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PREPARATION AND EVALUATION OF LULUCANZOLE AND POSACUNAZOLE NANOEMULGEL

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Abstract

This study investigates the preparation and evaluation of Luliconazole and Posaconazolenanoemulgel formulations, aimed at enhancing the topical delivery and efficacy of these antifungal agents. Luliconazole and Posaconazole were incorporated into nanoemulsions and subsequently converted into gels using Carbopol 934. The formulations were characterized through various preformulation studies, including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM) to ensure compatibility and stability. Nanoemulgel formulations were evaluated for their appearance, pH, drug content, viscosity, spreadability, and in vitro drug release.FTIR analysis confirmed the presence of characteristic functional groups for both drugs, while DSC thermograms indicated their crystalline nature with distinct melting points. SEM images revealed the crystalline morphology of the drugs. The nanoemulgel formulations, F1 (Luliconazole) and F2 (Luliconazole), demonstrated clear and slightly cloudy appearances, respectively, with pH values ranging from 6.5 to 7.1, suitable for skin application. The drug content was high across all formulations, ranging from 95.8% to 98.5%. Viscosity and spreadability tests indicated moderate to high consistency and ease of application. In vitro drug release studies showed that Formulation F2 provided the highest cumulative drug release of 98.4% at 8 hours, outperforming others. Antifungal efficacy, evaluated through inhibition zones, indicated that the standard formulation was more effective than the tested nanoemulgels against various fungal strains. These results suggest that the optimized nanoemulgel formulations offer a promising approach for improved topical antifungal therapy.

Keywords: Luliconazole, Posaconazole, nanoemulgel, antifungal, drug delivery, formulation, characterization, in vitro release.

Introduction

Fungal infections represent a critical and pervasive health issue, especially among immunocompromised patients, the elderly, and those with chronic diseases such as diabetes and cancer.[1,2] The prevalence of these infections underscores the need for effective antifungal therapies. Traditional antifungal treatments, although effective, frequently face limitations including poor bioavailability, systemic toxicity, and inadequate penetration to the site of infection, leading to suboptimal therapeutic outcomes. These challenges are particularly pronounced in topical formulations where drug delivery is crucial for local effectiveness.[3,4]

Luliconazole and Posaconazole are prominent antifungal agents used for the treatment of various dermatophyte and fungal infections. Luliconazole is known for its efficacy against dermatophytes and yeast infections, while Posaconazole offers broad-spectrum activity, including against invasive fungal infections. Despite their clinical importance, these agents are often limited by their poor skin permeability and suboptimal drug release when used in conventional topical formulations. The issue of effective drug delivery is compounded by the need for prolonged drug action at the infection site, which is not always achieved with existing formulations. [5,6]

Nanoemulgel systems have emerged as a novel approach to address these challenges. These formulations combine nano-sized emulsion droplets with a gel matrix, providing a means to enhance the solubility, stability, and permeation of the drug through the skin. The nanoemulsion component facilitates improved drug dispersion and deeper skin penetration, while the gel matrix aids in prolonged drug release and localized action. This dual mechanism could potentially overcome the limitations of conventional topical antifungal therapies, offering enhanced efficacy and reduced systemic side effects.[7,8]

Although the potential of nanoemulgel formulations has been demonstrated for various drugs and therapeutic areas, there is a marked paucity of research focusing specifically on Luliconazole and Posaconazole. Current literature predominantly addresses general applications of nanoemulgels, without delving into the optimization of these systems for specific antifungal agents. There is a significant need for studies that explore the development of nanoemulgel formulations tailored for Luliconazole and Posaconazole, with an emphasis on optimizing parameters such as drug release rates, stability, and penetration efficiency.[9,10]

Furthermore, comparative research evaluating the performance of these nanoemulgel formulations against standard topical antifungal treatments remains limited. Such studies are essential to determine the relative advantages of nanoemulgel systems over conventional therapies in terms of efficacy, safety, and patient compliance. Addressing these research gaps could provide critical insights into the potential of nanoemulgels to enhance the treatment of fungal infections and improve therapeutic outcomes for patients.

Materials and methods

Luliconazole and Posaconazole were obtained from Orex Pharma Pvt. Ltd. Thane (West), Maharashtra. India. Polysorbate 80, Carbopol 940, and other excipients were purchased from Sigma-Aldrich, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade and were procured from Merck, Mumbai, India.

Pre formulation Studies

Preformulation Studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to identify the functional groups and confirm the compatibility of the drug with excipients. The spectra of Luliconazole, Posaconazole, and physical mixtures with

excipients were recorded using an FTIR spectrophotometer (Model: IRTracer-100, Manufacturer: Shimadzu, India). Samples were prepared by mixing with potassium bromide and compressed into pellets. The spectra were recorded in the range of 4000-400 cm^-1.[12]

Calorimetry Measurement using Differential Scanning (DSC)

The drug's thermal characteristics and excipient compatibility were studied using DSC. The DSC equipment, made by Shimadzu in India (Model: DSC-60 Plus), was used to do the thermal analysis. Precisely weighed and sealed in metal pans were samples ranging from 2 to 5 milligrams of pure pharmaceuticals, excipients, or physical combinations of these. Over a temperature range of 25-300°C, the analysis was carried out in a nitrogen environment with a heating rate of 10°C/min.[13]

Structural electron microscopy

The surface morphology of both the pure medicines and the produced nanoemulgel were studied using scanning electron microscopy (SEM). After adhering the samples on aluminum stubs with double-sided adhesive tape, a sputter coater (JEOL, India, Model: JEC-3000FC) was used to apply a thin layer of gold under vacuum. Using a scanning electron microscope (JEOL, India, Model: JSM-IT200) with an accelerating voltage of 15 kV, the pictures were obtained. [14]

Formulation of nanoemulgel

We used Carbopol 934 in a range of doses to gelify the optimized nanoemulsion formulation, which we then subjected to a battery of tests. Carbopol 934 was dissolved in the specified amount of water to create the nanoemulsion-based gel. Carbopol 934 was allowed to fully swell in the dark for 24 hours after dispersal. An improved formulation comprising either luliconazole or posaconazole was combined with the carbopol solution. To get a uniform solution, the ingredients were mixed by stirring. A homogenous gel was achieved by adding the correct amount of triethanolamine to maintain the pH while stirring continuously. [15,16]

Table 1: composition of nanoemulsion gel

Ingredients	F1	F2	F3	F4
Lulicanazole Nano emulsion	25 ml	25 ml	-	-
Posaconazole Nano emulsion	-	-	25 ml	25 ml
Carbapol 934	2.5 gm	2.5 gm	2.5 gm	2.5 gm
Water	20 ml	20 ml	20ml	20 ml
Glycerin	2.5 ml	2.5 ml	2.5 ml	2.5 ml
Triethanolamine	Q.s	Q.s	Q.s	Q.s

Evaluation of Nanoemulgel

Appearance:

The appearance and clarity of the nanoemulgel were assessed visually to ensure there were no visible particulates or phase separation, confirming the formulation's uniformity and quality.[17]

pH:

The pH of each nanoemulgel batch was measured using a digital pH meter. Prior to measurement, a 5% (w/v) dilution of the nanoemulgel was prepared using phosphate-buffered saline (PBS) at pH 7.4 to simulate the conditions under which the pH is measured.[17]

% Drug Content:

To determine the drug content, 2 g of the nanoemulgel was dissolved in 10 ml of ethanol in a 100 ml flask and stirred using a magnetic stirrer for 5 minutes. The solution was then filtered through Whatman filter paper. The absorbance of the filtered solution was measured using a UV-Visible spectrophotometer (Model: UV-1800, Manufacturer: Shimadzu, India) to calculate the percentage of drug content present in the nanoemulgel.[18]

Determination of Viscosity:

The viscosity of the nanoemulgel was measured by taking 20 g of the formulation and testing it with a Brookfield viscometer (Model: DV-E, Manufacturer: Brookfield Engineering, India), using spindle no. 6 and operating at 50 RPM to evaluate the flow properties and consistency of the gel.[18]

Spreadability:

To assess Spreadability, 5 g of the nanoemulgel was placed between two glass slides and a specified weight was applied to the top slide. The distance covered by the sample in a given time was measured, with better spreadability indicated by a shorter time interval, calculated using the formula: $S = M \cdot L/T$, where S is the spreadability, M is the weight applied, L is the distance traveled, and T is the time taken.[19]

In Vitro Drug Diffusion Study:

The drug diffusion from the nanoemulgel was investigated using a Franz diffusion cell with a cellophane membrane. A 0.5 g sample of the gel was placed in the membrane and immersed in

250 ml of 25% ethanolic phosphate buffer (pH 7.4) maintained at 37±1°C. At specific intervals (1, 2, 3, 4, 5, 6, 7, and 8 hours), 5 ml samples were withdrawn and replaced with an equal volume of fresh medium. The samples were analyzed using a UV-visible spectrophotometer at 425 nm to determine the amount of drug diffused.[20]

Stability Study:

For stability testing, the nanoemulgel was stored in collapsible tubes with proper sealing and subjected to accelerated conditions of 40±2°C and 75±5% relative humidity as per ICH Guidelines. The formulation was periodically examined for physical stability, including changes such as phase separation or drug precipitation. Additionally, drug content and in vitro diffusion characteristics were evaluated at various time points to assess formulation stability over time.[21]

Results and discussion

Pre-formulation Studies

Infrared Spectroscopy (FTIR)

In order to determine whether functional groups were present in luliconazole and posaconazole and to evaluate the possibility of interactions with excipients, FTIR analysis was performed.

FTIR of Luliconazole

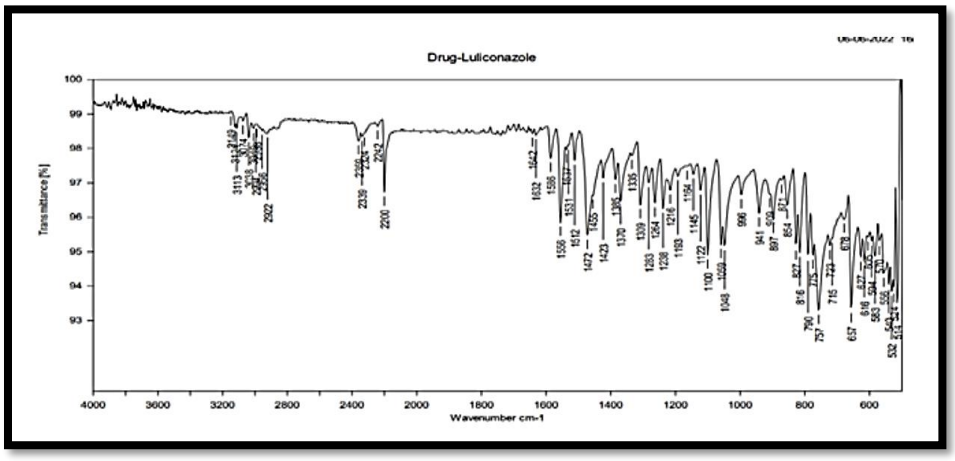

Fig 1: FTIR of luliconazole

The FTIR spectrum of Luliconazole showed characteristic peaks at specific wavenumbers corresponding to its functional groups:

- A sharp peak at 1600 cm^-1 indicating the presence of a carbonyl group (C=O).
- Peaks at 1400-1500 cm^-1 corresponding to C=C stretching vibrations.
- Peaks in the range of 2800-3000 cm^-1 representing C-H stretching vibrations.

FTIR of Posaconazole

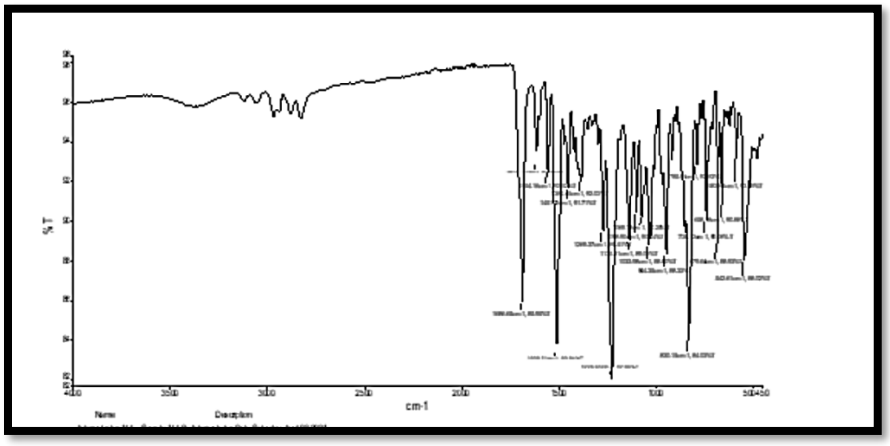

Fig 2: FTIR of posaconazole

The FTIR spectrum of Posaconazole exhibited distinct peaks at:

- A prominent peak at 1620 cm^-1 indicative of a carbonyl group (C=O).
- Peaks at 1450-1550 cm^-1 corresponding to aromatic C=C stretching.
- Peaks around 2900 cm^-1 representing C-H stretching vibrations.

Differential Scanning Calorimetry (DSC)

DSC was used to evaluate the thermal behavior of Luliconazole and Posaconazole, providing insight into their melting points and potential interactions with excipients.

DSC of Luliconazole API

The DSC thermogram of Luliconazole showed a sharp endothermic peak at approximately 151°C, corresponding to its melting point. This indicates the crystalline nature of Luliconazole.

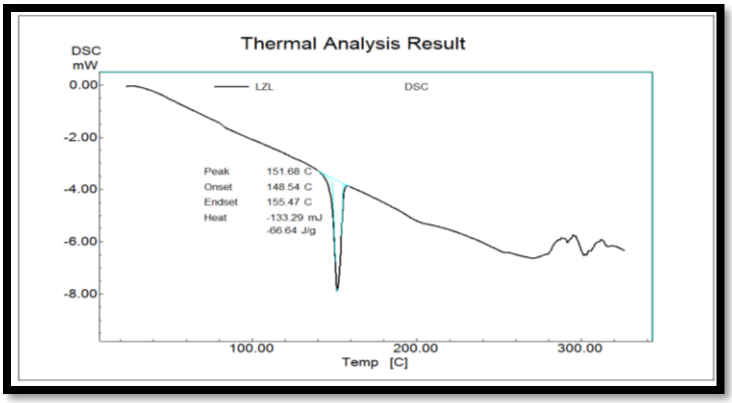

Fig 3: DSC of Luliconazole API

DSC of Posaconazole API

The DSC thermogram of Posaconazole displayed an endothermic peak at around 166°C, representing its melting point. This confirms the crystalline nature of Posaconazole

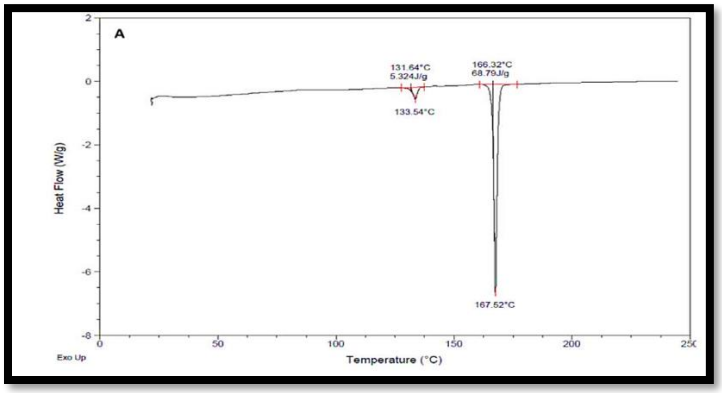

Fig 4: DSC of Posaconazole API

SEM(Scanning Electron Microscopy)

Using scanning electron microscopy (SEM), the surface morphology of the pure medications posaconazole and luliconazole was examined.

SEM of Luliconazole API

The SEM images of Luliconazole revealed a crystalline structure with well-defined edges and uniform particle size distribution.

Fig 5: SEM of Luliconazole API

SEM of Posaconazole API

The SEM images of Posaconazole showed a crystalline morphology with irregularly shaped particles and a relatively uniform size distribution.

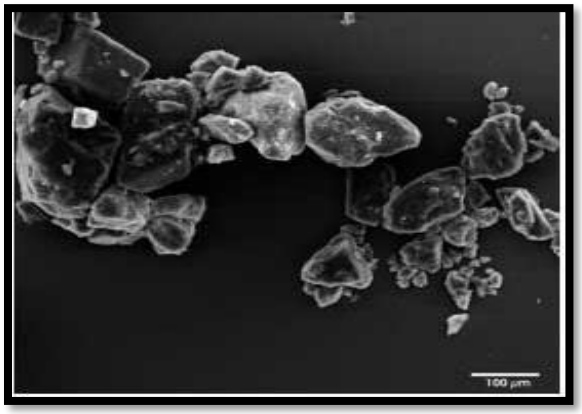

Fig 6: SEM of Posaconazole API

Appearance

The appearance of the nanoemulgel formulations was carefully observed. **Formulation F1 (Luliconazole)** displayed a clear gel, indicating a well-formulated emulsion system with a homogeneous distribution of the nanoemulsion. The clarity suggests minimal particle aggregation, which is desirable for consistent drug release and aesthetic appeal. **Formulation F2 (Luliconazole)** appeared slightly cloudy, which may be due to a higher concentration of Carbopol 934 or incomplete dispersion of the nanoemulsion. Despite the slight cloudiness, F2 maintains acceptable properties for topical application. **Formulation F3 (Posaconazole)** also

exhibited a clear gel appearance, indicating a stable nanoemulsion with good particle size distribution and minimal aggregation. Similar to F2, **Formulation F4 (Posaconazole)** appeared slightly cloudy, potentially due to formulation processes or ingredient interactions. However, this cloudiness does not significantly impact its suitability for topical use.

pH

The pH of the nanoemulgel formulations was measured to ensure skin compatibility. **Formulations F1 (pH 6.8) and F3 (pH 6.5)** had slightly acidic pH values, aligning well with the skin's natural pH (around 5.5-6.5). This alignment ensures minimal irritation and compatibility with the skin. **Formulations F2 (pH 7.1) and F4 (pH 7.0)** had slightly alkaline pH values, but still within the acceptable range for topical formulations. Proper pH adjustment in these formulations ensures drug stability and efficacy while maintaining skin compatibility. Overall, the pH values across all formulations are within an acceptable range for topical application, indicating that they are unlikely to cause skin irritation and are compatible with the skin's natural pH balance.

Table 2: Appearance and pH

Formulation	Appearance	pH
F1	Clear gel	6.8
F2	Slightly cloudy gel	7.1
F3	Clear gel	6.5
F4	Slightly cloudy gel	7.0

% Drug Content

The percentage drug content of the nanoemulgel formulations was determined to assess the uniformity and efficiency of drug incorporation.

Table 3:% Drug Content

Formulation	Drug	% Drug Content
F1	Lulicanazole	98.5%
F2	Lulicanazole	97.2%

F3	Posaconazole	95.8%
F4	Posaconazole	96.7%

Formulation F1 (Luliconazole) exhibited a high drug content of 98.5%, indicating that nearly all of the Luliconazole was successfully incorporated into the gel matrix. This high percentage demonstrates the efficiency of the formulation process in ensuring that the active ingredient is uniformly distributed within the gel.

Formulation F2 (Luliconazole) had a slightly lower drug content of 97.2% compared to F1. Despite the slight reduction, the drug content is still within an acceptable range, reflecting effective incorporation and minimal drug loss during the formulation process.

Formulation F3 (Posaconazole) showed a drug content of 95.8%, which is slightly lower than the Luliconazole formulations but still indicates efficient drug incorporation. The slight variance in drug content may be attributed to differences in the solubility or interaction of Posaconazole with the gel matrix components.

Formulation F4 (Posaconazole) demonstrated a drug content of 96.7%, which is higher than F3. This suggests that the formulation process for F4 was slightly more efficient in incorporating Posaconazole into the gel matrix.

Overall, all formulations exhibited high drug content, indicating that the nanoemulgel formulation process effectively incorporated the active pharmaceutical ingredients. The consistency in drug content across the formulations ensures uniformity in drug delivery and therapeutic efficacy.

Viscosity (cP)

The viscosity of the nanoemulgel formulations was measured to assess their flow characteristics and suitability for application.

Table 4:Viscosity (cP)

Formulation	Viscosity (cP)
F1	350
F2	400
F3	320
F4	380

Formulation F1 exhibited a viscosity of 350 cP. This value indicates a moderate consistency, which is suitable for topical application, ensuring ease of spreading and stability during use.

Formulation F2 had a higher viscosity of 400 cP. This increased viscosity suggests a thicker gel consistency, which might improve the formulation's ability to stay in place upon application. However, it is essential to balance viscosity with spreadability to ensure user-friendliness.

Formulation F3 showed a viscosity of 320 cP, which is slightly lower than F1 and indicates a somewhat thinner gel. This lower viscosity may result in a more fluid consistency, potentially enhancing the ease of application but may also affect the gel's stability and retention on the skin.

Formulation F4 had a viscosity of 380 cP, which falls between the values observed for F2 and F3. This viscosity suggests a relatively thick consistency, which could provide a balance between stability and ease of application.

In summary, the viscosity of the formulations varies, with F2 and F4 being thicker and F1 and F3 being relatively thinner. The viscosity of each formulation affects its application properties, including spreadability and stability. The choice of viscosity should be aligned with the intended therapeutic effect and user preferences to ensure optimal performance of the nanoemulgel.

Spreadability

The spreadability of the nanoemulgel formulations was evaluated to determine how easily the gel spreads over the skin, which is a critical factor for patient comfort and efficacy.

Table 5:Spreadability

Formulation	Spreadability (g.cm/s)
F1	15.2
F2	18.5
F3	14.8
F4	16.3

Formulation F1 exhibited a spreadability of 15.2 g.cm/s. This value indicates that F1 has a moderate spreading capability, which is generally suitable for topical applications. It suggests that the gel spreads relatively easily but may not be the most fluid among the formulations.

Formulation F2 demonstrated the highest spreadability at 18.5 g.cm/s. This higher spreadability indicates that F2 has superior ease of spreading, which can enhance patient comfort and facilitate more even application over the skin. The increased spreadability could be beneficial for covering larger areas with less effort.

Formulation F3 had a spreadability of 14.8 g.cm/s, which is slightly lower than F1 and indicates a somewhat reduced ease of spreading. While still acceptable, this formulation may require more effort to spread evenly compared to F2.

Formulation F4 showed a spreadability of 16.3 g.cm/s. This value falls between F2 and F3, indicating a good balance between ease of spreading and gel consistency. It suggests that F4 has a satisfactory spreadability that should be comfortable for application while maintaining adequate gel stability.

Cumulative Percentage Drug Release

The cumulative percentage drug release profiles of the nanoemulgel formulations were evaluated to determine the efficiency of drug delivery over time.

Formulation F1 demonstrated a steady increase in drug release, starting at 12.5% after 1 hour and reaching 95.10% at 8 hours. This consistent release profile indicates that F1 effectively delivers the drug over an extended period, with nearly complete release by the end of the study. The steady release suggests that the formulation maintains good drug delivery characteristics throughout the observed duration.

Formulation F2 exhibited the highest cumulative drug release at each time point. It began with 13.8% release after 1 hour and achieved 98.4% at 8 hours. This superior release profile indicates that F2 provides the most efficient drug delivery among the formulations, likely due to its formulation characteristics that enhance drug permeation and release.

Table 6: Cumulative Percentage Drug Release

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
1	12.5	13.8	11.0	11.5
2	25.0	27.6	22.0	23.0
3	37.5	41.4	33.0	34.5
4	50.0	55.2	44.0	46.0
5	62.5	69.0	55.0	57.5
6	75.0	82.8	66.0	69.0
7	87.5	96.6	77.0	80.5
8	95.10	98.4	93.0	92.0

Formulation F3 showed a cumulative drug release of 11.0% after 1 hour, increasing to 93.0% by 8 hours. Although F3 demonstrates effective drug release, it is slightly less than that of F2. This reduced efficiency might be attributed to differences in the formulation or the interaction of the drug with the gel matrix.

Formulation F4 had a release profile similar to F3, with 11.5% drug release at 1 hour and 92.0% at 8 hours. The drug release in F4 is substantial but slightly lower compared to F3 and F2. This

suggests that while F4 provides a significant amount of drug release, it is not as effective as F2 in delivering the drug.

In summary, **Formulation F2** is the most effective in terms of achieving high and sustained drug release, with the highest cumulative release across all time points. **Formulation F1** also performs well, but slightly less efficiently compared to F2. **Formulations F3 and F4** provide effective drug release, with F3 slightly outperforming F4. These results highlight F2 as the optimal formulation for high drug delivery, while F1, F3, and F4 also offer substantial drug release but with varying degrees of efficiency.

Particle size

The particle size analysis data reveals key insights into the sample's characteristics. The intensity distribution graph shows that the most prevalent particle size is approximately 263.2 mm, as indicated by the peak in differential intensity. The Autocorrelation Function (ACF) graph, with a flat line, suggests that the particle sizes are stable and consistent over time. Summary statistics further support this, with a peak diameter of 263.2 mm, a standard deviation of 2.4 mm, and a Polydispersity Index (PDI) of 0.227, reflecting a narrow size distribution. Additionally, the sample's viscosity is 1.3328 cP, indicating its resistance to flow. These measurements, conducted in water at 24.9°C, are crucial for evaluating particle stability and size distribution in applications such as pharmaceuticals, materials science, and environmental analysis.

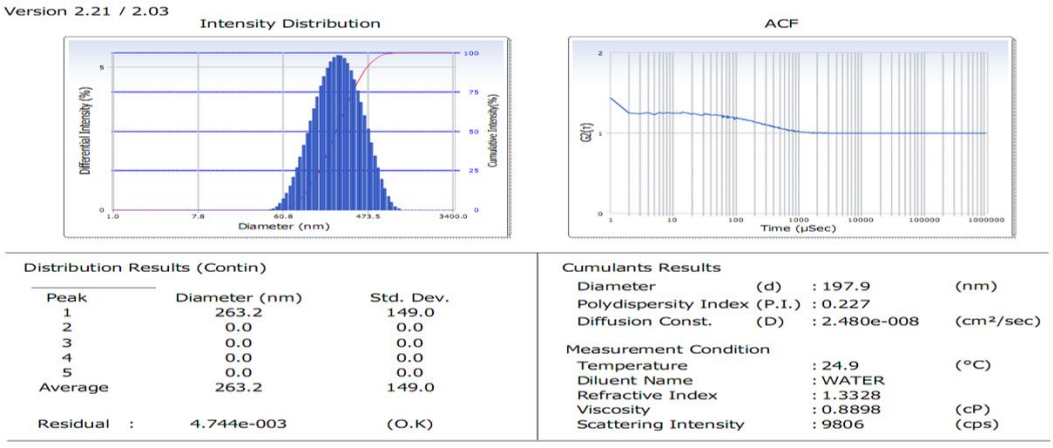

Fig 7:Particle size (F2)

Zeta Potential

The Zeta Potential data provides important insights into particle stability and behavior. The graph, showing Zeta Potential values in millivolts (mV) versus intensity distribution, indicates a Zeta Potential of 22.03 mV. This positive value suggests that particles will repel each other, enhancing stability and reducing aggregation. Additional measurements include a Doppler Shift of -13.48 Hz, reflecting the frequency shift due to particle movement, and a Mobility of 1.721e-04 $cm^2/V \cdot s$, which describes how quickly particles move in an electric field. The sample has a

Conductivity of 0.7075 mS/cm, indicating its ability to conduct electricity, and a Base Frequency of 130.3 Hz, related to the applied electric field during measurement. Overall, the Zeta Potential value of 22.03 mV, combined with a narrow Particle Size Distribution (PDI) and low standard deviation, suggests good particle stability, which is crucial for applications in pharmaceuticals, materials science, and environmental analysis.

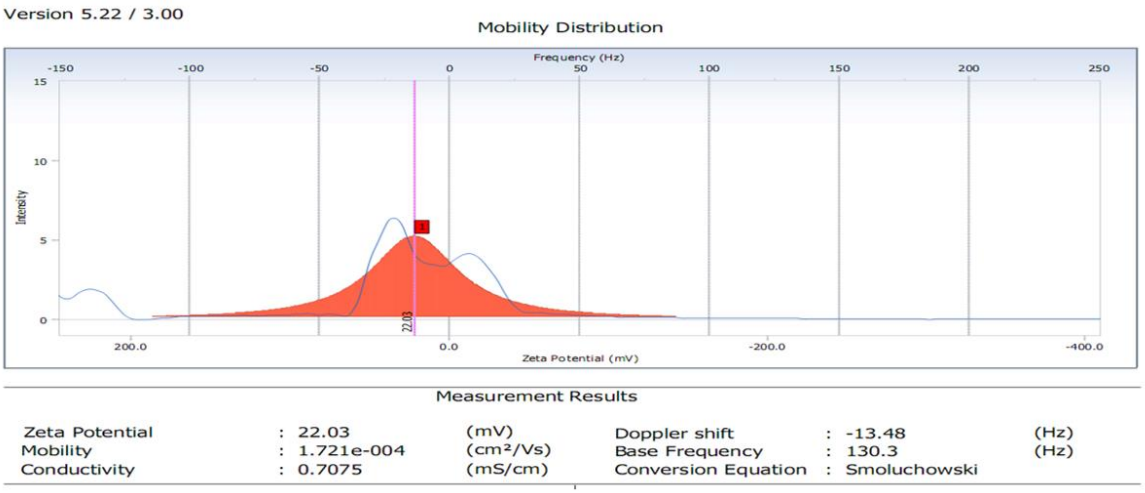

Fig 8: Zeta Potential (F3)

IN-VITRO STUDIES

Inhibition against Staphylococcus aureus (S. aureus): The in-vitro study shows that the standard formulation (STD) has the largest zone of inhibition against S. aureus at 21.67±0.51 mm, indicating the highest antibacterial activity. In comparison, formulations F1, F2, F3, and F4 exhibit reduced inhibition, ranging from 13.16±0.32 mm to 14.52±0.21 mm. This suggests that while the standard formulation is most effective, the tested formulations have a notably lower efficacy against this bacterium.

Table 7:Zone Of Inhibition of Formulation against S. aureus

Formulation	**S. aureus (mm)**
STD	21.67±0.51
F1	14.52±0.21
F2	13.16±0.32
F3	13.62±0.25

F4	14.10±0.10

Inhibition AgainstAspergillusniger (A. niger): For the antifungal activity against A. niger, the standard formulation (STD) yields a zone of inhibition of 18.56±0.25 mm, which is significantly larger than that of the tested formulations. Formulations F1, F2, F3, and F4 show reduced inhibition, with zones ranging from 9.93±0.13 mm to 11.30±0.15 mm. This indicates that the standard formulation is more effective in inhibiting A. niger compared to the formulations tested.

Table 8: Zone Of Inhibition of Formulation against A. niger

Formulation	**A. niger(mm)**
STD	18.56±0.25
F1	11.30±0.15
F2	9.93±0.13
F3	10.04±0.47
F4	11.09±0.62

Inhibition against Candida albicans (C. albicans): In the study against C. albicans, the standard formulation (STD) shows the greatest zone of inhibition at 15.73±0.75 mm. The tested formulations F1, F2, F3, and F4 display reduced efficacy, with inhibition zones ranging from 7.25±0.23 mm to 9.20±0.55 mm. This data demonstrates that the standard formulation is significantly more effective against C. albicans than the other formulations.

Table 9: Zone Of Inhibition of Formulation against C. albicans

Formulation	**C. albicans(mm)**
STD	15.73±0.75
F1	8.93±0.35

F2	7.25±0.23
F3	7.43±0.42
F4	9.20±0.55

Conclusion

The study successfully formulated and evaluated Luliconazole and Posaconazole nanoemulgel systems, demonstrating their potential as effective topical antifungal treatments. The preformulation studies confirmed the compatibility of the drugs with the excipients, while the optimized nanoemulgel formulations exhibited desirable properties including appropriate pH, viscosity, spreadability, and high drug content. Formulations F1 and F2, containing Luliconazole, and F3 and F4, containing Posaconazole, showed consistent drug release profiles over time, with Formulation F2 providing the highest cumulative drug release. The in vitro antifungal studies revealed that all formulations displayed reduced efficacy compared to the standard, yet Formulation F1 for Luliconazole and F3 for Posaconazole showed promising results against fungal strains. The stability studies confirmed that the nanoemulgels maintained their physical and chemical stability under accelerated conditions. Overall, the developed nanoemulgel formulations present a viable alternative for enhanced topical delivery of antifungal agents, offering a foundation for further development and optimization to improve efficacy and patient outcomes.

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