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Original Article

Design and Development of Antifungal Topical Gel Loaded with Solid Lipid Nanoparticles for Wound Healing

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ABSTRACT

Background: The topical administration of antifungal drugs by Solid Lipid Nanoparticles (SLNs) has enormous potential. This study aimed to develop a topical 5-flucytosine-loaded SLNs gel to improve the efficacy of the well-known antifungal drug in the treatment of wound healing. **Materials and Methods:** In order to create 5-flucytosine SLNs, a five-level, two-factor Central-composite design was used. Stearic acid and Poloxamer 407 concentrations of surfactants were chosen as independent factors, and particle size and %Entrapment Efficiency (%EE) were chosen as dependent variables. The produced 5-Flucytosine-SLNs were examined using SEM analysis, zeta potential, polydispersity index, and particle size measurements. Additionally, Carbopol 934 was used to incorporate the improved 5-Flucytosine-SLN formula into gel. **Results:** The outcomes demonstrated that 5-Flucytosine-SLNs had colloidal sizes with an essentially spherical shape and no aggregation. 5-Flucytosine-SLNs were discovered to have a particle size of 720.4 nm and an Entrapment Efficiency (EE) of 90.28%. The *in vitro* release, among other assessment criteria, was evaluated for the improved SLN gels. **Conclusion:** The study's conclusions imply that the topical gels made with 5-Flucytosine-loaded SLNs must be effective in the management of wound healing.

Keywords: 5-Flucytosine, Solid lipid nanoparticle, Central-composite design, Topical delivery, Optimization.

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INTRODUCTION

The diverse applications of Nanoparticles (NPs) across a range of biological, pharmacological, and medical fields have led to a high level of value in recent years. When seen structurally, they scarcely even approach 100 nm in size. Several drugs, including vaccines, tiny hydrophobic and hydrophilic chemicals, and biological molecules, can be controlled by these NPs.[1] NPs can be utilized as scaffolds for tissue engineering, for targeted medication delivery, and for disease diagnosis, among other things.[2] Nanoparticles (NPs) are frequently used as drug delivery systems, cellular scaffolds, carbon nanotubes, nanofibers, and nanocapsules. In order to successfully deliver a given drug at a precise time and place for maximal efficacy, it is imperative to manage particle size, surface characteristics, and other aspects of NP production as a drug delivery system.[3] In addition to being biocompatible and biodegradable, the NPs used for drug delivery should also have the following characteristics: prompt release, optimal mechanical properties, and ease of production. Surface modification enables the tracking of NPs that are ingested through phagocytosis or the circulatory system and then preserved in the circulatory system.[4]

SLNs are advantageous in many ways, including their low toxicity, ease of incorporation, ability to improve the bioavailability of lipophilic compounds, ability to stop the degradation of molecules sensitive to chemicals, light, moisture, and oxidation,

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ability to provide sustained drug release, and minimal negative effects of drug molecules that have been encapsulated. High pressure homogenization, solvent evaporation, and precipitation from both microemulsions and emulsions including organic solvents are the main manufacturing techniques utilized for the fabrication of lipid nano dispersions based on solid lipids. Triglycerides, stearic acid, waxes, and emulsifiers make up the majority of the structure of SLNs. Several approaches were taken into consideration while making SLNs, with the solvent emulsification/evaporation process described as being the most pertinent. As a result, an organic solvent that is water-miscible (like acetone) is used to dissolve the lipophilic substance. After the organic solvent has evaporated and the temperature of the medium has dropped to room temperature, the lipid-containing phase is then emulsified in a phase of water. The lipid hardens in the aqueous medium due to the solvent's evaporation, creating the nanoparticle dispersion.[5]

Fungal skin infections are one of the most prevalent dermatological issues nowadays. According to research, roughly 40 million people in developing and underdeveloped nations have fungal diseases. Onychomycosis and tinea have dermatophytes as one of their common causes. For the treatment of a fungus infection, both physicians and patients have a variety of options at their disposal, including liquid preparations as well as solid, semisolid, and liquid forms. Both the cosmetics and pharmaceutical industries have embraced the creams and transparent clear gels. Candida species is one of the fungus in charge of the most prevalent superficial cutaneous fungal infection. Systemic candidiasis can result from candida overgrowth in deeper tissues and blood when the immune system is compromised.

Greek in origin, dermatophyte is also known as a plant's epidermis. Three types of fungi called dermatophytes cause cutaneous illnesses in both humans and animals. Three types of asexual dermatophytes are recognized: Trichophyton, Microsporum, and Epidermophyton. These can result in a variety of illnesses, including Tinea corpora (ringworm of the body), Tinea faciei (facial ringworm), Tinea pedis (athlete's foot), and Tinea cruris (jock itch). The most prevalent and common group of mycoses are fungal infections of the skin and nails. Skin mycoses are currently one of the most prevalent types of infections, affecting more than 20–25% of the global population due to the high incidence of superficial mycotic infections that has increased in recent decades.[6]

Topical therapy modalities offer a number of advantages over alternative delivery methods, including non-invasiveness, usability, targeting infection areas, less side effects and interactions between drugs, increased patient compliance, and more cost treatment.[7] In comparison to oral pharmaceutical therapy, these properties make topical therapy an appropriate therapeutic option for superficial cutaneous fungal infections. Targeted skin areas can simply receive appropriate concentrations of antifungal medicines with topical therapy if drug release and penetration are sufficiently managed.[8,9] Moreover, topical antifungal delivery reduces drug-related side effects since significantly lower amounts of the medicines are produced in the blood. Higher oral doses are necessary to produce equivalent local drug concentrations in comparison to other treatment modalities, which may have negative implications. Oral administration is also connected to dangerous adverse effects, including serious liver damage, and medication interactions.[9-11]

MATERIALS AND METHODS

Materials

5-Flucytosine and Poloxamer 407 were obtained from Yarrow Chemicals, Mumbai. Stearic acid was purchased from Loba chemie Pvt. Ltd.

All other chemicals were made locally and were of the analytical variety. Carbopol and Triethanolamine were purchased from S.D. Fine Chem. Ltd, Mumbai, India.

Fourier transform Infrared Spectroscopy (FTIR)

FTIR spectra obtained with a Perkin Elmer FTIR Emission spectrometer has been studied for all the prepared samples and all the spectra components are recorded in the frequency range 4000 to 600 cm^{-1}. For this analysis, KBr pellets were employed.[12,13]

Powder x-ray Diffraction (XRD)

The XRD patterns of samples were obtained at room temperature using Cu-K radiation as the X-ray source and a Smart Lab X-ray diffractometer (Rigaku, Japan). 100 mA of current and 45 kV of voltage were applied. The samples were kept in a small glass container and scan at 2°/min with steps of 0.02°/sec from 2 to 10° to 50°.[12,13]

Methods

Preparation of solid lipid nanoparticles with 5-Flucytosine using lipid (stearic acid)

SLNs were created using a two-step process. In a round-bottomed flask, 300 mg of lipid and 200 mg of surfactant were merged and heated to 90°C to create a homogenous mixture. Hot water (25 mL at 90°C) and the drug were added to this hot melt combination while being magnetically stirred at a rate of 1200 rpm. To create a microemulsion of SLNs, the pre-emulsion was subjected to a pulsed mode of sonication for 15 min with pulse ON for 2 sec and OFF for 1 sec. The energy used was 10 million Joules and 40% amplitude (MJ) at 90°C. The hot-microemulsion was then brought to room temperature and kept at 4°C for storage. After 24 hr, the sample was centrifuged at 23000 rpm (5736xg) for 2 hr with a Thermo to remove excess surfactant, Electron LED GmbH model Sorvall LYNX 6000 was used. with a Whatman Anodisc 25 filter with a 20 nm pore size, and allowed to dry naturally at 40°C.

By adjusting the concentration of lipids, surfactants, and drugs, a number of samples were created. To ensure reproducibility, each experiment was run at least five times.[14]

Characterization of Prepared Solid lipid nanoparticles

Particle size and Zeta potential

Lite sizer (Anton Par, Nano Series ZS, UK) was used to measure the SLN particle size using photon correlation spectroscopy. To avoid aggregation, SLN were diluted before analysis and subjected to ultrasonication. At 25°C, at a fixed angle of 90°, the measurement was made in triplicate. Utilizing a Lite sizer (Anton Par, Nano Series ZS, UK), the zeta potential of SLN was determined. Prior to measurements, samples were diluted using a conducting solution.[15]

Determination of the entrapment efficiency percentage (EE%)

The entrapment efficiency % of each manufactured 5-Flucytosine SLN was estimated by assessing the amount of free drug present in the dispersion medium. Ultra-centrifugation was used to separate the free drugs from the formulation of the nano lipid dispersion. Here, a Remi cooling centrifuge (Mumbai, India) was used to centrifugate a nano lipid dispersion for 90 min. The resulting solution's clear supernatant was adequately diluted with water before being examined using an Ultraviolet (UV) spectrophotometer (Shimadzu 1800, Japan) at 285 nm. Equation (1) was used to determine the EE%.

$$EE\% = [(W_{initial}\ drug - W_{free}\ drug)/W_{initial}\ drug] * 100 \quad (1)$$

Where "$W_{initial\ drug}$" refers to the initial drug mass employed in the experiment and "$W_{free\ drug}$" refers to the free drug mass discovered in the supernatant following centrifugation of the aqueous dispersion.[16]

Surface morphology

Utilizing Field Emission Scanning Microscopy (FE-SEM), the surface morphology of the improved SLNs was investigated. A thin coating was created on the copper grid with carbon coating by dropping a drop of diluted SLNs dispersion onto it for FE-SEM examination. As samples were examined using H-7500 FE-SEM (Hitachi Ltd., Japan), the grid was air dried.[17]

Incorporation of optimized SLNs into gel base

To achieve the necessary viscosity for topical administration, a hydrogel was created. Optimally loaded 5-flucytosine SLNs were softly levigated in 0.25% Carbopol 934 gel, pre-hydrated for an overnight period, and Triethanolamine was then used to neutralize the reaction. The final gel has a 5-Flucytosine concentration of 0.25% (w/w) in it.

Evaluation of 5- Flucytosine SLN gel

Determination of pH

The SLN gel formulation the pH was measured with a calibrated pH meter. Three samples on average were used to take the readings.[18]

Spreadability

The spreadability of the gel was tested by spreading it in a circle on a glass plate that was 2 cm in diameter and previously marked, then testing it again on another glass plate. For five min, weight was applied to the second plate. After the gel had been distributed, the circle's diameter was measured. The gel's capacity to spread is indicated by the rise in diameter.[19]

Viscosity

Using a Brookfield viscometer, the viscosity of the solid lipid nanoparticle gel was measured. The gel's temperature was held constant at 25°C. The viscometer was attached to the Helipath T-bar Spindle No.05, which was then submerged in a beaker containing 25 g of SLN gel. The viscometer was run at various revs, and the reading in centipoises (cps) was recorded.[20]

Drug content estimation

7.4 Ph phosphate buffer was used to dilute 1 mL of 5-Flucytosine-loaded SLN carrying gel. It was ultracentrifuged for 30 min at 4°C at 4000 rpm, and then the vesicles were disrupted with the appropriate amount of water. Next, 1 mL of the supernatant liquid was taken, and appropriate dilutions were made. It was then analyzed by UV spectrophotometer at 285 nm, and the percentage of drug content could be calculated using the formula below.[21]

$$[\%\ drug\ content = practical\ drug\ content/theoretical\ drug\ content \times 100]$$

In vitro drug release studies

Franz diffusion cells and a dialysis membrane were used for *in vitro* diffusion research. In the donor compartment, 0.5 mg of 5-flucytosine-loaded SLN gel was added, while the recipient compartment received 30 mL of 7.4 pH PBS. At predetermined intervals, 1 mL aliquots of samples were taken from the sampling port. An identical volume of new dissolving medium was used to replace the samples that were removed. Measurements of means and standard deviations were made throughout the experiment in triplicate. Using a UV spectrophotometer, the samples were examined at 285 nm. It took 18 hr to complete the release study. Time was plotted against the total amount of medication released.[22]

RESULTS

FTIR Studies

The analysis of the 5-Flucytosine FTIR spectra revealed that the typical absorption peaks for C-H alkyne were at 2921.21 cm^{-1}, C=C aromatic was at 1468.81 cm^{-1}, Ar-O-CH3 was at 1227.81 cm^{-1}, C=O vibrations was at 1683.42 cm^{-1}, and CN and CC stretches were at 2921.21 cm^{-1}. This serves as more evidence of 5-Flucytosine's purity [Figure 1].

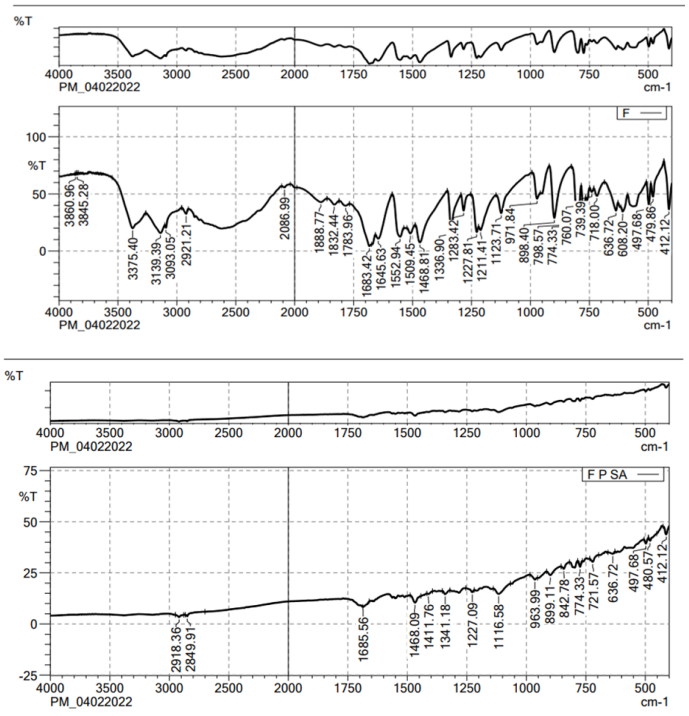

Figure 1: FTIR spectra of a) 5-Flucytosine and b) 5-Flucytosine+Poloxamer 407+Stearic acid.

XRD

The crystalline structure of the produced SLNs was examined using a powder X-ray diffraction technique the XRD patterns show the different peaks of the SLN formulation as well as the pure components [Figure 2].

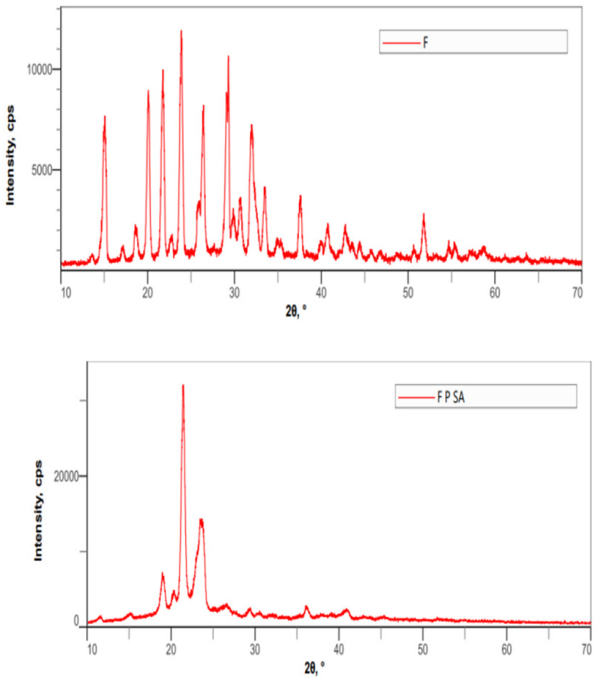

Figure 2: XRD spectra of a)5-Flucytosine b) F-P-SA.

Table 1: **Experimental runs projected and their responses.**

		Factor 1	Factor 2	Response 1	Response 2
Std	Run	A: Stearic acid (mg)	B: Poloxamer 407 (mg)	Particle size nm	EE %
3	1	150	400	631.8	65
1	2	150	100	720.4	99.45
7	3	250	37.868	673.2	85
2	4	350	100	719.5	91
9	5	250	250	733.7	87
13	6	250	250	733.7	84
10	7	250	250	733.7	85
5	8	108.579	250	735.6	96.746
6	9	391.421	250	764	89.295
8	10	250	462.132	633.7	59
12	11	250	250	733.7	87
4	12	350	400	735.4	76
11	13	250	250	733.7	86

Optimization of preparation of solid lipid nanoparticles

The central-composite Design was used to explore the impact of chosen variables and their interactions on the maximum and minimum PS. Table 1 shows the results of 13 experimental trails and their observed reactions. The %EE of experimental formulations was the amount of drug entrapped, was ranged between 65% to 99.45%, and PS, which will be identified in the range between 631.8nm to 764nm. To examine all of the experiment findings for specific reactions, the fx model and ANOVA were utilized [Figure 3].

Using the desirability function [D], you can optimize a variety of series of models obtained from experimental research. The overlay graph was created by adjusting each response to particle size and Entrapment efficiency from maximum to minimum. All of the variables that were chosen were included in the design space. The contour plot for the critical responses [Figure 4] was placed on the combined desirability plot for all answers, which revealed a maximum D value of 0.560 at optimal concentrations of independent variables [Figure 5].

Entrapment Efficiency

Solid lipid nanoparticle formulations with entrapment efficiencies ranging from 90.28% show higher EE than other surfactant formulations. Poloxamer 407 has the highest phase transition and is solid at normal temperature. Surfactant (Poloxamer 407) in the optimized formulation with lipid (stearic acid) showed the highest EE 90.28 (%).

Particle size

In order to determine the particle size of the prepared 5-Flucytosine-SLNs, a test was performed (Figure 6).720.4 nm was the size range of the particles. All of the 5-Flucytosine-SLNs that have been created have particle sizes that are less than 1000 nm, and as a result, they are all suitable for local and topical treatments, according to the results of the particle size analysis. According to the results, solid lipid nanoparticles made with a greater lipid and surfactant content have larger particle size.

Zeta potential

The magnitude of the zeta potential indicates the possible stability of the colloidal system. All of the particles will repel one another and exhibit dispersion stability if they have a strong negative or positive zeta potential. The zeta potential of the improved solid lipid nanoparticles was discovered to be -21.6 mV, indicating that the solid lipid nanoparticles produced were stable and did not aggregate (Figure 7).

Scanning electron microscopy

A formulation including 5-flucytosine, stearic acid, poloxamer407, and water was able to produce spherical, distinct spheres when it was made using the hot melt extrusion process, according to SEM. in Figure 8.

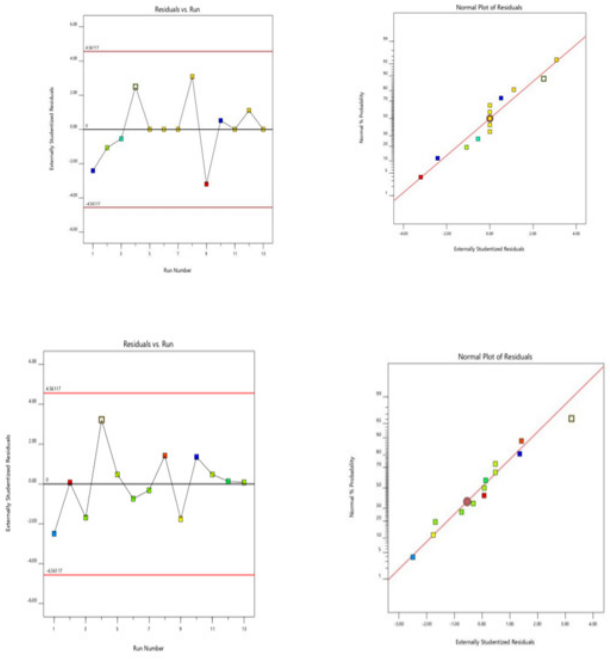

Figure 3: The residuals vs run and normal plot for PS and EE.

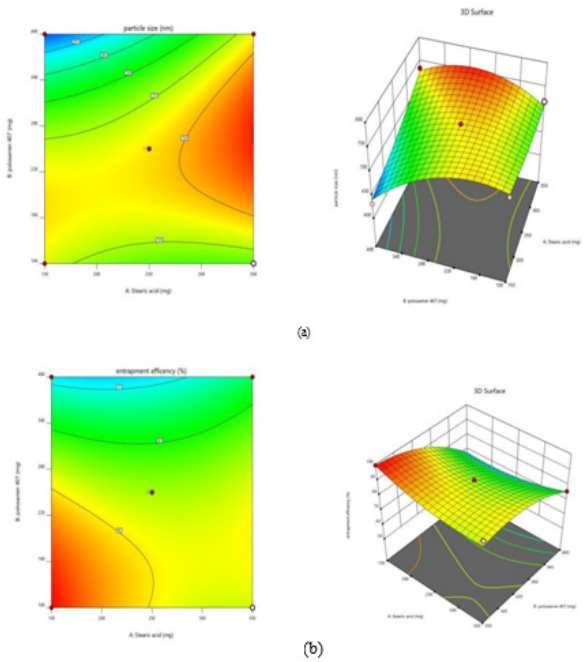

Figure 4: Contour and 3-D response surface graphs for a) PS and b) Entrapment efficiency.

Evaluation of 5-Flucytosine SLN Topical gel

pH determination

SLN-loaded topical gels' pH was measured using a pH meter that had been calibrated. The average of three samples served as the basis for the readings.

Spreadability

The spreadability rating suggests that a small amount of shear can easily spread the gel.

Viscosity and Rheological studies

The viscosity and rheological parameters of 5-Flucytosine SLN loaded topical gel were determined using spindle no. 5 on a Brookfield digital viscometer.

Drug content estimation

A UV spectrophotometer was used to estimate the drug content. Drug content of optimized formulation were found to be a 93.24±0.83% w/w, which represents good content uniformity.

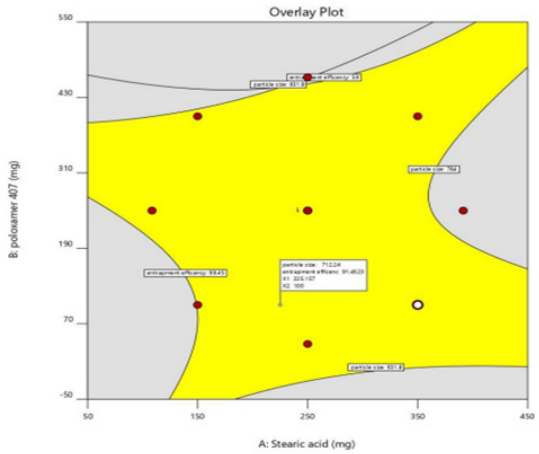

Figure 5: Overlay plot of optimized formula.

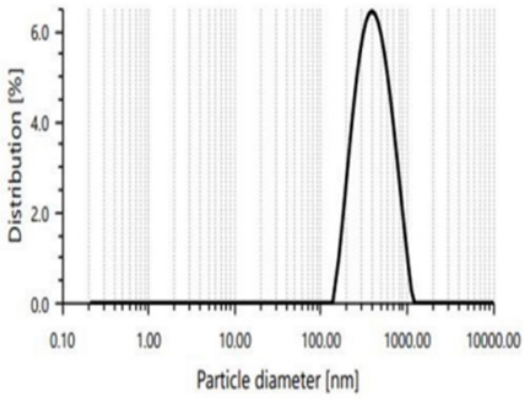

Figure 6: Particle size analysis.

In vitro drug release studies

Drug release studies are essential to predict the reproducibility of drug release rate and duration [Figure 9]. The importance of polymer dissolution on drug release from matrices has been known for ensuring the SLN topical gel drug release performance.

DISCUSSION

FTIR Studies

Drug and polymer compatibility was indicated by the presence of all the 5-Flucytosine characteristic peaks in the spectra of the drug and polymer mixture and drug physical mixture. The spectrum demonstrated that there has been no appreciable alteration to the drug's chemical composition. In all of the IR spectra, the functional group peaks of 5-Flucytosine remain unchanged.

XRD

The basic SLNs' XRD patterns revealed concentrations of pure lipid and surfactant. However, several of the 5-Flucytosine distinctive peaks were also seen in the drug-loaded SLNs, along with extremely strong stearic acid intensity peaks observed at 20-22°.This confirms the existence/ stability of lipid after formulation.

Optimization of preparation of solid lipid nanoparticles

Response 1: effect of independent variables on PS

The factor coding has been coded. Type III - Partial is the sum of squares. The model has an F-value of 52.82, indicating that it is

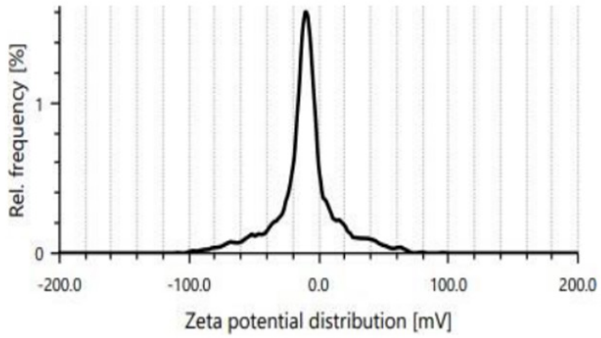

Figure 7: Zeta potential analysis.

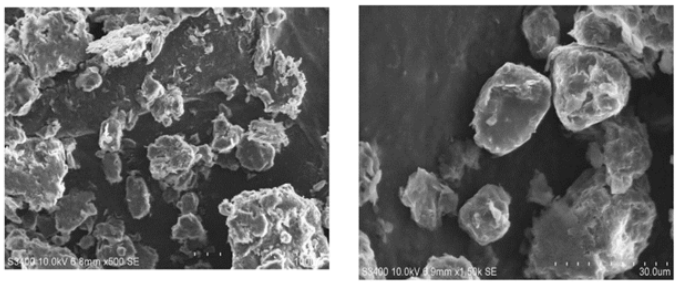

Figure 8: Scanning electron microscopy.

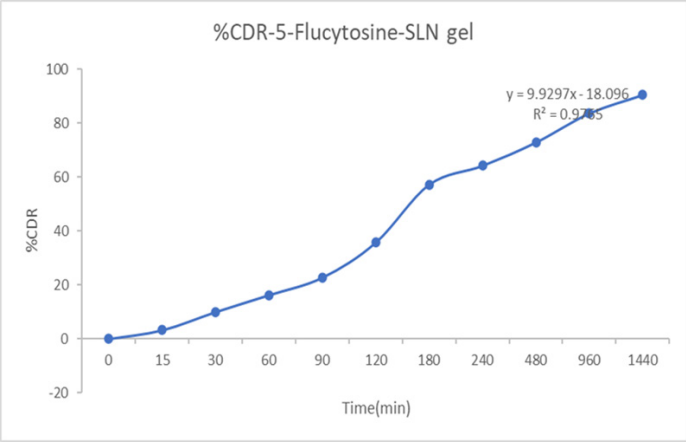

Figure 9: *In vitro* drug release profile of optimized formulation.

significant. There is barely a 0.01% possibility that an F-value this large may occur owing to noise. P-values less than 0.0500 suggest that model terms are significant. A, B, AB, A^2, B^2 are important model terms in this scenario. Values larger than 0.1000 imply that the model terms are not significant. Model reduction may improve your model if there are many inconsequential model terms (except those required to enable hierarchy).

$$PS = +733.70 +17.86\ A -16.07\ B +26.13\ AB +8.09\ A^2 -40.09\ B^2$$

Response 2: effect of independent variables on EE

The factor coding has been coded. Type III - Partial is the sum of squares. The model's F-value of 43.35 indicates that it is significant. There is barely a 0.01% possibility that an F-value this large may occur owing to noise. P-values less than 0.0500 suggest that model terms are significant. B, AB, A^2, and B^2 are important model terms in this scenario. Values larger than 0.1000 imply that the model terms are not significant. Model reduction may improve your model if there are many inconsequential model terms (not including those required to support hierarchy). The F-value of 8.19 indicates that the Lack of Fit is considerable. A large Lack of Fit F-value owing to noise is only 3.50% likely. We want the model to fit, so a significant lack of fit is undesirable.

$$EE = +85.80 -0.9984\ A -10.78\ B +4.86\ AB +3.70\ A^2 -6.81\ B^2$$

Using this method of desirability, a formulation produced a PS of 712.236 percent and an EE of 91.4498 percent. Using these projected ideal concentrations, a new formulation SLN was developed and tested. Theoretical and actual values were compared to validate the experimental design. The design was found to be accurate with less than 3% relative error.

Evaluation of 5-Flucytosine SLN Topical gel

The pH value of the 5-flucytosine SLN loaded topical gel's optimal formulation was 6.28±0.39 at 25°C, which is deemed to be within the acceptable range for topical preparations. The spreadability of topical gels based on carbopol was found to be in the range of 14.20±0.460 g.cm/sec, indicating that they can be applied to the skin's surface without much difficulty**.** The consistency of a gel system is determined by the solid fraction to liquid fraction ratio. The viscosity of 5-Flucytosine SLN loaded topical gel was found in the range of 31600 cps at 5 rpm. The drug releases from the 5-Flucytosine loaded SLN bearing topical gel were studied by subjected to *in vitro* drug release study for a period of 15min-24hr. The improved formulation had the greatest order of *in vitro* drug release data. The total percentage of drugs released in 24 hr was recorded. The drug release of 5-Flucytosine loaded SLN bearing topical gel was found to be 90.4% in 24 hr. The gel formulation including 5-flucytosine-SLN displayed much faster drug release till the end of 4 hr, followed by controlled release.

CONCLUSION

The characterization of 5-Flucytosine was analyzed by melting point analysis and FTIR. The results from the pre-screening study were implemented in the design of expert software by using central-composite design. Thirteen formulations F1 – F13 were prepared with varying amounts of lipid and Surfactant. The runs suggested by the software Design Expert® were prepared and were tested for two responses i.e., percentage entrapment efficiency and Particle size. This data was entered into Design Expert software and formulations were suggested depending upon the ranges entered and the selected design i.e., Central composite design. The design was analyzed and the responses measured were entrapment efficiency and Particle size. The one suggested optimized batch was selected. These were further validated. The validation was carried out by preparing the batches and observing the responses. A difference in predicted and experimental values. was recorded as the percent error which was within the range of ± 8%. SEM was used to examine the morphology of the optimized SLN formulation, ensuring the creation of nanoparticles. The particle size study revealed that the vesicle size average range was 720.4 nm. The drug entrapment efficiency of the SLN dispersion was analyzed the result was found to be 90.28% and the Zeta potential of optimized solid lipid nanoparticles was found to be -21.6mV which indicates that the produced solid lipid nanoparticles were stable with no agglomeration. The SLNs were then, loaded into topical gel The optimized SLN gels were studied for various evaluation parameters such as pH, spreadability, viscosity, *in vitro* release. By conducting an *in vitro* drug release analysis of the manufactured SLN gel, it was discovered that the SLN formulation had a more regulated release. Based on the various studies on SLN dispersion and SLN gel, it was possible to conclude that the optimized 5- Flucytosine loaded SLN gel was efficacious in treating wounds and may be further studied to convert it into a commercial product due to the enhanced antifungal activity.

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FUNDING

This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Grant No. 4584].CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SLN: Solid lipid nanoparticles; **EE:** Entrapment efficiency; **NPs:** Nanoparticles; **FTIR:** Fourier transform infrared spectroscopy; **XRD:** Powder x-ray diffraction.

SUMMARY

This study sought to harness the promising advantages of Solid Lipid Nanoparticles (SLNs) for the topical delivery of antifungal drugs, specifically 5-flucytosine. The objective was to create a gel formulation loaded with 5-flucytosine-loaded SLNs to enhance the effectiveness of this widely recognized antifungal medication in the context of wound healing. The preparation of the solid lipid nanoparticles was fine-tuned using optimization principles before incorporating them into topical gels. The resulting gel formulations underwent a comprehensive assessment of various attributes to demonstrate their efficacy.

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