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Design Formulation, Development and Optimization of Solid Lipid Nanoparticle Containing Fluconazole and Its Anti-Fungal Activity

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Abstract

though fluconazole is a commonly used triazole antifungal agent that works well against a variety of fungal infections, its low absorption and poor water solubility sometimes restrict its clinical performance. The present study aimed to design, develop, and optimize fluconazole-loaded solid lipid nanoparticles (SLNs) to enhance its antifungal efficacy. Using Tween 80 as the surfactant and stearic acid as the lipid, solid lipid nanoparticles were created by the solvent emulsification–evaporation method. Pre-formulation studies confirmed the purity, stability, and compatibility of fluconazole with selected excipients. The prepared SLN formulations were assessed for their "physical appearance, particle size, polydispersity index, zeta potential, drug entrapment efficiency, surface morphology, in vitro drug release, antifungal activity, and stability". The optimised formulation (SLNs-4) had the maximum entrapment efficiency of 94.76%, "a high negative zeta potential of −30.2 mV," suggesting strong colloidal stability, and a mean particle size of 164.27 nm. In vitro drug release studies demonstrated a sustained release pattern, while antifungal evaluation against Candida albicans showed enhanced inhibitory activity compared to conventional fluconazole. The physical stability of the formulation under accelerated circumstances was validated by stability studies. Overall, fluconazole-loaded SLNs represent a promising nanocarrier system for improving antifungal therapy by enhancing drug stability, controlled release, and therapeutic effectiveness.

Keywords; Fluconazole, Solid Lipid Nanoparticle, Antifungal, Triazole Antifungal Agent, Drug, Pre-Formulation Studies.

INTRODUCTION

Solid lipid nanoparticles (SLNs) have emerged as an advanced drug delivery system due to their ability to enhance drug solubility, stability, and bioavailability while minimizing toxicity (Uner *et al*., 2017). Prepared using physiologically compatible solid lipids, SLNs combine the advantages of traditional colloidal carriers with improved physical stability and controlled drug release characteristics (Duan et al., 2020). Their nanoscale size and lipid-based composition make them particularly suitable for topical and transdermal drug delivery applications (Sastri et al., 2020).

Fluconazole, a widely used antifungal agent, exhibits limitations such as poor aqueous solubility and reduced skin penetration when formulated using conventional dosage forms (Wu et al., 2021; Hernández- Esquivel et al., 2022). These drawbacks can compromise therapeutic efficacy, especially in topical treatments (Singh et al., 2022). Incorporation of fluconazole into SLNs offers a promising strategy to overcome these limitations by enhancing drug solubility, prolonging drug retention at the site of application, and improving permeation through the skin layers (Koroleva et al., 2022).

The lipid matrix of SLNs provides protection to the encapsulated drug from chemical degradation, while the nanoparticulate structure enables controlled and sustained drug release (Chevalier et al., 2022; Ghasemi et al., 2020).

Additionally, SLNs are biodegradable, non-toxic, and can be produced using scalable techniques, making them suitable for pharmaceutical development (Shah and Pathak 2010). Therefore, the formulation of fluconazole-loaded SLNs represents an effective approach to improve antifungal therapy by enhancing drug delivery performance, stability, and patient compliance)(Sastri et al., 2020).

DRUG PROFILE

Fluconazole

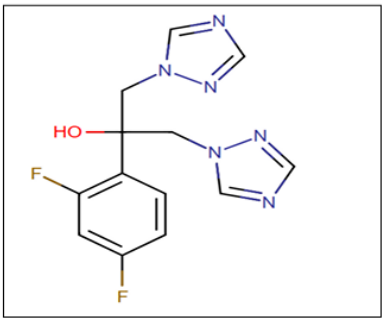

Figure 1: Fluconazole

(a). Weight: 306.2708
(b). Chemical Formula: C13H12F2N6O
(c). Synonyms

- Difluconazole
- Diflucan
- Fluconazole
- Fluconazol
- Triflucan
- Fluconazolum

(d). Background

The antifungal medication fluconazole, sometimes referred to as Diflucan, is used to treat superficial and systemic fungal infections in a range of tissues. The FDA gave it its first approval in 1990. This medication belongs to the same class of azole antifungals as itraconazole and ketoconazole. Among the numerous benefits of fluconazole over other antifungal medications is the possibility of oral administration. This drug has very few adverse effects. One dosage has been shown to be an effective therapy for vaginal yeast infections.

(i) Pharmacodynamics

It has been shown that fluconazole exhibits fungal static action against most strains of the following bacteria, curing fungal infections:

In order to cure fungal infections and accompanying symptoms, steroidal inhibition in fungal cells interferes with the manufacture and development of cell walls as well as cell adhesion.

(ii) Mechanism of action

The enzyme lanosterol 14-α-demethylase, which is reliant on fungal cytochrome P450, is highly selectively inhibited by fluconazole. The usual function of this enzyme is to change lanosterol into ergosterol, which is required for the formation of fungal cell walls. Lanosterol 14-α-demethylase's heme group contains a single iron atom that binds to the free nitrogen atom on the azole ring of fluconazole. By preventing oxygen activation, this stops the formation of ergosterol by inhibiting the demethylation of lanosterol. Fungal growth is therefore stopped when methylated sterols build up in the fungal cellular membrane. The fungal cell plasma membrane's structure and functionality are adversely affected by these accumulating sterols. A change in the quantity or activity of "the target enzyme (lanosterol 14-α-demethylase)", a change in the enzyme's accessibility, or both might result in fluconazole resistance. Research is still being done, and other processes could potentially be involved.

(iii) Protein binding

Fluconazole has a modest protein binding rate, estimated to be between 11 and 12%.

(iv) Metabolism

The liver metabolises fluconazole very little. Fluconazole is a CYP2C9, CYP3A4, and CYP2C19 inhibitor. When healthy participants received a 50 mg radiolabeled dosage of fluconazole, two metabolites were found in their urine: "a fluconazole N-oxide metabolite (2%), and a glucuronidated metabolite on the hydroxyl moiety (6.5%)". The same study found no evidence of fluconazole's metabolic cleavage, indicating a different metabolism from other drugs in the same medication class that undergo significant liver metabolism.

(v) Route of elimination

Fluconazole is mostly eliminated via renal excretion in healthy volunteers; around 80% of the dosage is found in the urine unaltered. Metabolites in the urine account for around 11% of the dosage. In one research, 93.3% of a 50 mg radiolabeled dosage of fluconazole was observed to be eliminated in the urine.

(vi) Toxicity

Overdose information

Overdoses of fluconazole have been linked to paranoia and hallucinations, sometimes in tandem. Use supportive therapy in overdose situations. Lavage of the stomach can be required. Other techniques like haemodialysis or forced diuresis could also be employed.

A note on liver toxicity

This medication has a risk of hepatotoxicity, according to the FDA label. There have been isolated but severe reports of severe liver toxicity, particularly in fluconazole users with significant underlying medical problems. When using fluconazole, this patient group is more likely to die. Patients exhibiting aberrant liver function test results during treatment require vigilant monitoring to detect the progression of hepatic injury. If fluconazole usage is considered to be the root cause of liver damage, it should be halted and medical help should be sought. Hepatotoxicity caused by fluconazole is typically reversible.

MATERIAL AND METHOD

The Material and Method section of a research study outlines the tools, chemicals, equipment, and experimental procedures used to conduct the investigation. It includes details about the materials such as active pharmaceutical ingredients (e.g., fluconazole), lipids, surfactants, solvents, and other excipients. It also describes the techniques and instruments employed for formulation, as well as the characterization methods like "particle size analysis, zeta potential measurement, drug entrapment efficiency, and in vitro drug release studies". This section ensures reproducibility by providing a clear and concise account of how the research was carried out.

Selection of drug and chemical

Table 1: List of chemical, List of glassware's, and List of instruments used

S. No.	Name of Chemicals	Company
1	Fluconazole	Devlife Corporation PVT. LTD.
2	Methanol	Rankem
3	Ethanol	Merck India Ltd. Mumbai, India
4	Acetonitrile	Merck India Ltd. Mumbai, India
5	Ethyl cellulose	Sigma eldrich
6	Carbopol 934	Sulab
7	Triethanolamine	Loba
8	Propylene glycol	Merck
9	Methyl paraben	Merck
10	Distilled water	Vizag Chemicals
	List of Glassware's	Type/Company
1.	Test tubes	Borocil
2.	Petri dishes	Borocil
3.	Glass rod	Borocil
4.	Beaker	Borocil
5.	Conical flask	Borocil
6.	Measuring cylinder	Borocil
7.	glass slide	Borocil
8.	Volumetric flask	Borocil
S. No.	**Name of Instrument**	**Company**
1	Electronic Weighing Balance	A & D Company HR 200
2	Mechanical Stirrer	Remi Motors, India.
3	Magnetic Stirrer	MC Dalal & amp; Co India
4	UV Visible Spectrophotometer	Shimadzu 1700
5	Stability Chamber	Inlab Equipments Madras PVT (LTD)

Pre-formulation studies of selected drug

Fluconazole's physicochemical characteristics, which are essential for creating a stable and efficient topical drug delivery system, were assessed by pre-formulation tests. These studies included assessment of organoleptic properties, solubility, pH, melting point, spectroscopic characterization, calibration curve preparation, and drug–excipient compatibility to support formulation design and quality assurance (Srinivasan et al., 2025).

1. **Organoleptic properties:** Fluconazole was evaluated for color, odor, and physical appearance by visual and sensory inspection. The drug was examined for uniformity, absence of discoloration, and any abnormal odor to confirm purity, stability, and suitability for topical formulation (Del Rosso et al., 2013).
2. **Solubility study of fluconazole:** Solubility was determined by adding a known quantity of fluconazole to different solvents such as water, ethanol, and methanol. The mixtures were stirred thoroughly and visually observed for clarity, undissolved particles, and any physical changes. The results helped identify a suitable solvent for further formulation development (Kumar and Rao 2022).
3. **pH determination of fluconazole:** A digital pH meter that had been calibrated was used to measure the pH of a diluted solution of fluconazole in

distilled water. The instrument was standardized using buffer solutions before analysis. The stabilized pH value was recorded to assess drug stability and compatibility with formulation excipients (Zuberi et al., 2023).

4. **Melting point determination:** The capillary tube method was used to find fluconazole's melting point. A tiny amount of the medication was put in a melting point equipment after being loaded into a capillary tube. The temperature at which the drug changed from solid to liquid was recorded to confirm purity and physical characteristics (Singh et al., 2022).

5. Spectroscopic analysis and calibration of fluconazole

(i) **Determination of λmax:** "Fluconazole (1 mg/mL)" was made into a stock solution in methanol. This led to the dilution of a workable solution at 100 µg/mL. The solution was scanned between 200–400 nm using a Shimadzu 1700 double-beam UV–Visible spectrophotometer to determine the wavelength of maximum absorbance (λmax) (Gupta et al., 2021).

(ii) **Standard calibration curve analysis:** The principal stock solution for calibration was made by dissolving "100 mg of fluconazole in methanol and diluting it to 100 mL". To create the working solution, 1 mL was diluted with 10 mL of methanol. Serial dilutions were prepared, and absorbance was measured at the identified λmax. The calibration curve was constructed using absorbance versus concentration data (Pontes-Quero et al., 2021).

6. **Preparation of calibration curve:** Working solutions of fluconazole at concentrations of 20, 40, 60, 80, 100, and 120 µg/mL were prepared by serial dilution. Absorbance of each solution was measured at λmax using methanol as blank. A linear calibration curve was obtained, confirming adherence to Beer–Lambert's law within the selected concentration range (Kumar et al., 2021).

7. **FT-IR spectroscopy of fluconazole:** FT-IR studies were conducted for pure fluconazole and its physical mixtures with selected excipients using the KBr pellet method. One milligramme of the sample and one hundred milligrammes of dry KBr were combined, dried, and then compressed into pellets. Spectra were recorded in the range of 4000–400 cm^{-1} to identify characteristic functional groups and to assess drug–excipient compatibility (Srisayam et al., 2014).

Preparation of Fluconazole containing Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLNs) loaded with fluconazole were made via solvent emulsification evaporation. Fluconazole and the selected solid lipid (either stearic acid or glyceryl monostearate) were dissolved in a mixture of ethanol and acetone (1:1), forming the organic phase. Then, under constant magnetic stirring at 70–80°C, this organic solution was introduced dropwise to an aqueous phase that had been heated and contained Tween 80 as a surfactant to create a coarse emulsion. To create a homogenous nanoemulsion, the emulsion was then homogenised at high speed and then probe sonicated to minimise droplet size. The organic solvents were evaporated under continuous stirring for 2–3 hours, "leading to the solidification of lipid and the formation of solid lipid nanoparticles". The resultant SLN dispersion was kept for further analysis and characterisation after being allowed to cool to ambient temperature.

Table 2: Composition of Solid Lipid Nanoparticles Formulation

S. No.	Formulate ion code	Flucon-azole (%)	Solid Lipid (Stearic Acid) (mg)	Tween 80 (Surfactant) (%)	Ethanol: Acetone (1:1) (ml)	Aqueous Phase (Water) (ml)	Stirring Time (hrs)
1	F1	1.0	300	1.0	5	10	3
2	F2	1.0	250	1.0	5	10	3
3	F3	1.0	200	1.0	5	10	3
4	F4	1.0	150	1.0	5	10	3
5	F5	1.0	100	1.0	5	10	3

Evaluation Parameters of Fluconazole-Containing Solid Lipid Nanoparticles

The fluconazole-loaded "solid lipid nanoparticles (SLNs)" were evaluated using various parameters to assess their physical characteristics, stability, and drug-loading efficiency. "The physical appearance of the SLNs" was examined by visual inspection to evaluate particle size, uniformity, color consistency, dispersion clarity, and the presence of aggregation or phase separation. These observations helped determine the physical stability and overall quality of the formulation (Penjuri et al., 2016). Dynamic light scattering (DLS) was used to assess "the particle size and polydispersity index (PDI)". After appropriately diluting the nanoparticle dispersion with distilled water, it was examined at room temperature. Particle size and PDI values provided information on size distribution uniformity and stability, which are critical for effective topical or transdermal drug delivery (Abbas et al., 2018).

A Malvern Zetasizer was used to measure the SLNs' zeta potential in order to assess their "surface charge and colloidal stability". Diluted samples were analyzed by laser Doppler velocimetry, and the recorded zeta potential values indicated the electrostatic stability of the nanoparticle system (Seema et al., 2015). The surface appearance and structural characteristics of the SLNs were investigated using scanning electron microscopy (SEM). Dried samples were sputter-coated with a thin conductive metal layer and examined under an electron beam. SEM images provided detailed information on particle shape, surface texture, and size distribution (Pandya et al., 2019).

By using methanol to break apart the SLNs and release the encapsulated fluconazole, the drug entrapment efficiency was calculated. The drug content was quantified using UV-Visible spectrophotometry, and the entrapment efficiency was calculated to assess the drug-loading capacity of the SLN formulation. The entrapment efficiency was calculated using the formula:

$$\textbf{Entrapment efficiency } \% = \frac{\textbf{Total drug conc.} - \textbf{Supernatant drug conc.}}{\textbf{total drug conc.}} \times \mathbf{100}$$

This approach offers a precise measurement of the amount of fluconazole effectively encapsulated within the solid lipid nanoparticles, ensuring reliable evaluation of the formulation's drug-loading efficiency (Krishna et al., 2021).

In Vitro Drug Release Study of Fluconazole-Loaded Solid Lipid Nanoparticles

Fluconazole-loaded solid lipid nanoparticles' in vitro drug release profile was evaluated by means of the dialysis bag diffusion technique. A dialysis bag holding a predetermined amount of the nanoparticle suspension was immersed in "a beaker filled with 100 millilitres of phosphate buffer solution (pH 7.4)". The apparatus was regulated to a temperature of 37 ± 2 °C with continuous agitation at 100 rpm employing a magnetic agitator to simulate physiological conditions. To maintain sink conditions, 2 mL aliquots were taken out of the release medium at scheduled times and quickly replaced with an equivalent volume of brand-new phosphate buffer. To measure the quantity of fluconazole released over time, the collected samples were appropriately diluted and subjected to "UV-visible spectrophotometry at 427 nm". To clarify the mechanism of drug release, "the release data were fitted to a number of kinetic models":

- **Zero-order model:** The rate of drug release is constant regardless of concentration.
- **First-order model:** The residual medication concentration determines the release rate.
- **Higuchi model:** Drug release follows a diffusion mechanism proportional to the square root of time.
- **Korsmeyer-Peppas model:** The drug release mechanism from the system of "polymeric solid lipid nanoparticles" is analysed using a log-log plot.

Anti-fungal Activity (Well Diffusion Assay)

(i) Sabouraud Dextrose Agar (SDA) medium Preparation

To prepare 100 mL of Sabouraud Dextrose Agar (SDA) medium, 6.5 grams of SDA powder were precisely weighed using a digital balance. In order to guarantee complete dissolving, the powder was added gradually while swirling in 100 mL of distilled water in a conical flask. The mixture was carefully heated on a hot plate with constant stirring until it became transparent, signifying "the complete dissolution of the components". After loosely covering the flask with a cotton stopper, the medium was autoclaved for 15 minutes at 121 °C and 15 pressure to sterilise it. The medium was aseptically transferred onto sterile petri dishes after being sterilised and allowed to cool to between 45 and 50 °C. The plates were left undisturbed to allow the agar to

solidify and then stored at 2–8 °C until needed (Aslan et al., 2023).

(ii) Well Diffusion Assay of Fluconazole-Loaded Solid Lipid Nanoparticles formulation against Candida albicans

After the preparation of Sabouraud Dextrose Agar (SDA) medium plates Well Diffusion Assay was performed. To guarantee equal growth, a sterile cotton swab was used to uniformly distribute a standardised "suspension of Candida albicans" throughout the agar's surface. "A sterile cork borer" was used to aseptically punch wells with a consistent diameter of 6 mm into the agar. Each well was filled with a specified volume of the Fluconazole-Loaded Solid Lipid Nanoparticles formulation. The plates were incubated at 28–30 °C for 24–48 hours. After incubation, the antifungal activity was assessed by measuring the diameter of the zone of inhibition around each well, indicating the extent of fungal growth inhibition by the formulation (Hashem et al., 2022).

Stability Studies

In accordance with ICH requirements, "the formulation of fluconazole-loaded solid lipid nanoparticles" was sealed and put through accelerated stability testing. The samples were stored under two specific environmental conditions: “25 ± 2 °C with 60 ± 5% relative humidity and 40 ± 2 °C with 70 ± 5% relative humidity”, for duration of three months. Stability evaluations were performed at scheduled intervals on days 30, 45, 60, and 90 to monitor changes in “key parameters such as particle size and entrapment efficacy”. These assessments were conducted to evaluate the physical stability of the formulation, ensuring that it maintained its consistency, quality, and effectiveness when exposed to stress storage conditions (Mundada and Borate 2025).

RESULTS AND DISCUSSION

Pre-formulation study of drug

Organoleptic properties

Table 3: Organolesptic properties and solubility study of Fluconazole

Drug	Organoleptic properties	Observation
Fluconazole	Color	White
	Odor	Odourless
	Appearance	Crystalline powder
	State	Powder
Drug	Solvents	Observation/Inference
Fluconazole	DMSO	Soluble
	Chloroform	Sparingly soluble
	Methanol	Freely soluble
	Ethanol	Soluble
	Water	Slightly soluble

Based on the results presented in Table 3, the organoleptic properties of fluconazole were found to be within acceptable and expected ranges for a pharmaceutically pure compound. The drug was observed to be white in color, odorless, and presented as a crystalline powder, confirming its solid-state characteristics. These findings indicate that the fluconazole sample used was of good quality, free from physical impurities or degradation. The absence of any unusual odor and the consistent powder form suggest chemical stability and suitability for further formulation development. Overall, these organoleptic characteristics support the drug's integrity and acceptability for pharmaceutical use.

Solubility study

The solubility study of fluconazole, as shown in Table 3, demonstrates its varying solubility across different solvents. Fluconazole was found to be freely soluble in methanol and soluble in both ethanol and DMSO, indicating good compatibility with organic solvents commonly used in formulation development. It showed sparing solubility in chloroform and was only slightly soluble in water, which is consistent with its known limited aqueous solubility. These results are important for selecting appropriate solvents during formulation, especially for enhancing drug solubility and bioavailability. To increase fluconazole's dispersion and therapeutic efficacy, sophisticated drug delivery methods such solid lipid nanoparticles are required due to its poor water solubility.

pH determination

Table 4: pH of Fluconazole

Drug	Observed	Reference
Fluconazole	pH	
	5.7	4.0 to 6.5
	Melting point	
	141°C	137°C to 142°C

The pH of the fluconazole solution was observed to be 5.7, as shown in Table 4, which falls within the acceptable reference range of 4.0 to 6.5. This indicates that the drug

maintains suitable acidic to slightly acidic properties, contributing to its chemical stability and compatibility with various formulation components. A pH of 5.7 is also favorable for topical applications, as it is close to the natural pH of the skin, reducing the risk of irritation.

Melting point

According to Table 4, "the measured melting point of fluconazole was 141 °C", which is within the stated standard range of 137 °C to 142 °C. This confirms the drug's identity and purity, as a sharp melting point within the standard range typically indicates the absence of impurities or degradation. Consistency with the reference range also suggests that the fluconazole sample used is pharmaceutically acceptable and stable, making it suitable for further formulation development.

Lambda max of Fluconazole

Table 5: Lambda max of fluconazole

S. No	Drug	UV absorption maxima (Lambda max)
1.	Fluconazole	259.0 nm

Double beam UV visible spectrophotometer (Shimadzu-1700) was used to determine the lambda max (absorption maxima) of a substance. The UV absorption maxima (λmax) of fluconazole was found to be 259.0 nm, as shown in Table 5. This value is consistent with previously reported data and confirms the proper identification of the drug through UV-Visible spectrophotometry. The λmax at 259 nm indicates strong absorbance in the UV region, which is suitable for the quantitative estimation of fluconazole in various formulations. This parameter is essential for developing accurate and reliable analytical methods for drug analysis and quality control.

Calibration curve of Fluconazole

Table 6: Calibration curve of fluconazole

Concentration (µg/ml)	Absorbance
20	0.232
40	0.341
60	0.439
80	0.529
100	0.636
120	0.745
Mean	**0.487**
SD	**0.189301**
%RSD	**38.87**

The absorbance values obtained for fluconazole at various concentrations showed a linear increase with concentration, indicating adherence to Beer-Lambert's law within the tested range (20–120 µg/mL). A strong connection between absorbance and concentration is shown in the calibration curve data, which is necessary for precise quantitative analysis.

The mean absorbance was calculated to be 0.487, with a standard deviation (SD) of 0.1893. However, "the percent relative standard deviation (%RSD) was found to be 38.87%", which is relatively high and suggests significant variability in the measurements. Ideally, a %RSD below 2% is preferred for analytical precision. The elevated %RSD may be due to experimental errors such as inconsistent dilution, cuvette cleanliness, or instrument fluctuations. Further refinement in the procedure is recommended to improve precision and ensure the reliability of the calibration curve for routine drug analysis. The drug's response exhibited a linear relationship across the investigated concentration range. "The linear regression equation" was determined to be $y = 0.0051x + 0.133$, with a correlation coefficient of $R^2 = 0.9992$.

Functional group identified by Infra-Red spectroscopy

Table 7: Interpretation of IR spectrum of Fluconazole

S. No.	Peak obtained	Reference peak	Functional group	Name of functional group
1	3449.95	3500-3400	N-H stretching	Primary amine
2	1623.95	1662-1626	C=C stretching	Alkene
3	1112.98	1124-1087	C-O stretching	Secondary alcohol
4	969.26	980-960	C=C bending	Alkene

The interpretation of the IR spectrum of fluconazole, as shown in Table 7, confirms the presence of key functional groups consistent with its known chemical structure. A strong peak observed at 3449.95 cm^{-1} corresponds to N-H stretching, indicative of a primary amine group. This aligns well with the reference range of 3500–3400 cm^{-1}.

The peak at 1623.95 cm^{-1} falls within the range for C=C stretching vibrations, confirming the presence of alkene groups in the structure. Additionally, a peak at 1112.98 cm^{-1} corresponds to C–O stretching, characteristic of secondary

alcohols, while the peak at 969.26 cm^{-1} represents C=C bending, further supporting the presence of alkenes.

Overall, the IR spectral data validate the structural integrity of fluconazole and confirm the presence of its functional groups, ensuring that the drug used in the study retains its chemical identity and has not undergone degradation or structural modification.

Characterization of fluconazole loaded Solid Lipid Nanoparticles formulation

Physical Appearance

Table 8: Physical Appearance Solid Lipid Nanoparticles SLNs formulation

Parameter	Observation
Color	White to a very pale color
Odor	Mild or absent
Appearance	Colloidal suspension
State	Liquid

The physical appearance of the fluconazole-loaded solid lipid nanoparticle formulation, as presented in Table 8, indicates desirable and acceptable characteristics. The formulation was observed to be white to very pale in color with a mild or no detectable odor, suggesting the absence of contamination or degradation. The appearance as a colloidal suspension and its liquid state confirm successful formulation of the nanoparticles in a stable dispersion. These physical attributes are important indicators of product quality, stability, and patient acceptability, particularly for topical or transdermal applications. The uniformity and clarity of the suspension also suggest proper nanoparticle formation without visible aggregation.

Particle size of Solid Lipid Nanoparticles formulation (SLNs)

Table 9: Particle size of Solid Lipid Nanoparticles (SLNs)

S. No	Formulation code	Particle size (nm)	PI Value %
1.	Particle size of SLNs 1	201.8 nm	23.6 %
2.	Particle size of SLNs 2	244.6 nm	34.5 %
3.	Particle size of SLNs 3	180.39 nm	25.1 %
4.	Particle size of SLNs 4	164.27 nm	24.3 %
5.	Particle size of SLNs 5	174.93 nm	28.2 %

According to Table 9's particle size study, all formulations of "fluconazole-loaded solid lipid nanoparticles (SLNs)" are within the nanometre range, with diameters ranging from 164.27 nm to 244.6 nm. These values are suitable for topical and transdermal drug delivery, as nanoparticles below 300 nm can enhance skin penetration and drug absorption.

Formulation SLNs 4 exhibited the smallest particle size (164.27 nm), suggesting a more efficient and stable dispersion. The polydispersity index (PI value), expressed as a percentage, ranged from 23.6% to 34.5%, indicating moderate uniformity in particle distribution. Although ideal PI values are typically below 20% for highly monodisperse systems, the observed values are acceptable for lipid-based nanocarriers and suggest a relatively homogeneous formulation.

Overall, the results demonstrate successful formation of “solid lipid nanoparticles” with appropriate size and distribution, which are critical parameters influencing the stability, release profile, and bioavailability of fluconazole in the final formulation.

Zeta potential of Solid Lipid Nanoparticles (SLNs)

Table 10: Zeta potential of Solid Lipid nanoparticles (SLNs) Formulation

S. No	Formulation code	Zeta potential (mV)
1.	Zeta potential of SLNs 1	-14.0 mV
2.	Zeta potential of SLNs 2	-21.4 mV
3.	Zeta potential of SLNs 3	-16.6 mV
4.	Zeta potential of SLNs 4	-30.2 mV
5.	Zeta potential of SLNs 5	-11.6 mV

The zeta potential values of the five solid lipid nanoparticle (SLN) formulations, as presented in Table 10, provide insight into “the surface charge and stability of the nanoparticles”. One important measure of colloidal stability is zeta potential; larger absolute values (positive or negative) often indicate better particle repulsion, which lowers the chance of aggregation. Among the formulations tested, SLNs 4 exhibited the highest negative zeta potential at –30.2 mV, indicating excellent electrostatic stability and suggesting it is the most stable formulation in terms of preventing particle aggregation. In contrast, SLNs 5 showed the lowest zeta potential at –11.6 mV, which may be insufficient to maintain long-term dispersion stability. The other formulations displayed intermediate values ranging

from –14.0 mV to –21.4 mV, indicating moderate stability. Overall, the results suggest that SLNs 4 is the most promising candidate with respect to zeta potential, likely contributing to better physical stability in suspension compared to the other formulations.

SEM analysis of Optimized formulation

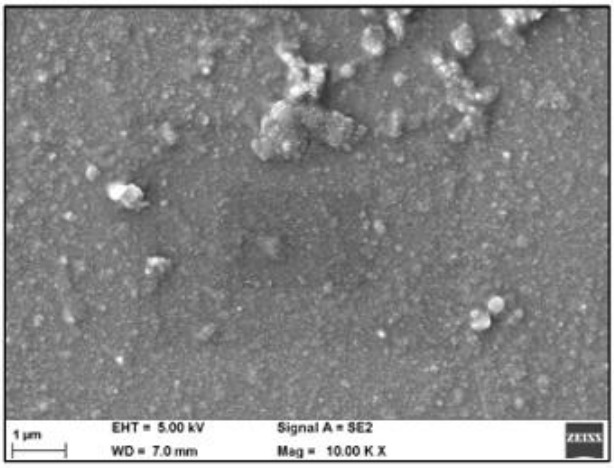

Figure 2: Scanning elsectron microscope (SEM)

The produced Solid Lipid Nanoparticles' (SLNs) surface shape and structural features were revealed by "the Scanning Electron Microscopy (SEM) investigation". At a magnification of 10,000x, the image allowed for visualization of the particle surface, shape, and distribution. The assessment helped to understand the quality of the formulation process, particularly the effectiveness of emulsification, sonication, and solvent evaporation steps in achieving a nanoscale particulate system. Observations from the SEM image are useful in evaluating parameters such as particle aggregation, surface smoothness, and uniformity, which are critical for determining formulation stability and performance. Furthermore, the morphological characteristics observed serve as supportive evidence for successful nanoparticle fabrication and are important for correlating with other evaluation parameters such as particle size analysis, zeta potential, and drug release behavior.

Entrapment efficacy

According to Table 11, the entrapment effectiveness of "solid lipid nanoparticles (SLNs)" loaded with fluconazole varied from 76.34% to 94.76%, demonstrating efficient drug encapsulation inside the lipid matrix. Among the formulations, SLNs4 exhibited the highest entrapment efficiency at 94.76%, suggesting optimal interaction between the drug and lipid components in this formulation. High entrapment efficiency is crucial for maximizing drug loading, reducing dosing frequency, and improving therapeutic effectiveness. Formulations such as SLNs3 (86.52%) and SLNs5 (81.46%) also demonstrated strong encapsulation capabilities, whereas SLNs2 showed the lowest efficiency (76.34%), which may be due to suboptimal lipid-drug compatibility or formulation conditions. Overall, the results reflect “the potential of SLNs as an effective delivery system for fluconazole”, with SLNs4 emerging as the most promising formulation based on its superior drug loading capacity.

Table 11: Entrapment efficacy of Solid Lipid Nanoparticles (SLNs) Formulation

S. No	Formulations	Entrapment efficacy (%)
1.	Entrapment efficacy of SLNs 1	79.68 %
2.	Entrapment efficacy of SLNs2	76.34 %
3.	Entrapment efficacy of SLNs3	86.52 %
4.	Entrapment efficacy of SLNs4	94.76 %
5.	Entrapment efficacy of SLNs5	81.46 %

In Vitro drug release study

Table 12: In-vitro drug release studies

Time (hrs)	Cumulative % Drug released	% drug remaining	Square root time	Log cumulative % drug remaining	Log time	Log cumulative % drug released
0	0	100	0.000	2.000	0.000	0.000
1	21.87	78.13	1.000	1.893	0.000	1.340
2	32.45	67.55	1.414	1.830	0.301	1.511
4	43.85	56.15	2.000	1.749	0.602	1.642
6	54.33	45.67	2.449	1.660	0.778	1.735
8	65.77	34.23	2.828	1.534	0.903	1.818
10	76.52	23.48	3.162	1.371	1.000	1.884
12	87.66	12.34	3.464	1.091	1.079	1.943
15	97.98	2.02	3.873	0.305	1.176	1.991

Table 13: Correlation value (R2 value)

Formulation	Model	Kinetic parameter values
SLNs Formulation	Zero Order	$R^2 = 0.957$
	First Order	$R^2 = 0.801$
	Higuchi	$R^2 = 0.991$
	Korsmeyerpeppas	$R^2 = 0.629$

Over a 15-hour timeframe, the in vitro drug release investigation using fluconazole-loaded SLNs showed "a sustained and controlled release profile", with a cumulative drug release of around 97.98% by the research's conclusion. The release mechanism was ascertained by fitting the release data into a variety of kinetic models. Among the evaluated models, the Higuchi model demonstrated "the highest correlation coefficient ($R^2 = 0.991$)", indicating that the drug release was governed by a diffusion-controlled mechanism within the matrix system. Strong correlation was also demonstrated by the Zero Order model (R2 = 0.957), suggesting a nearly constant release rate that is unaffected by drug concentration—a desirable property for sustaining long-term therapeutic doses. In contrast, the First Order model ($R^2 = 0.801$) and Korsmeyer-Peppas model ($R^2 = 0.629$) demonstrated lower correlation values, suggesting that the release was not purely concentration-dependent nor governed by anomalous transport. These results confirm that the formulated SLNs effectively sustained the release of Fluconazole through a matrix diffusion mechanism, which may enhance the drug's bioavailability and reduce dosing frequency for topical or systemic applications.

Results of anti-fungal activity of Solid Lipid Nanoparticles formulation

Anti-fungal activity of SLNs

Table 14: Anti-fungal activity of SLNs against Candida albicans fungus

S. No.	Sample Name (mg/ml)	Zone of Inhibition (mm) Of *Candida albicans*
1.	Control (C)	0 mm
2.	SLNs (0.50 mg/ml) (C1)	3.6 mm
3.	SLNs (1 mg/ml) (C2)	6.4 mm
4.	SLNs (1.5 mg/ml) (C3)	10.7 mm

Figure 3: Anti-fungal activities of Solid Lipid Nanoparticles (SLNs) against Candida albicans fungus

Table 14 shows that the antifungal activity of "solid lipid nanoparticles (SLNs)" loaded with fluconazole against Candida albicans is clearly concentration-dependent. The control sample (without drug) showed no zone of inhibition, confirming that the observed antifungal activity was due to the drug-loaded SLNs.

The SLNs showed "a moderate zone of inhibition of 3.6 mm" at a dosage of 0.50 mg/mL (C1). This increased to 6.4 mm at 1 mg/mL (C2) and reached a maximum of 10.7 mm at 1.5 mg/mL (C3). The progressive increase in the zone of inhibition with increasing concentration suggests that higher drug loading within the SLNs enhances the release and availability of fluconazole at the site of infection.

These results confirm the effectiveness of SLNs in delivering fluconazole for antifungal therapy and support their potential as a controlled-release topical formulation. The improved activity at higher concentrations also indicates that the formulation retains the therapeutic efficacy of the drug while offering the added benefits of a nanocarrier system, such as sustained release and improved skin penetration.

Stability study

Over the course of 90 days, the optimised solid lipid nanoparticle (SLN) formulation was subjected to two

distinct storage conditions: "25 ± 2 °C/60 ± 5% RH and 40 ± 2 °C/70 ± 5% RH". Particle size and entrapment effectiveness both were comparatively constant throughout the trial, with only little variations noted, according to the data shown in Table 22. At 25 °C, the particle size varied slightly from the initial 164.27 nm to 163.61 nm at 90 days, while entrapment efficiency remained consistently high, ranging from 94.76% to 94.78%. Similarly, under the accelerated condition of 40 °C, particle size showed minor variation (from 164.27 nm initially to 165.54 nm at 90 days), and entrapment efficiency remained between 94.67% and 94.84%. These little modifications imply that "the SLN formulation" exhibits good chemical and physical stability during both rapid and long-term storage circumstances. The consistent particle size and high entrapment efficiency over time indicate that the formulation maintains its structural integrity and drug-holding capacity, making it a promising candidate for further development and commercialization.

Table 15: Stability Study of optimized formulation (Solid Lipid Nanoparticles)

S. No.	Time (Days)	250C±2 0C and 60 ± 5% RH		40^0C±2 ^{0}C and 70 ±5% RH	
		Particle size (nm)	Entrapment efficiency (%)	Particle size (nm)	Entrapment efficiency (%)
1.	0	164.27 nm	94.76 %	164.27 nm	94.76 %
2.	30	160.34 nm	94.65 %	163.42 nm	94.83 %
3.	45	166.21 nm	94.53 %	159.37 nm	94.67%
3.	60	164.45 nm	94.71 %	167.23 nm	94.72 %
4.	90	163.61 nm	94.78%	165.54 nm	94.84 %

SUMMARY AND CONCLUSION

The pre-formulation studies of fluconazole confirmed its pharmaceutical suitability and stability. The drug exhibited acceptable organoleptic properties (white, odorless, crystalline powder) and a melting point (141 °C) within the standard reference range, indicating high purity. Its pH (5.7) was appropriate for skin application, and functional group analysis via FTIR verified its structural integrity. Fluconazole showed high solubility in “organic solvents like methanol, ethanol, and DMSO, but poor aqueous solubility”, justifying the need for lipid-based delivery systems to enhance bioavailability. UV spectroscopy revealed a λmax at 259 nm, enabling reliable drug quantification, although the calibration curve showed high %RSD, suggesting the need for method refinement. “Solid lipid nanoparticles (SLNs)” were successfully developed to enhance fluconazole delivery. Among the five formulations, SLNs4 consistently outperformed others, with the smallest particle size (164.27 nm), the highest zeta potential (–30.2 mV), and maximum entrapment efficiency (94.76%). SEM analysis confirmed the spherical, porous morphology of the nanoparticles. SLNs4 exhibited sustained release behaviour in in vitro drug release tests, with zero-order kinetics (R2 = 0.957) indicating regulated release over time. The antifungal efficacy of SLNs increased with concentration, demonstrating a clear dose-dependent inhibition of Candida albicans, further supporting the effectiveness of the formulation. The optimised formulation was confirmed to be physically and chemically stable after 90 days of stability testing, which revealed negligible "changes in particle size and entrapment efficiency at ambient temperature and under accelerated circumstances".

The formulation and evaluation of “fluconazole-loaded solid lipid nanoparticles (SLNs)” successfully addressed the drug’s solubility limitations and improved its delivery potential. The optimized formulation, SLNs4, emerged as the most effective, exhibiting excellent physical characteristics, high drug entrapment, and robust stability. Its sustained, zero-order drug release profile and significant antifungal activity indicate strong potential for controlled topical or transdermal antifungal therapy. These results provide credence to the viability of SLNs as a viable nanocarrier technology for improving fluconazole's stability and therapeutic efficacy. It is advised to do more in-vivo research and scale up the formulation to confirm its commercial potential and clinical usefulness.

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