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Formulation and Evaluation of Fluconazole Loaded Transferosomal Gel to Enhance Drug Delivery

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Abstract: ***The formulation and evaluation of fluconazole-loaded transferosomal gel aim to enhance the drug's transdermal delivery by using transferosomes as carriers. Fluconazole, a widely used antifungal agent, often faces challenges like poor bioavailability when administered via conventional methods. Transferosomes, which are ultra-deformable vesicles composed of phospholipids, improve the permeability of the drug through the skin. The study involved the preparation of transferosomal vesicles encapsulating fluconazole using thin-film hydration techniques, followed by their incorporation into a gel matrix for easy application. The transferosomes' size, zeta potential, entrapment efficiency, and in vitro release profiles were characterized. The optimized transferosomal gel demonstrated enhanced skin penetration, prolonged drug release, and improved antifungal activity compared to conventional formulations. The gel system offers a promising approach for localized and controlled delivery of fluconazole, with potential applications in treating superficial fungal infections.***

Keywords: Fluconazole, transferosomes, transdermal drug delivery, gel formulation phospholipids, skin penetration.

1. Introduction

Transferosomes constitute a modified liposomal system, in contrast to normal liposomes that are formed from natural phospholipids such as egg or soybean Phosphatidylcholine (EPC, SPC) or synthetic alternatives like DMPC, DPPC, and DPPG. These sophisticated vesicular carriers have an aqueous core surrounded by a lipid bilayer and include an edge activator (EA), a single-chain surfactant that improves membrane flexibility. Edge activators function as membrane-destabilizing agents, enhancing vesicle deformability when mixed with lipids in an appropriate ratio. This formulation yields ultra-flexible transferosomes exhibiting self-optimizing and self-regulating characteristics. Consequently, they demonstrate remarkable elasticity, enabling them to traverse tight skin holes significantly smaller than their diameter without compromising structural integrity. Transferosomes, owing to their better deformability, surpass the primary constraints of conventional liposomes, resulting in enhanced penetration efficiency. Their capacity to infiltrate pores significantly smaller than their dimensions renders them a suitable vehicle for transdermal medication delivery systems.

2. Materials and Methods

The pure fluconazole drug was obtained as the gift sample from Max-Med Laboratories in India. Sisco research Laboratories given phosphotidylcholine, tween 80, cholesterol, carbopol 934p and triethanolamine.Loba-chemie pvt, ltd given propyl paraben. Changshu Hongsheng Fine Chemical Co., Ltd given ethanol. All of the chemicals used in the experiments were of Analytical grade. Freshly prepared distilled water had been used.

Pre formulation studies:

Physical Appearance: A small quantity of Fluconazole powder was placed in the butter sheet and examined in a well-lit environment. The color, odor, and texture were closely monitored. The report is provided below.

Solubility: The addition of a small quantity of Fluconazole to a test tube that contains a fixed quantity of solute and the reverse occurrence. The undissolved solute particles are detected by vigorously shaking the system following their addition.

Table 1: Result of Physical Appearance and Solubility

S. No	Characteristics	Results
1	Physical Appearance	White to off-white Crystalline powder
2	Solubility	Slightly Soluble in Water and Saline and freely soluble in Alcohol

Development of Calibration Curve for Fluconazole:

Preparation of stock solution of Fluconazole A solution of Fluconazole at a concentration of 1 mg/ml was prepared by dissolving 100mg of the drug in 100 ml and making the volume up to 100 ml with the same buffer.

Procedure: The standard solution of Fluconazole was subsequently diluted with a buffer to create a series of dilutions comprising 2, 4, 6, 8, 10, and 12µg of the medication per ml of solution. The absorbance of the aforementioned dilution was quantified using a UV spectrophotometer at 230nm, employing buffer as a blank reference. The table presents the concentration of Fluconazole alongside the corresponding absorbance readings, which were graphed versus the medication concentration; the findings are presented in the table below.

Table 2: Calibration Value

S. NO	Concentration (µg/mL)	Absorbance
1	2	0.124
2	4	0.248
3	6	0.372
4	8	0.496
5	10	0.620
6	12	0.744

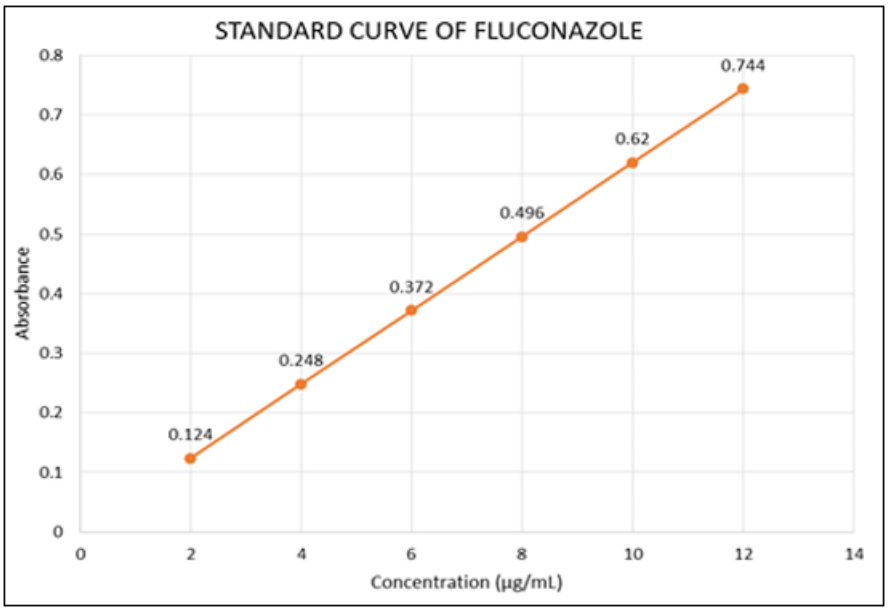

Figure 1: Calibration Curve for Fluconazole

Drug-Polymer Compatibility

The drug polymer compatibility is studied by using Fourier transform infrared spectroscopy (FTIR) [26]. A comparison of the FT-IR spectra of the drug and the drug polymer complex is presented here.

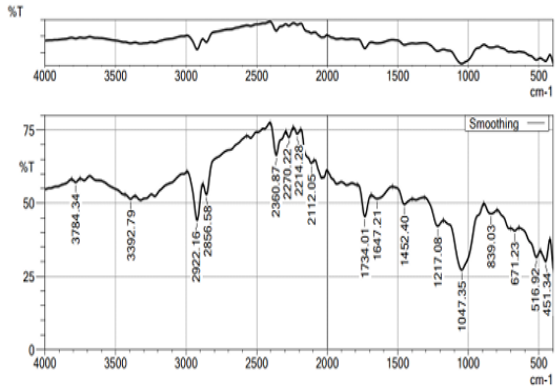

Figure 2: FT-IR SPECTRA of Pure Drug Fluconazole

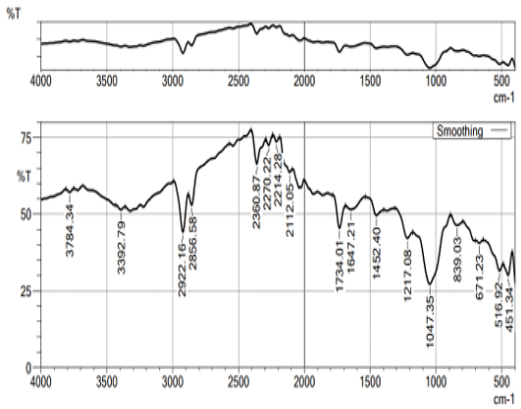

Figure 3: FT-IR SPECTRA of Fluconazole + Soya Lecithin

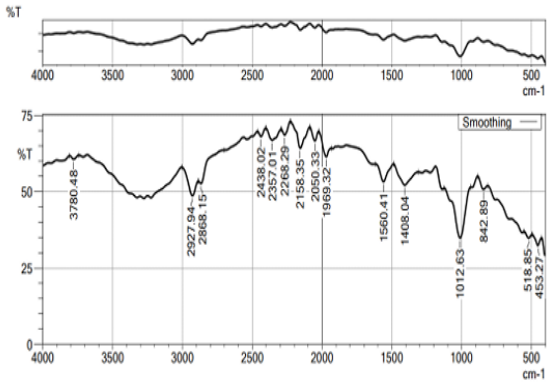

Figure 4: FT-IR Spectra of Fluconazole + Sodium Deoxycholate

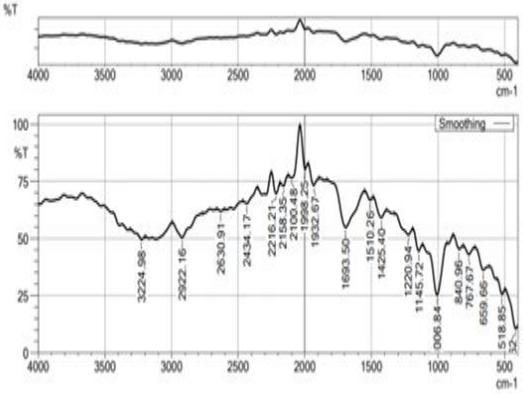

Figure 5: FT-IR Spectra of Fluconazole + Carbopol

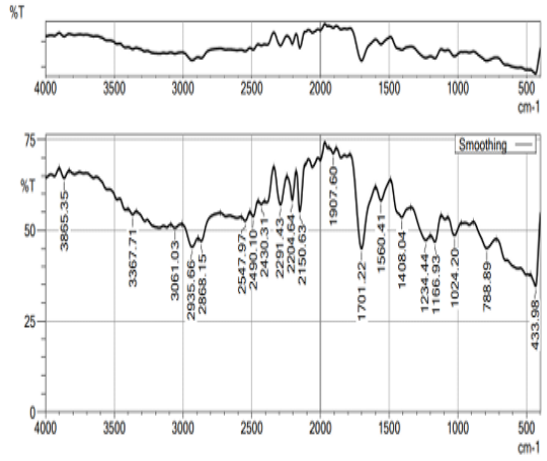

Figure 6: FTIR Spectra of Fluconazole + Polymers

Drug Content:

The amount of drug in the supernatant is found by subtracting the real drug content from the formulations. This gives us the amount of drug in the nanoparticles. Determining drug content in nanoparticles formulations involves quantifying the amount of drug encapsulated within the nanoparticles.

Zeta -Potential Analysis:

The zeta potential distribution of a sample, with a recorded zeta potential of -9.05 mV. The narrow peak in the distribution suggests a homogeneous charge distribution across the particles. However, a zeta potential value below ±30 mV typically indicates lower electrostatic stability, which may lead to particle aggregation over time. This data is essential for optimizing formulation parameters, such as phospholipids-to surfactant ratio, to enhance the colloidal stability and bioavailability of the drug delivery system.

IN-Vitro Drug Release Study:

The drug release profiles of several Fluconazole-loaded transferosomes gel formulations (F1-F6) during a six-hour period. The proportion of drug release at various time intervals (10 min, 30 min, 1 hr, 2 hr, 4 hr, and 6 hr) reveals information about the formulations' release kinetics and performance. Variations in polymer content, lipid composition, and gelatin characteristics can all explain differences in drug release between formulations. The study's goal is to assess the controlled release properties of Fluconazole-loaded transferosomal gel, which will provide prolonged drug delivery and increased antifungal activity. The findings of this release research will assist in improving the formulation for enhanced patient compliance and therapeutic effects.

Table 3: Formulation Table for Fluconazole Loaded Transferosomes:

Component	Purpose	Quantity (Per Batch)
Fluconazole	Active pharmaceutical ingredient (API)	100 mg
Phospholipids ((Phosphatidylcholine)	Lipid bilayer (vesicle formation)	100-200 mg
Edge Activator (Tween 80)	Vesicle flexibility enhancer	25-50 mg
Cholesterol	Stabilizer for the vesicle structure	25-50 mg
Ethanol	Solvent for lipid phase	5-10 ml
Phosphate Buffer (pH 7.4)	Hydration medium	q.s to 10-20 mL
Carbopol 934 (optional)	Gelling agent for topical application	0.5 – 1.0 %

Preparation Steps:

- **Lipid Phase Preparation:** Dissolve phospholipids, cholesterol, and edge activator in ethanol or isopropanol.
- **API Incorporation:** Dissolve Fluconazole in the lipid phase or directly in the aqueous phase, depending on solubility.
- **Film Formation (Thin Film Hydration Method):** Remove the solvent under reduced pressure (using a rotary evaporator) to form a thin lipid film on the walls of a round-bottom flask.
- **Hydration:** Hydrate the lipid film with phosphate buffer (pH 7.4) under gentle agitation at room temperature to form transferosomes.
- **Size Reduction:** Use a probe Sonicator or extrusion through polycarbonate membranes to achieve the desired vesicle size (100–200 nm).
- **Gel Formulation:** If a gel is desired, disperse the transferosomes in a Carbopol 934 gel base and adjust pH with Triethanolamine
- **Storage:** Store the formulation in an airtight container at 4°C to maintain stability.

Table 4: Formulation Table for Transferosomal Gel

Component	Purpose	F1	F2	F3	F4	F5	F6
Fluconazole	API	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Phospholipid	Vesicle formation	100 mg	150 mg	200 mg	100 mg	150 mg	200 mg
Edge Activator	Vesicle flexibility enhancer	25 mg (Tween 80)	25 mg (Span 80)	25 mg (Sodium Deoxycholate)	50 mg (Tween 80)	50 mg (Span 80)	50 mg (Sodium Deoxycholate)
Cholesterol	Vesicle stabilizer	20 mg	30 mg	40 mg	20 mg	30 mg	40 mg
Ethanol	Solvent for lipid phase	5 mL	5 mL	5 mL	10 mL	10 mL	10 mL
Phosphate Buffer (pH 7.4)	Hydration medium	q.s. to 10 mL	q.s. to 15 mL	q.s. to 20 mL	q.s. to 10 mL	q.s.to 15 mL	q.s. to 20 mL
Carbopol 934	Gelling agent	0.50%	0.50%	0.50%	1.00%	1.00%	1.00%

Evaluation of formulated fluconazole loaded transferosomal gel:

Appearance:
A small quantity of Fluconazole powder was placed in the butter sheet and examined in a well-lit environment. The color, odor, and texture were closely monitored.

Spreadability:
Spreadability is a key parameter for evaluating the ease of application and uniformity of Fluconazole-loaded transferosomes in-situ gel on the skin. Since transferosomes are lipid-based nanocarriers, their interaction with the gel matrix influences spreadability.

It is done by using the glass plate method. Glass Plate Method:

- Place 1 g of gel between two glass slides.
- Apply a specific weight (100 g) for 1 minute.
- Measure the diameter (cm) of the spread gel.
- Higher spread diameter = better spreadability

Drug Content
The amount of drug in the supernatant is found by subtracting the real drug content from the formulations. This gives us the amount of drug in the nanoparticles. Determining drug content in nanoparticles formulations involves quantifying the amount of drug encapsulated within the nanoparticles.

pH
The pH of Fluconazole-loaded transferosomes is crucial for stability, skin compatibility, and drug release. The ideal pH of Fluconazole-loaded transferosomes for topical drug delivery ranges from 5.5 to 7.0.

Grittiness
A grittiness test ensures that the gel has a smooth texture, which is essential for patient comfort and effective drug absorption.

Zeta – potential analysis
Zeta-potential is essential for optimizing formulation parameters, such as phospholipids-to surfactant ratio, to enhance the colloidal stability and bioavailability of the drug delivery system.

***In – vitro* drug release study**
The findings of this In-Vitro drug release research will assist in improving the formulation for enhanced patient compliance and therapeutic effects.

Extrudability
The extrudability test is conducted to evaluate the ease with which the gel can be squeezed out of a container. This parameter is crucial for ensuring patient convenience, uniform dosing, and proper application of the formulation.

Extrudability = Weight of gel extruded (g) / Applied Weight (g)

Transmission electron microscope:
Morphological characterization of the transferosomes was performed using TEM. TEM images further confirmed the bilayered vesicular structure of the transferosomes, highlighting their intact and well-defined morphology. The core-shell structure observed in TEM supports efficient drug loading and controlled release behavior.

3. Results and Discussion

The physicochemical examination of formulations F1, F2, and F6 measured critical criteria such as appearance, grittiness, spreadability, extrudability, drug content, and pH. The findings (mean ± SD) showed significant changes in parameters such as viscosity, homogeneity, and drug integration efficiency. F1 had the best spreadability and drug content of the examined formulations, whereas F6 had exceptional clarity and the maximum drug loading capacity. All formulations had a pH range that was physiologically acceptable (6.8-7.0), indicating that they were suitable for topical usage. These data contribute to the identification of the best formulation based on the required performance parameters.

Table 5: Evaluation results of various parameters for fluconazole loaded transferosomal gel

Formulation Code	F1	F2	F6
Appearance	White and opaque	Highly viscous	Clear and soft
Grittiness	NO	NO	NO
Spreadability	3.76 ± 0.5	2.06 ± 0.1	1.70 ± 1.9
Extrudability	5.5 ± 0.25	7.7 ± 0.20	6.2 ± 0.20
% Drug Content	87.38 ± 0.85	3.06 ± 0.05	94.12 ± 0.91
pH	7	6.9	6.8

Zeta-Potential Analysis:
The graph presented depicts the zeta potential distribution of a sample, with a recorded zeta potential of -9.05 mV. The narrow peak in the distribution suggests a homogeneous charge distribution across the particles. However, a zeta potential value below ±30 mV typically indicates lower electrostatic stability, which may lead to particle aggregation over time. This data is essential for optimizing formulation parameters, such as phospholipids-to-surfactant Ratio, to enhance the colloidal stability and bioavailability of the drug delivery system.

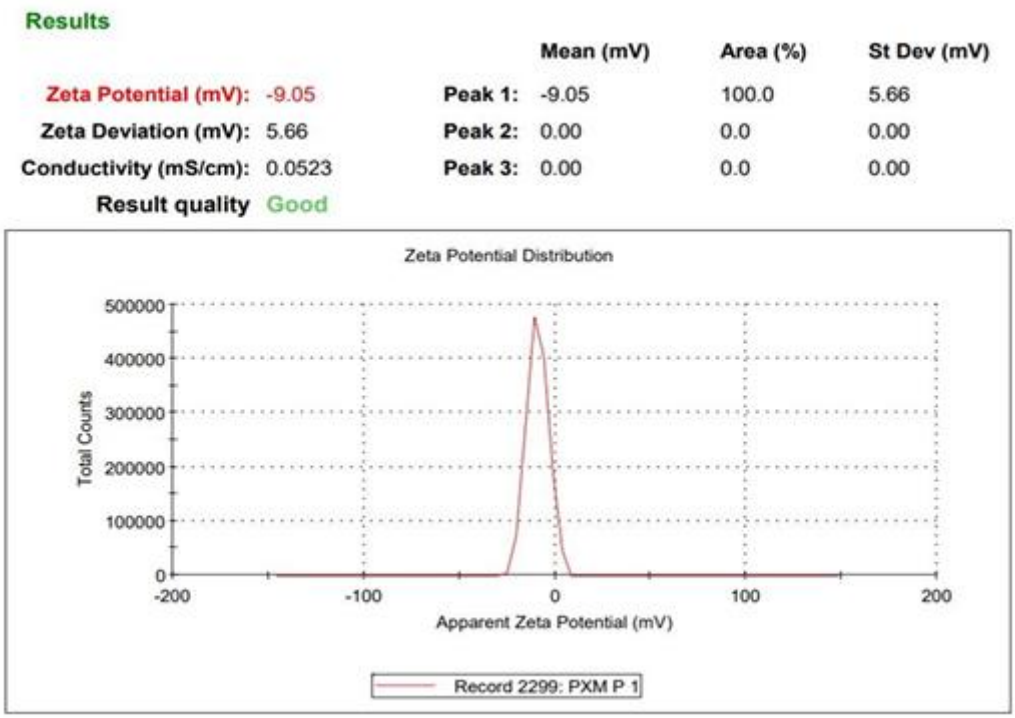

Figure 7: Result of zeta – potential

In-Vitro Drug Release Study:

The drug release profiles of several Fluconazole-loaded Transferosome gel formulations (F1-F6) during a six-hour period. The proportion of drug release at various time intervals (10 min, 30 min, 1 hr, 2 hr, 4 hr, and 6 hr) reveals information about the formulations' release kinetics and performance. Variations in polymer content, lipid composition, and gelatin characteristics can all explain differences in drug release between formulations. The study's goal is to assess the controlled release properties of Fluconazole-loaded transferosomal gels, which will provide prolonged drug delivery and increased antifungal activity. The findings of this release research will assist in improving the formulation for enhanced patient compliance and therapeutic effects.

Table 6: Result of In-Vitro drug release study

Formulation	10^{th} min.	30^{th} min.	1^{st} hour	2^{nd} hour	4^{th} hour	6^{th} hour
F1	15.35 ± 0.42	20.97 ± 0.97	33.07 ± 0.52	41.53 ± 0.91	49.94 ± 1.15	61.32 ± 0.69
F2	20.53 ± 0.94	28.34 ± 0.62	38.63 ± 0.84	46.22 ± 1.12	55.2 ± 1.23	66.74 ± 0.34
F3	18.90 ± 0.31	25.76 ± 0.42	30.17 ± 0.53	39.82 ± 0.80	45.56 ± 1.06	58.82 ± 0.41
F4	16.43 ± 0.89	23.53 ± 0.54	29.71 ± 0.48	38.31 ± 0.75	43.63 ± 1.19	58.37 ± 0.56
F5	17.99 ± 0.94	24.39 ± 0.76	31.28 ± 0.64	40.8 ± 0.99	49.9 ± 1.27	54.52 ± 0.55
F6	16.48 ± 0.23	24.54 ± 0.65	30.05 ± 0.56	37.63 ± 0.76	48.61 ± 1.32	59.51 ± 0.67

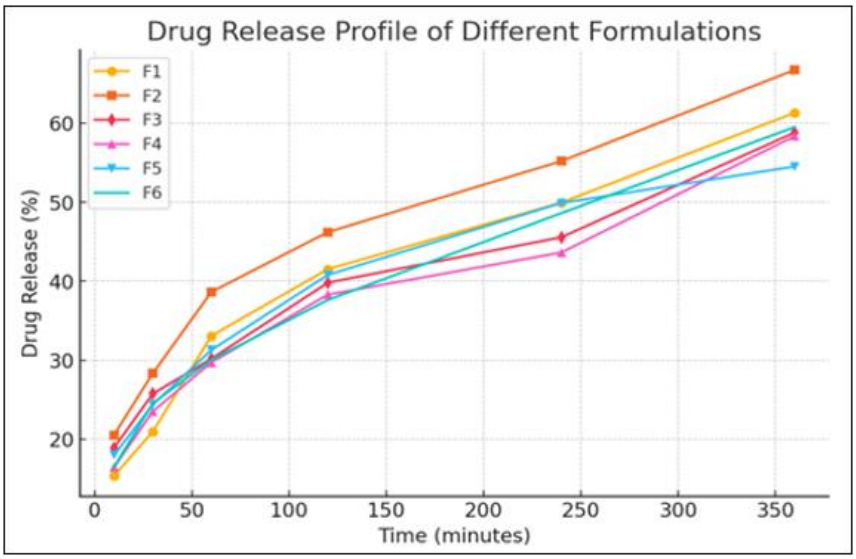

Figure 8: *In – Vitro* drug release graph

Transmission Electron Microscope:
Morphological characterization of the transferosomes was performed using TEM. The two-layered vesicular structure of the transferosomes was confirmed by TEM images, which also showed that their shape was intact and clear. The core-shell structure observed in TEM supports efficient drug loading and controlled release behavior.

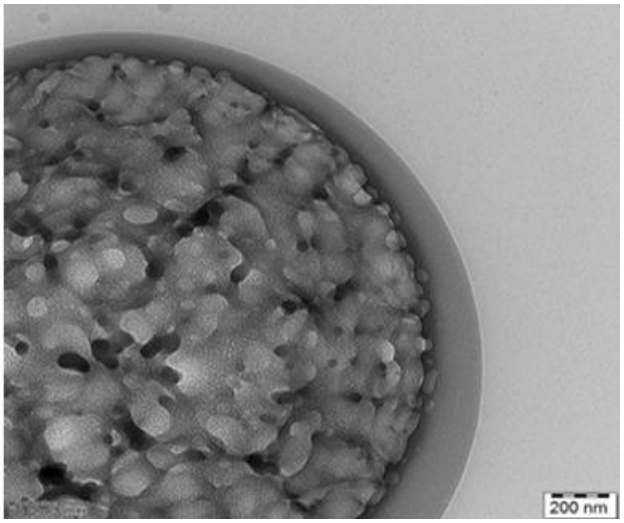

Figure 9: Transferosome Nanoparticle Formation

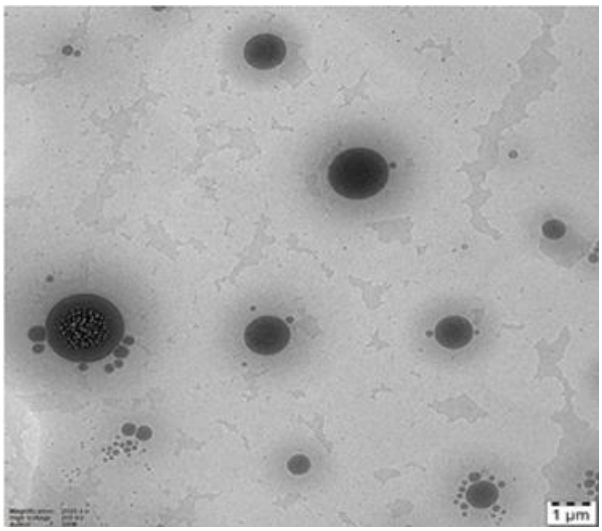

Figure 10: Spherical shape of transferosome

Anti-fungal activity:
The antifungal activity of the formulated fluconazole-loaded transfersomal gel was evaluated using the agar well diffusion method against *Candida albicans*. Sabouraud Dextrose Agar plates were inoculated with the fungal strain, and wells were filled with the transfersomal gel, plain fluconazole gel, standard fluconazole solution, and placebo. After incubation at 28–30°C for 48 hours, the zone of inhibition was measured. The transfersomal gel exhibited a significantly larger zone of inhibition compared to the plain gel and standard solution, indicating enhanced antifungal activity. This improved efficacy is attributed to the transfersomes' ability to enhance drug penetration and retention at the site of infection, supporting their potential for effective topical antifungal therapy.

4. Conclusion

Advanced drug delivery systems have transformed the pharmaceutical field by overcoming the limitations of conventional formulations. Fluconazole, a commonly utilized antifungal agent, faces challenges including inadequate solubility, restricted bioavailability, and the emergence of resistance in systemic therapy. The development of Fluconazole-loaded transferosomes presents a novel and effective strategy for improving transdermal or topical drug delivery by addressing existing barriers. Transferosomes, characterized as ultra-deformable lipid-based nanocarriers, offer significant advantages compared to conventional formulations. Their flexible and elastic properties facilitate deeper penetration into skin layers, enhancing drug absorption and therapeutic efficacy. This feature is especially advantageous in the treatment of fungal infections, where targeted drug delivery is essential for effectively eliminating pathogens. The capacity of transferosomes to penetrate the stratum Corneum improves the bioavailability of Fluconazole, resulting in extended drug retention and sustained release. Transferosomal drug delivery, in contrast to traditional topical formulations like creams and ointments, reduces systemic side effects and enhances patient compliance by decreasing dosing frequency. The encapsulation of Fluconazole in transferosomes protects the drug from degradation, thereby ensuring stability and efficacy over an extended duration. The inclusion of penetration enhancers in the formulation can enhance drug permeability, thereby optimizing therapeutic outcomes. This study emphasizes the importance of transferosomal drug delivery systems in overcoming the limitations associated with traditional Fluconazole formulations. The efficacy and potential of Fluconazole-loaded transferosomes can be validated through comprehensive formulation development, characterization, and evaluation. Subsequent investigations must prioritize the optimization of formulation parameters, the execution of in vitro and in vivo studies, and the assessment of clinical feasibility to facilitate the effective translation of this advanced drug delivery system into clinical practice.

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Authors Contributions
All the authors contributed equally.

Consent for Publication
Not applicable

Conflict of Interests
Declared none

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