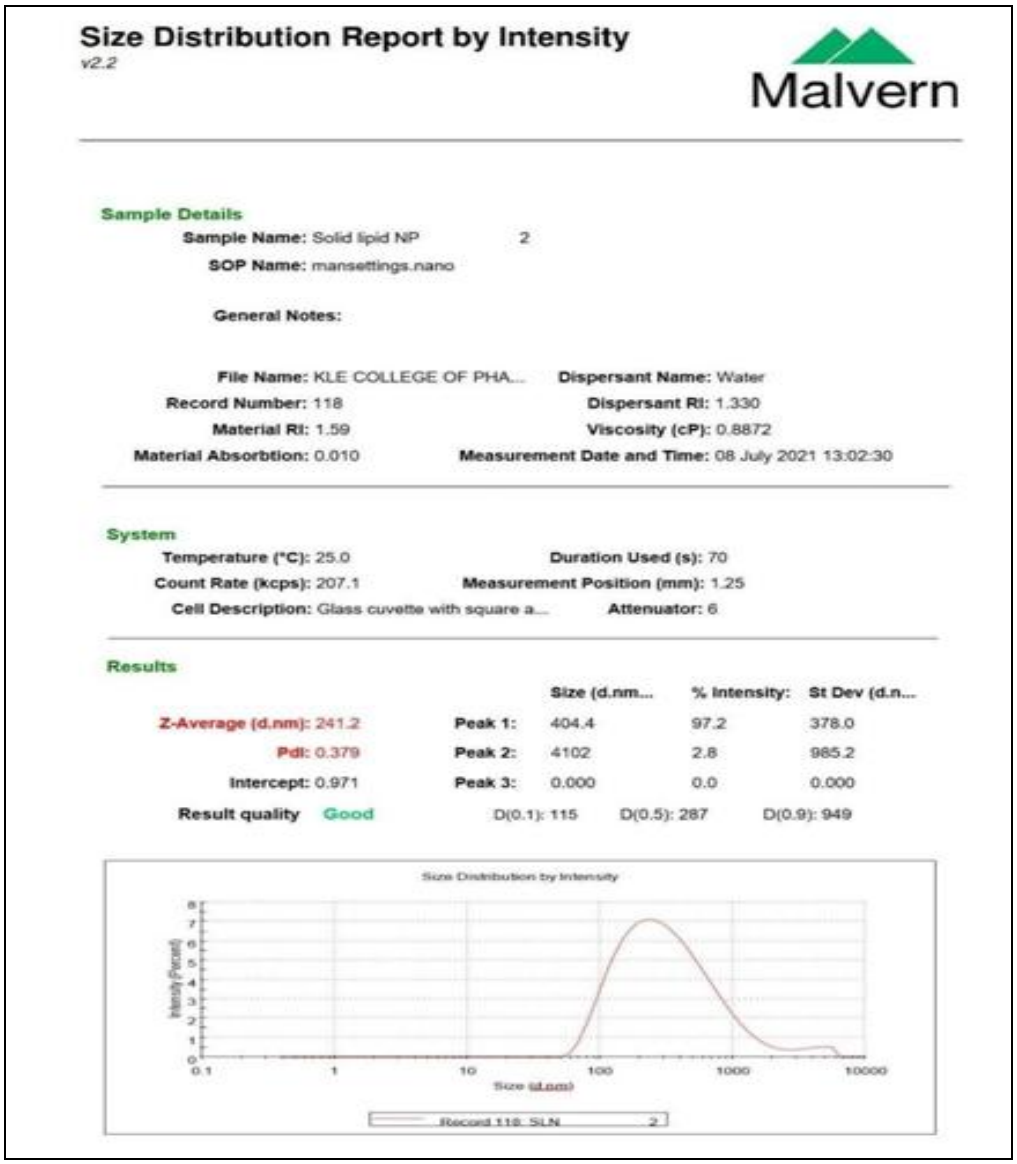


FIG. 8: SEM OF SOLID LIPID NANOPARTICLE OF LULICONAZOLE

The SEM studies carried out for the pure drug were approximately 100-200µm. The SEM study of solid lipid nanoparticles in Fig. 7 & 8 depicted that nanoparticles were smooth and spherical with a size range of 100-500nm.

Estimation of Particle Size and Zeta Potential:



Size Distribution Report by Intensity

v2.2

Malvern

Sample Details

Sample Name: Solid lipid NP 2

SOP Name: mansettings.nano

General Notes:

File Name: KLE COLLEGE OF PHA... **Dispersant Name:** Water

Record Number: 118 **Dispersant RI:** 1.330

Material RI: 1.59 **Viscosity (cP):** 0.8872

Material Absorbtion: 0.010 **Measurement Date and Time:** 08 July 2021 13:02:30

System

Temperature (°C): 25.0 **Duration Used (s):** 70

Count Rate (kcps): 207.1 **Measurement Position (mm):** 1.25

Cell Description: Glass cuvette with square a... **Attenuator:** 6

Results

		Size (d.nm...	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 241.2	Peak 1:	404.4	97.2	378.0
PdI: 0.379	Peak 2:	4102	2.8	985.2
Intercept: 0.971	Peak 3:	0.000	0.0	0.000

Result quality Good D(0.1): 115 D(0.5): 287 D(0.9): 949

FIG. 9: PARTICLE SIZE OF OPTIMIZED FORMULATION (F4)

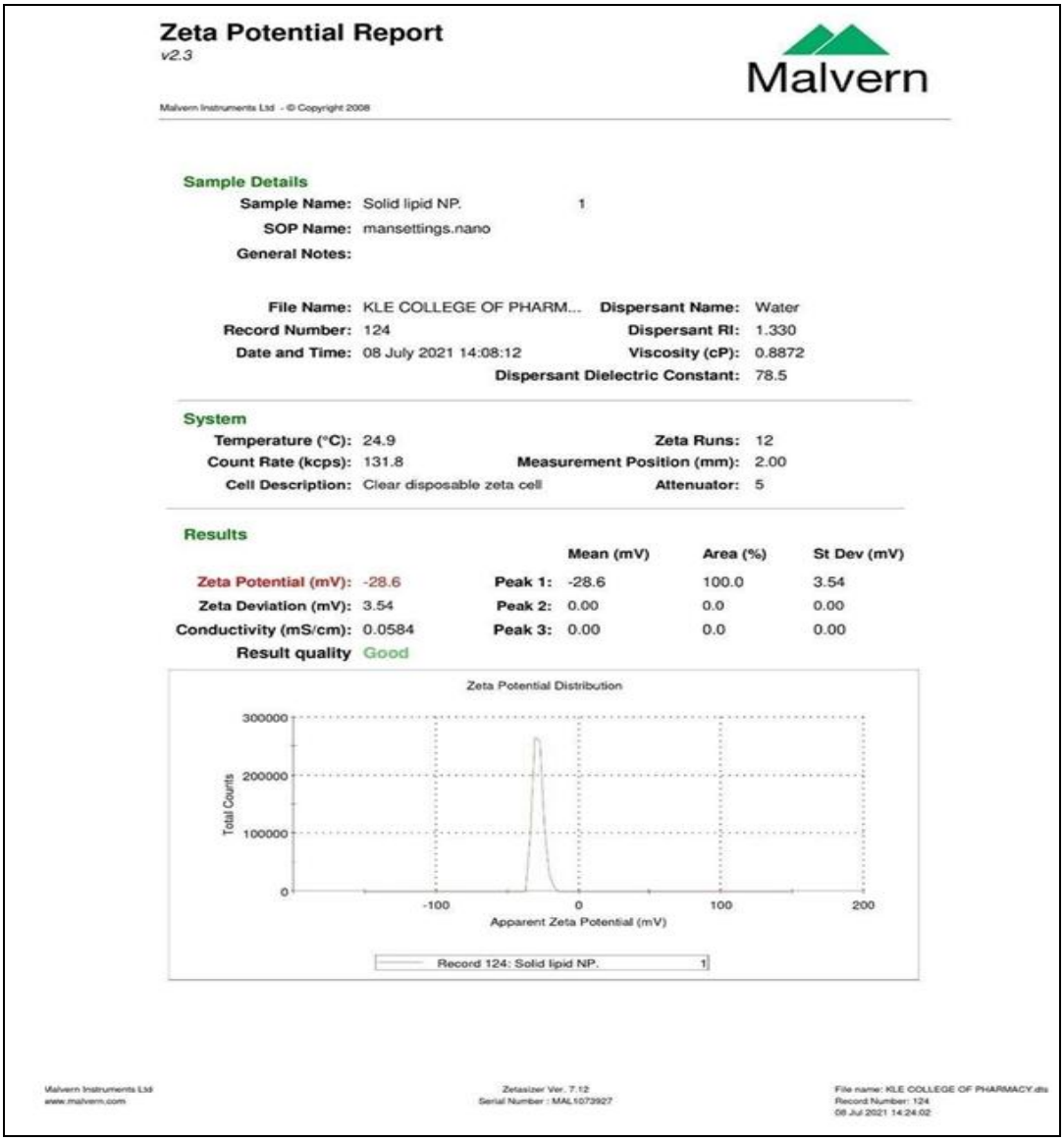


FIG. 10: ZETA POTENTIAL OF OPTIMIZED FORMULATION (F4)

Particle size and PDI were characterized for the optimized formulation and was found to be 241.2 nm and PDI of 0.379, respectively. A formulation's zeta potential demonstrates the extent of repulsion between similarly charged particles. During storage, repulsive forces prevent particle aggregation. Thus, zeta potential indicates a formulation potential physical stability. The optimum zeta potential range is 30 mV to +30 mV. The optimized formulation zeta potential was determined to be -28.6 mV. Hence, the formulation was found to have good stability, as shown in **Fig. 9** & **10.**

Estimation of Drug Content Uniformity: The drug content of formulations F1-F8 was found to be in the range of 89-97%. The highest drug content in the formulation F4 was reported to be 97.81±0.5% and the lowest drug content observed in the formulation F5 was reported to be 89.42±0.02% as shown in **Table 4.**

TABLE 4: DRUG CONTENT FOR FORMULATIONS (F1-F8)

Formulations	Drug content (%)
F1	91.36±0.08
F2	90.64±0.12
F3	95.73±0.37
F4	97.81±0.53
F5	89.42±0.02
F6	92.14±0.06
F7	93.96±0.17
F8	96.84±0.05

Determination of Entrapment Efficiency: Entrapment Efficiency (EE) of formulation F1-F8 was calculated using equation 2. The % EE was reported to be in 83-96 % range. The lowest

entrapment was found to be of formulation F5 which showed 83.05 % and the highest entrapment was showed by formulation F4 which was found to be 96.78% as shown in the **Table 5.**

TABLE 5: ENCAPSULATION EFFICIENCY OF FORMULATIONS (F1-F8)

Formulations	Entrapment Efficiency (%)
F1	87.17±0.54
F2	90.53±0.72
F3	92.99±0.09
F4	96.78±0.16
F5	83.05±0.58
F6	84.77±0.03
F7	89.40±0.82
F8	91.44±0.51

Physical Appearance and Measurement of pH: The optimized gel formulation F4 was evaluated for different physical parameters.

The appearance of the gel was found to be white, smooth, and homogeneous with a semi-solid consistency.

The gel did not contain any foreign material and was observed to be clear and suitable for application topically.

The pH of the optimized formulation was reported to be 6.4 ± 0.072, as shown in **Table 6.**

TABLE 6: PHYSICAL APPEARANCE AND PH VALUE FORMULATION (F4)

Formulation	Consistency	Grittiness	Appearance	pH
F4	Semi-solid	None	White	6.4±0.072

Spreadability: Spreadability is required to ensure proper dose distribution to the location of drug administration. It also influences the formulation, ease of application, patient compatibility, and extrudability of the container. The more uniform or even the application over the intended region, the greater the effectiveness. The greater the spreadability region, the greater its effects and formulations speradablity results are reported in **Table 7.**

TABLE 7: SPREADABILITY OF FORMULATIONS (F1-F8)

Formulations	Spreadability (mm)
F1	40±1.62
F2	35±2.01
F3	29±0.57
F4	41±0.12
F5	30±1.43
F6	41±0.76
F7	38±1.02

Formulation F4 demonstrated a maximal spreadability of 41±0.12mm, implying more therapeutic effects.

Determination of Viscosity: Viscosity was measured using a Brookfield viscometer. For spindle rotation, a 50 rpm speed was maintained, and the results were recorded after the gel content stabilized after about 30 seconds. The prepared gels were found to have a viscosity in the range of 4000-6000 cp. The optimized formulation F4 was found to have a viscosity of 5439±0.14 cp, as shown in **Table 8,** which is regarded as sufficient for topical application.

TABLE 8: VISCOSITY OF FORMULATION (F1-F8)

Formulations	Viscosity (cp)
F1	4731±0.18
F2	4259±0.15
F3	5168±0.27
F4	5439±0.14
F5	5541±0.21
F6	5276±0.25
F7	4982±0.13
F8	5431±0.16

Drug-Excipient Compatibility Studies: FTIR spectrum of drug and optimized formulation excipient were recorded by FT-IR spectrophotometer. The identical FT-IR spectrum was obtained by scanning from 4000-200 cm-1, as shown in **Fig. 11.**

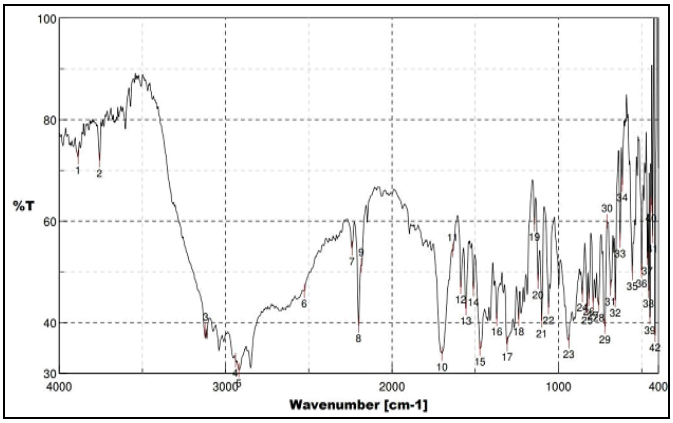


FIG. 11: FT-IR SPECTROSCOPY OF DRUG AND POLYMER

The FT-IR spectrum revealed that there was no significant difference in the location of the peak produced in the drug alone and a combination of the drug with excipients, indicating no interactions between the drug and the excipients.

***In-vitro* Drug Release Study:** The ability of gel formulation to deliver Luliconazole was determined by *in-vitro* drug release using Franz diffusion cell. **Table 9** and **Fig. 12** show the cumulative % release of Luliconazole from solid lipid nanoparticle gel through the dialysis membrane at different sampling intervals under conditions (temperature 32°C±0.5°C) that imitate the skin surface. The carrier's physicochemical characteristics are determinants of drug release from a carrier system and due to which *in-vitro* release profiles are predicted to differ accordingly.

Luliconazole was released in a sustained manner from the solid lipid NP-based gel. **Table 13** and **Fig. 12** depict the drug release of formulations F1-F4 up to 12 hours. Drug release for formulations was observed in the range of 42.03±0.54 to 48.14%±0.28%.

TABLE 9: % CUMULATIVE DRUG RELEASE OF FORMULATIONS (F1-F4)

Time (h)	% Cumulative DrugRelease (CDR)			
	F1	F2	F3	F4
0.5	7.07±0.13	6.18±0.34	7.88±0.12	8.53±0.44
1	10.80±0.09	7.90±0.17	11.27±0.38	17.00±0.17
2	11.09±0.65	12.55±0.42	13.57±0.61	19.08±0.09
3	16.20±0.23	18.68±0.71	20.57±0.42	22.97±0.38
4	20.87±0.04	23.01±0.06	24.58±0.11	29.71±0.21
5	23.27±0.15	27.02±0.04	31.69±0.27	32.43±0.05
6	29.69±0.63	32.87±0.22	35.78±0.43	38.34±0.29
7	31.70±0.34	39.66±0.12	39.87±0.61	41.26±0.37
8	37.45±0.22	41.79±0.14	43.00±0.23	45.64±0.41
12	42.03±0.54	45.25±0.15	46.34±0.31	48.14±0.28

TABLE 10: % CUMULATIVE DRUG RELEASE OF FORMULATIONS (F5-F8)

Time(h)	% Cumulative Drug Release			
	F5	F6	F7	F8
0.5	8.28±0.06	5.43±0.12	6.08±0.55	7.92±0.71
1	10.99±0.14	11.20±0.05	15.23±0.17	9.04±0.02
2	14.03±0.11	15.15±0.34	19.81±0.43	11.96±0.64
3	19.98±0.23	21.25±0.21	23.15±0.02	15.69±0.32
4	22.47±0.04	26.88±0.07	29.28±0.17	20.25±0.22
5	24.59±0.016	28.14±0.19	32.22±0.62	25.74±0.41
6	26.49±0.02	30.32±0.71	36.45±0.41	32.36±0.05
7	32.39±0.15	34.38±0.63	40.43±0.32	39.98±0.23
8	39.56±0.19	40.64±0.08	44.95±0.02	45.92±0.12
12	41.55±0.33	44.21±0.28	51.06±0.21	49.40±0.42

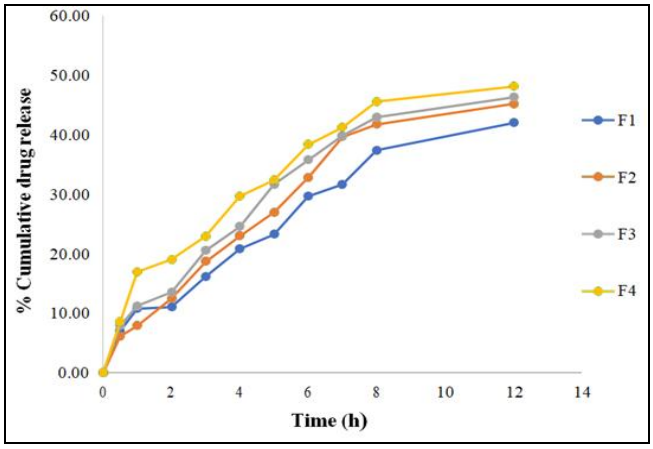


FIG. 12: % CUMULATIVE DRUG RELEASE OF LULICONAZOLE FROM SLN GEL (F1-F4)

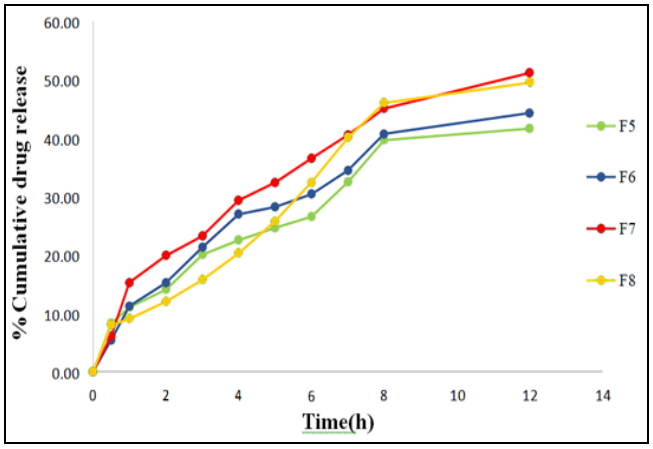


FIG. 13: % CUMULATIVE DRUG RELEASE OF LULICONAZOLE FROM SLN GEL (F5-F8)

Luliconazole was released in a sustained manner from the solid lipid NP-based gel. **Table 10** and **Fig. 13** depict the release of formulations F5- F9 for up to 12 hours. The drug release of all formulations was observed to be from the range of 41.55±0.33 to 51.06±0.21%. The most important characteristic of solid lipid nanoparticle-based gel is the comparatively sustained release profile which could be due to the presence of solid lipid that envelops the drug in the matrix. The SLN gel demonstrated a biphasic release pattern, with an initial burst release followed by a slower and continuous release. This drug release pattern could be due to the distribution of the drug in the nanoparticles, and it can be explained by the drug-enriched shell, in which the drug would not be entirely incorporated in the lipid matrix but would also adsorb on the surface of the particles from which it could immediately release which causes the initial burst release. The remaining drug encapsulated in the lipid matrix would release slowly. Initial burst release benefits the quick onset of action, whereas the slow, sustained release in the later phase can release the drug for a longer period. The prepared formulations were evaluated for % DC, % EE, spreadability, viscosity, and *in-vitro* diffusion studies. The DC and entrapment efficiency of the formulations F1-F8 were found to be in the range of 89-97% and 83-96%. Formulation F4 demonstrated the highest release of 97.81±0.5% drug content and 96.78% entrapment efficiency. All the formulations were further evaluated for spreadability, viscosity, and *in-vitro* studies. The results of formulation F4 were reported to be good compared to all the formulations, as it showed a spreadability value of 41±0.12 mm and viscosity of 5439±0.14 cp. All formulations were subjected to *in-vitro* testing in a Franz diffusion cell.

It was done for 12 hours. The biphasic release pattern of Luliconazole SLN gel exhibits an early burst release accompanied by a slow and continuous release.

Statistical Analysis: The results of eight formulations were analyzed in GraphPad Prism 9 using ANOVA. **Fig. 14** and **Table 11** indicates the *in-vitro* release of drug from the formulations. The results of ANOVA demonstrated that the results were significant for all measured responses. It was reported that the p-value <0.0001.

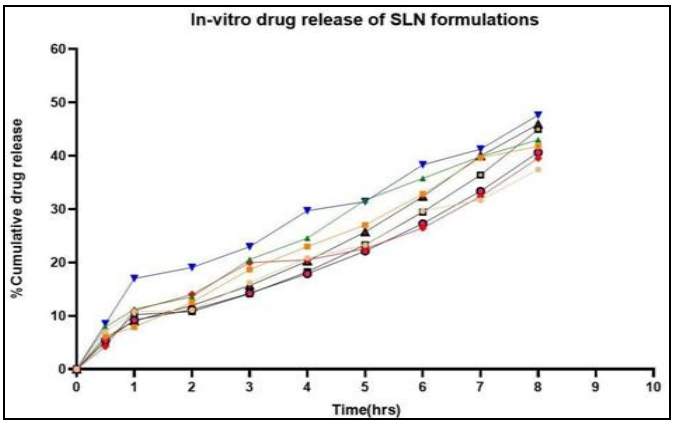


FIG. 14: STATISTICAL ANALYSIS USING ANOVA

TABLE 11: STATISTICAL ANALYSIS USING ANOVA DATA SUMMARY

Repeated measuresANOVA summary					
Assume sphericity?	No				
F	14.32				
P value	<0.0001				
P value summary	****				
Is there significantmatching (p<0.05)?	Yes				
Geisser-Greenhouse'sEpsilon	0.4428				
R squared	0.6141				
Was the matchingeffective?					
F	347.10				
P value	<0.001				
P value summary	****				
Is there significantmatching (p<0.05)?	Yes				
R squared	0.9503				
ANOVA table	**SS**	**DF**	**MS**	**F (DFn,DFd)**	**P value**
Treatment (betweencolumns)	433.30	7	61.89	F(3.098, 27.88)=14.32	p<0.0001
Individual (betweenrows)	13501	9	1500	F (9, 63)=347.10	p<0.0001
Residual (random)	272.30	63	4.32		
Total	14207	79			

***In-vivo* studies:**

Skin Irritability Study: IEAC committee had approved project proposal number 08/AKP/2020. On Newzeland white rabbits-After the formulation application, the animals were observed at 60 min, 4 hrs and daily for 14 days, as shown in **Table 12** and **Fig. 15.** Observations include the severity of skin injury and scoring of erythema.

TABLE 12: OBSERVATION OF SKIN IRRITABILITY STUDY ON RABBITS

Animal no	Clinical signs	Mortality	Erythema score
1(control)	NAD*	None	0
2	NAD	None	0
3	NAD	None	0
4	NAD	None	0

* NAD-No abnormality detected.

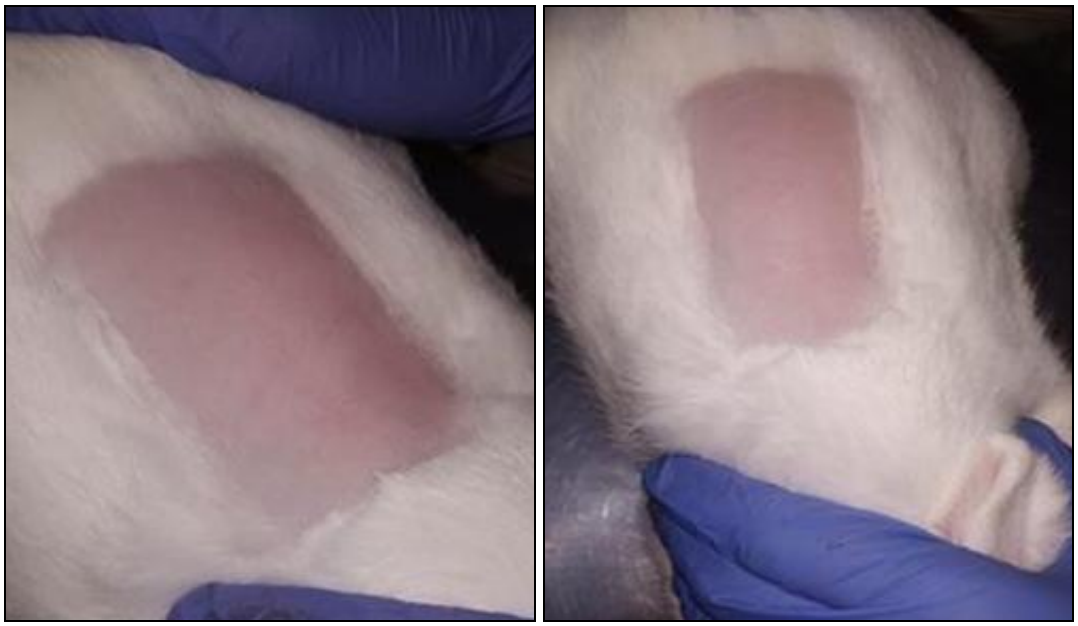


FIG. 15: SKIN IRRITABILITY STUDY ON RABBITS

During the observation period of 14 days, there was no erythema, dermal toxicity, gross pathological change, morbidity or mortality in any of the treated animals; hence the topical formulations can be considered as non-toxic as shown in **Fig. 15.**

Wistar Albino Rats: After applying formulation, the animals were observed at 30 min, 60 min, 4 hrs and daily for 14 days. Observations include skin injury severity and erythema scoring, as shown in **Table 13** & **Fig. 16.** During the observation period of 14 days, there was no erythema, dermal toxicity, gross pathological change, morbidity, or mortality in any of the treated animals; hence the topical formulations can be considered non-toxic. NAD-No abnormality was detected, as shown in **Fig. 16.**

TABLE 13: OBSERVATION OF SKIN IRRITABILITY STUDY ON RATS

Group	Animal No.	Clinical Sign	Mortality	Erythema Score
Initial dose100 mg/kg	1	NAD*	None	0
	2	NAD	None	0
	3	NAD	None	0
200 mg/kg	4	NAD	None	0
	5	NAD	None	0
	6	NAD	None	0
300 mg/kg	7	NAD	None	0
	8	NAD	None	0
	9	NAD	None	0

* NAD-No abnormality detected.

FIG. 16: SKIN IRRITABILITY STUDY ON RATS

Stability studies: After 2 months of storage, stability studies for the optimized formulation were performed, and solid lipid nanaoparticle gel was seen to be stable. During storage, there was no color, odor, or texture change, and no precipitate or drug crystals were discovered. The medication content of the optimized formulation did not vary much, as shown in **Table 14.**

TABLE 14: STABILITY STUDIES OF OPTIMIZED FORMULATION

Formulation	Appearance	pH value	Drug content
F4	White	6.3±0.032	91.21±0.53%

The final optimized formulation F4 was further evaluated to study the surface morphology, particle size, zeta potential, polydispersity index, *in-vivo*, and stability studies. The results of formulation evaluations indicated that the solid lipid nanoparticles were found to be spherical in shape. The particle size was determined to be 241.2nm, with a PDI of 0.379. The zeta potential result of -28.6mv demonstrated good stability of the formulation.

The skin irritation study confirmed the safety of Luliconazole-loaded nanoparticle-based gel for skin application. Luliconazole loaded-SLN gel treatment showed no indications of erythema or edema on the rat skin with primary irritation index (PII) of 0.0. A stability study of formulation F4 was performed, and appearance, pH, and drug content were evaluated after storage. It was found to be stable as no major change was observed in the results after keeping the formulations in the storage conditions. Statistical analysis was carried out using ANOVA and the results were proved to be statistically significant. The results are favorable and constitute a unique contribution of Luliconazole-SLN gel to topical drug delivery. This preliminary work provides a novel approach to improve skin targeting and allow a sustained release. The *in-vivo* characterization results support the function of solid lipid nanoparticle-based gel as a potential carrier for Luliconazole to achieve better therapeutic efficacy with low drug toxicity.

CONCLUSION: The present study would conclude with a series of experiments that Luliconazole loaded solid lipid nanoparticle-based gel would enhance the solubility, increasing the dermal bio-availability and providing a sustained release through the encapsulation in solid lipid nanoparticles. A series of characterization studies which showed uniform particle size in the nano range and a relatively mono-disperse distribution of PDI having a negative zeta potential, *in-vitro* and stability studies support the effective formulation of SLN as the safe and sustained release of drug over a time period. *An in-vivo* study showed no signs

indicating edema or erythema, suggesting that the prepared formulation would be safe and suitable for topical application. Statistical analysis tool ANOVA was selected to check the p-value and the significance, which resulted in a p-value of <0.0001, and the readings were found to be statistically significant. No major change was observed in stability studies after storing; hence, with the help of stability studies experimental data, it was proven to be stable formulations. As a result, the current investigation indicates that Luliconazole solid lipid nanoparticles-based gel can be effectively targeted to the skin to treat fungal infections.

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CONFLICTS OF INTEREST: No conflict of interest from the authors.

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