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DEVELOPMENT AND EVALUATION OF BIFONAZOLE-LOADED TRANSFEROSOMAL TOPICAL GEL FOR DEEPER DERMAL DELIVERY IN THE MANAGEMENT OF TINEA PEDIS AND TINEA CORPORIS

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ABSTRACT

The present study aimed to develop and evaluate a Bifonazole-loaded transferosomal gel for enhanced dermal drug delivery in the treatment of superficial fungal infections. Bifonazole exhibits limited skin penetration in conventional topical formulations results in substandard therapeutic results. In this present study Bifonazole Transferosomes were prepared using Soya lecithin phospholipids (vesicle formers) and Tween 80 (edge activator) by the thin-film hydration method. Total of 9 formulations F1-F9 were designed using 3^2 full factorial design. Two variables are soya lecithin amount and Tween 80 amount. The amount of drug kept constant in all the 9 formulations. All the formulations were evaluated for % entrapment efficiency and in-vitro drug membrane diffusion studies. Among all, F6 showed highest % EE and higher in-vitro drug diffusion. We concluded that F6 is the optimised formulation and further, this F6 optimised formulation was evaluated for vesicle size, PDI, and zeta potential. The best formulation F6 was incorporated into an empty Carbopol gel base to prepare Bifonazole transferosomal gel. This gel was evaluated for pH, spreadability, skin irritation, drug content, and viscosity. Furthermore, % of in-vitro membrane drug diffusion studies was conducted for both prepared Bifonazole transferosomal gel and the marketed Bifonazole (Brand: Bi-fone) gel. The transferosomal gel demonstrated significantly enhanced drug release, achieving 97.03% release at 9 h compared to 49.30% from the marketed gel. The enhancement factor was found to be 4.57 at 1 h and 1.97 at 9 h**,** indicating improved permeation.

Keywords: *Bifonazole; Transferosomes; Topical gel; Dermal drug delivery; Entrapment efficiency; In vitro drug release.*

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INTRODUCTION

Tinea pedis and tinea corporis are among the most prevalent superficial fungal infections caused primarily by dermatophytes such as *Trichophyton* species, affecting keratinised tissues of the skin and leading to significant morbidity worldwide [1,2]. These infections are often associated with high recurrence rates due to inadequate drug penetration and persistence of fungi in deeper skin layers [3,4]. Conventional topical antifungal formulations exhibit limited ability to penetrate the stratum corneum barrier, thereby reducing therapeutic efficacy and necessitating prolonged treatment durations [5]. Bifonazole, a broad-spectrum imidazole antifungal agent, acts by inhibiting ergosterol synthesis and disrupting fungal cell membrane integrity; however, its effectiveness is often compromised by poor dermal permeation and retention when administered through conventional dosage forms [6]. To overcome these limitations, novel vesicular drug delivery systems such as transferosomes have emerged as promising carriers for enhanced transdermal delivery. Transferosomes are ultra-deformable lipid vesicles composed of phospholipids and edge activators, which facilitate drug transport across the skin by exploiting hydration gradients and their flexible structure [7,8]. These vesicles can traverse intercellular lipid pathways and deliver drugs to deeper dermal layers more efficiently than conventional liposomes [9,10]. Furthermore, incorporation of transferosomes into topical gel formulations improves stability, patient compliance, and ease of application while maintaining sustained drug release [11,12].Therefore, the present study aims to develop and evaluate a Bifonazole-

loaded transferosomal topical gel to enhance dermal delivery for the management of tinea pedis and tinea corporis. This approach is expected to improve drug localisation at the site of infection, enhance therapeutic efficacy, and reduce recurrence rates compared to conventional formulations [13,14].

MATERIALS AND METHODS

Materials

Bifonazole was purchased from Yarrow Chem Products, Mumbai. Tween 80, Carbopol 940, triethanolamine, methyl paraben, chloroform, and methanol were procured from Loba Chemie Pvt. Ltd., Mumbai. All chemicals used were of analytical grade. Hi Media diffusion cell membrane with MWCO (Molecular Weight Cut Off) 12-14 kDa was used for diffusion studies.

Determination of λmax of Bifonazole

The maximum absorption wavelength (λmax) of Bifonazole was determined using a UV–Visible spectrophotometer to enable accurate quantitative analysis. A stock solution was prepared by dissolving accurately weighed Bifonazole in phosphate buffer (pH 7.4). The solution was scanned over a wavelength range of 200–400 nm using a quartz cuvette of 1 cm path length. The instrument was first calibrated using solvent blank.

Preparation of Calibration Curve

A calibration curve was constructed to establish the relationship between concentration and absorbance of Bifonazole. A primary stock solution (1000 µg/mL) was prepared and further diluted to obtain a working solution (100 µg/mL). From this, a series of standard solutions (10, 20, 30, 40, and 50 µg/mL) were prepared using phosphate buffer (pH 7.4). The absorbance of each concentration was measured at 254 nm using a UV spectrophotometer. A graph of absorbance versus concentration was plotted, and the linear regression equation was obtained, which was used for subsequent drug estimation.

Drug–Excipient Compatibility Studies (FTIR)

Drug–excipient compatibility studies were carried out using Fourier Transform Infrared Spectroscopy (FTIR) to identify any possible chemical interactions between Bifonazole and formulation excipients. The KBr pellet method was employed, where the sample was mixed with dry potassium bromide and compressed into a transparent pellet. The pellet was scanned over a range of 4000–400 cm^{-1}. FTIR spectra of pure drug, individual excipients, and physical mixtures were compared for any significant shifts or disappearance of characteristic peaks, indicating compatibility.

Preparation of Bifonazole Transferosomes

Bifonazole-loaded transferosomes were prepared using the **thin film hydration method**. Accurately weighed quantities of Bifonazole, soya lecithin, and Tween 80 were dissolved in a chloroform: methanol mixture (2:1 v/v) in a round-bottom flask to form a clear organic solution. The solvent was evaporated at 40°C to form a thin lipid film on the inner surface of the flask. The film was further dried in a desiccator to remove residual solvent. Hydration of the lipid film was carried out using phosphate buffer (pH 7.4) maintained at the same temperature, resulting in the formation of multilamellar vesicles. The dispersion was then subjected to sonication to reduce vesicle size and obtain a uniform transferosomal system.

Experimental Design

A 3^2 full factorial design was employed to optimise the formulation variables. Two independent variables, namely lecithin concentration and Tween 80 concentration, were varied at three different levels (low, medium, and high). This resulted in a total of nine formulations (F1–F9). The amount of drug, solvent composition, and hydration medium were kept constant. The design enabled evaluation of the effect of formulation variables on entrapment efficiency and drug release.

Table 1. Formulation Design of Bifonazole Transferosomes (3^2 Factorial Design)

Formulation Code	Lecithin (mg)	Tween-80 (% of lecithin)	Tween-80 (mg)	Bifonazole (mg)	Organic Solvent (mL) ($CHCl_3$: MeOH 2:1)	Hydration Buffer (mL)
F1	100	5%	5.0	100	10	10
F2	100	15%	15.0	100	10	10
F3	100	25%	25.0	100	10	10
F4	200	5%	10.0	100	10	10
F5	200	15%	30.0	100	10	10
F6	200	25%	50.0	100	10	10
F7	300	5%	15.0	100	10	10
F8	300	15%	45.0	100	10	10
F9	300	25%	75.0	100	10	10

Evaluation of Transferosomes

Entrapment Efficiency (%EE)

Entrapment efficiency was determined to evaluate the ability of transferosomes to encapsulate Bifonazole. The prepared dispersions were centrifuged at high speed to separate free drug from entrapped drug. The supernatant containing unentrapped drug was collected and analyzed using a UV spectrophotometer at 254 nm. The percentage entrapment efficiency was calculated by comparing the total drug content with free drug content.

In Vitro Diffusion Study

In vitro drug release studies were performed using a Franz diffusion cell to assess the release behavior of Bifonazole from transferosomes. A dialysis membrane was mounted between donor and receptor compartments. The receptor compartment was filled with phosphate buffer (pH 7.4) and maintained at 37 ± 0.5°C with continuous stirring. The formulation was placed in the donor compartment, and samples were withdrawn at predetermined intervals. The withdrawn samples were analyzed spectrophotometrically at 254 nm, and cumulative drug release was calculated.

Particle Size, Polydispersity Index (PDI), and Zeta Potential

The optimized formulation was characterized using dynamic light scattering technique. The particle size and PDI were determined to evaluate vesicle size distribution and uniformity. Zeta potential was measured to assess the stability of the formulation, as higher absolute values indicate better stability due to electrostatic repulsion.

Preparation of Transferosomal Gel

The optimised transferosomal formulation was incorporated into a Carbopol 940 gel base. Carbopol was dispersed in distilled water and allowed to hydrate completely. Propylene glycol and methyl paraben were added as a cosolvent and preservative, respectively. The pH was adjusted using triethanolamine to obtain a clear and stable gel. The transferosomal dispersion was then incorporated into the gel with gentle stirring to ensure uniform distribution.

Preparation of Bifonazole Transferosomal Topical Dermal Gel:

Among all nine formulations (F1–F9) of Bifonazole Transferosomes, the F6 formulation was found to be the best based on its % EE and *in-vitro* membrane diffusion studies. This F6 formulation was used for the preparation of Bifonazole transferosomal topical dermal gel.

Table 2: Ingredients, Category and Amount used for Preparation of 100 g of Empty Gel Base:

S. No.	Ingredient	Category	Amount (g)
1	Carbopol 940	To form firm and spreadable gel	2.5 g
2	Propylene glycol	Co-solvent	5 g
3	Methyl Paraben	Preservative	0.1 g
4	Ethanol	Organic solvent	5 g
5	Water	Solvent	87.4 g
Total Quantity			100 g
Note: A small amount of Triethanolamine (TEA) was added to the above Carbopol gel base to adjust the pH to 6.0			

Evaluation of Transferosomal Gel

pH Measurement

The pH of the gel was determined by dispersing the gel in distilled water and measuring using a calibrated digital pH meter to ensure skin compatibility.

Spreadability

Spreadability was evaluated using the slip and drag method to determine ease of application. The time required for the upper slide to move under the applied weight was recorded.

Viscosity

Viscosity of the gel was measured using a Brookfield viscometer at controlled temperature and rotational speed. This parameter indicates flow behaviour and consistency of the gel.

Drug Content

Drug content was determined by dissolving a known quantity of gel in phosphate buffer (pH 7.4), followed by filtration and spectrophotometric analysis at 254 nm to ensure uniform drug distribution.

Skin Irritation Study

A skin irritation study was performed to assess the safety of the formulation. The gel was applied to the skin and observed for any signs of redness, swelling, or irritation over a specified period

Comparative Drug Release Study

The in vitro drug release profile of the optimised transferosomal gel was compared with a marketed Bifonazole gel using a Franz diffusion cell. This comparison was carried out to evaluate the enhancement in drug release and performance of the developed formulation.

RESULTS & DISCUSSION

λmax of Bifonazole

The absorption spectrum obtained exhibited a prominent peak at 254 nm with an absorbance of 0.699, indicating the λ max of Bifonazole. Thus, based on the spectral analysis, 254 nm was selected as the λ max of Bifonazole for all further UV spectrophotometric investigations

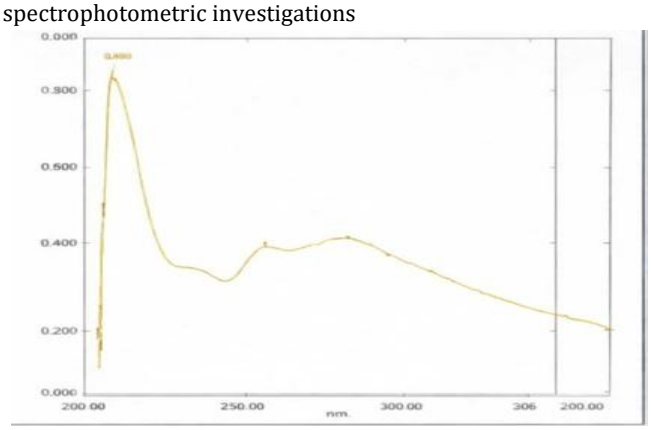

Figure 1: UV Absorption Spectrum of Bifonazole showing λmax at 254 nm

Calibration Curve of Bifonazole

The calibration curve demonstrated a linear relationship between concentration and absorbance within the range of 10–50 µg/mL, confirming adherence to Beer–Lambert's law. The regression equation showed good linearity (R^2= 0.9578), indicating reliability of the method.

Table 3: Calibration Data of Bifonazole

Concentration (µg/mL)	Absorbance
10	0.326
20	0.496
30	0.643
40	0.843
50	0.891

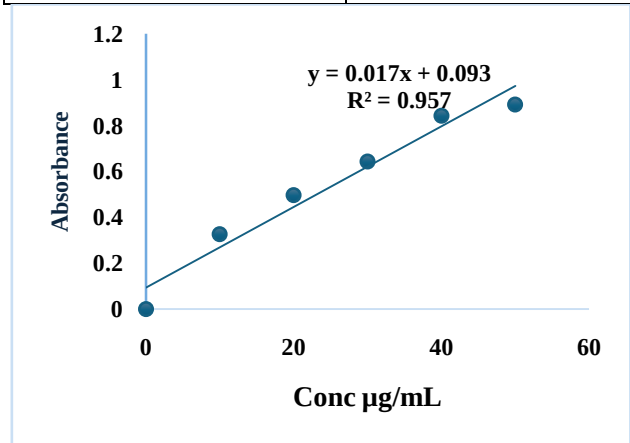

Figure 1: Calibration Curve of Bifonazole

FTIR Compatibility Studies

The FTIR spectrum of pure Bifonazole (Figure 2) showed characteristic peaks corresponding to O–H stretching (3442 cm^{-1}), aromatic C–H stretching (3030 cm^{-1}), and C=N/C=C stretching (1642 cm^{-1}), confirming its structural integrity. The spectrum of the physical mixture (Figure 43 exhibited all major

peaks of Bifonazole along with peaks of excipients such as lecithin and Tween 80 without any significant shift or disappearance. This indicates the absence of chemical interaction between drug and the excipients. The retention of functional group peaks confirms compatibility and stability of the formulation. Hence, the selected excipients are suitable for the preparation of Bifonazole transferosomal gel.

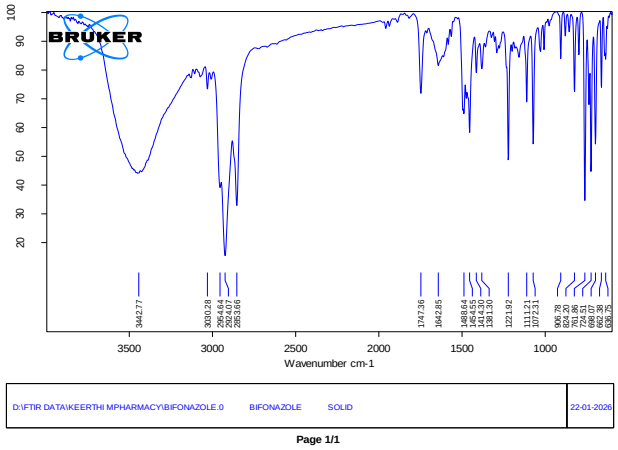

Figure 2: FTIR Spectrum of Pure Bifonazole

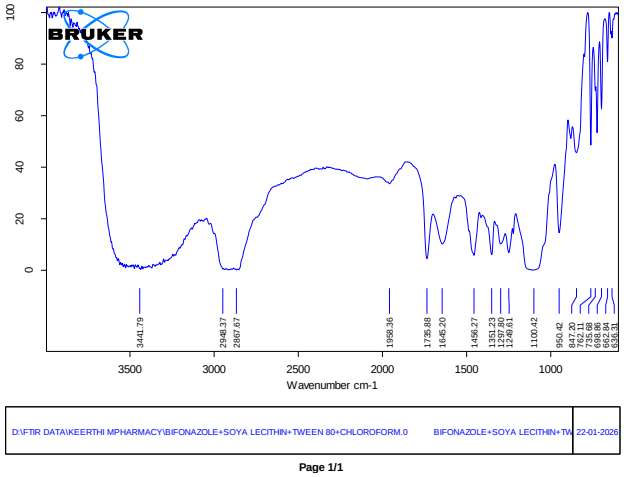

Figure 3: FTIR Spectrum of Bifonazole, Excipients, and Physical Mixture

Entrapment Efficiency

Among all nine formulations, formulation F6 exhibited the highest entrapment efficiency of 89.36%, indicating superior drug encapsulation within the transferosomal vesicles. The higher entrapment efficiency observed in F6 may be attributed to the optimised ratio of non-ionic surfactant and Tween 80. Formulations F1 and F2 showed comparatively lower entrapment efficiencies. Based on the entrapment efficiency results, F6 was selected as the optimised formulation for further evaluation studies, such as particle size analysis, PDI, zeta potential measurement, and incorporation into gel base.

Table 4: Entrapment Efficiency of Formulations F1–F9

Formulation	% EE
F1	69.84
F2	72.15
F3	74.63
F4	78.27
F5	82.41
F6	89.36
F7	86.18
F8	83.52
F9	80.74

In-vitro Drug Diffusion Studies

The percentage drug release data clearly indicate that all formulations exhibited sustained release over 9 hours. Among them, formulation F6 showed the highest drug release (86.23%), indicating superior permeation and optimised formulation composition. The enhanced release may be attributed to the ideal ratio of lecithin and Tween 80, which improves vesicle deformability and drug diffusion. Other formulations showed comparatively lower release, confirming the significance of formulation variables. Thus, F6 was selected as the optimised formulation for further studies.

Table 5 : Percentage (%) of Bifonazole Drug Released During In-Vitro Membrane Diffusion Studies

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.06	15.69	17.51	17.58	15.70	15.60	15.79	14.63	14.80
2	15.34	24.69	22.33	21.81	18.57	18.23	24.41	14.74	17.76
3	22.47	29.60	31.42	30.53	25.46	24.86	30.07	23.73	25.92
4	26.02	38.66	39.46	31.74	34.88	33.85	34.11	33.19	34.74
5	29.98	40.48	43.09	38.93	38.88	42.65	43.18	39.79	35.65
6	43.54	42.65	49.29	42.97	47.50	57.47	48.04	42.57	45.17
7	53.34	57.75	52.36	57.49	52.98	67.44	56.93	51.56	48.04
8	67.46	67.45	66.81	67.73	62.05	70.15	66.81	67.46	52.00
9	76.76	75.44	69.51	76.70	71.00	86.23	76.61	70.16	60.62

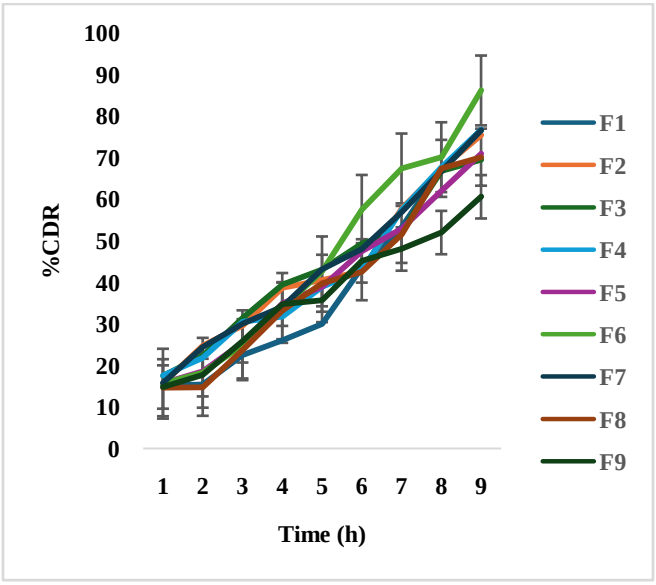

Figure 4: % Drug Release Profile of Transferosomal Formulations

In-vitro Drug Release Kinetics Study

The kinetic analysis revealed that the drug release from formulation F6 best followed the zero-order model (R^2 = 0.9793), indicating a nearly constant drug release rate. The Higuchi model also showed good correlation (R^2 = 0.9311), suggesting diffusion-controlled release. The Korsmeyer–Peppas model (R^2 = 0.9397) with release exponent n = 0.835 indicates a non-Fickian diffusion mechanism, involving both diffusion and polymer relaxation. Overall, the formulation exhibited controlled and sustained drug release behavior.

Table 5. Kinetic Modeling of Drug Release from Optimized Formulation (F6)

Kinetic Model	Equation Used	R^2 Value
Zero Order	C vs t	0.9793
First Order	Log (100 – C) vs t	0.8871
Higuchi Model	C vs √t	0.9311
Korsmeyer–Peppas Model	Log (Mt/M∞) vs Log t	0.9397

Particle Size and PDI Analysis

The particle size analysis of the optimized formulation (F6) showed an average vesicle size of 126.8 nm with a low PDI value of 0.169, indicating a narrow size distribution and good uniformity (Figure 5). The nanoscale size suggests enhanced dermal penetration and improved drug delivery. The low PDI (<0.3) confirms that the formulation is monodispersed and stable. These results indicate that the sonication process effectively reduced vesicle size and produced a homogeneous transferosomal system.

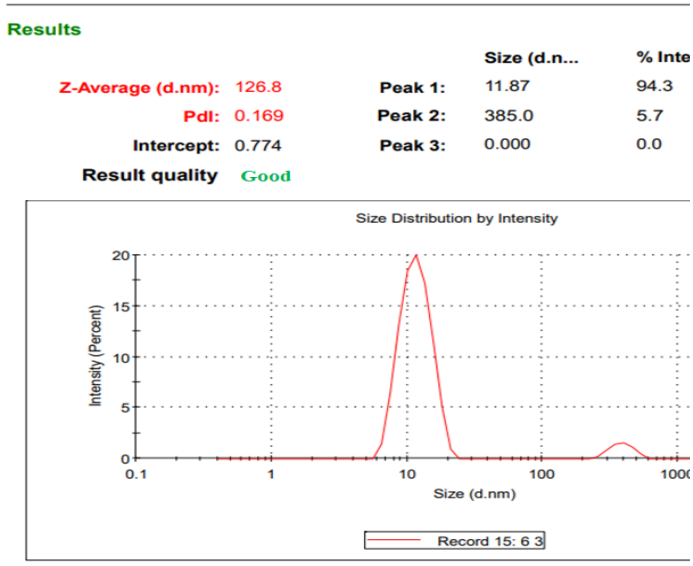

Figure 5: Particle Size Distribution and PDI of Optimised Formulation (F6)

Zeta Potential

The zeta potential of the optimized formulation was found to be **–32.0 mV**, indicating good electrostatic stability of the transferosomal vesicles (Figure 6). The high negative charge prevents aggregation by providing sufficient repulsive forces between particles. This ensures long-term stability of the formulation. The result confirms that the prepared transferosomes are physically stable and suitable for topical drug delivery applications.

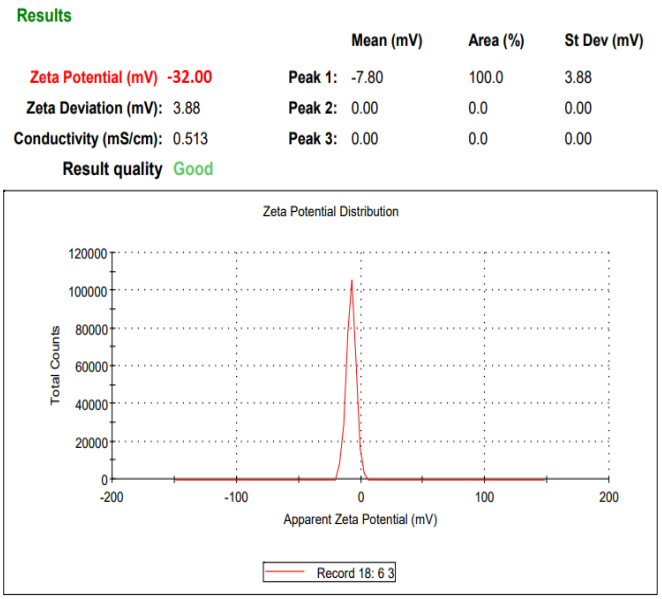

Figure 6: Zeta Potential Distribution of Optimised Formulation (F6)

Evaluation of Transferosomal Gel

The prepared gel showed suitable physicochemical properties with pH (6.3), good spreadability, high drug content (97.2%), and appropriate viscosity. No skin irritation was observed, indicating safety.

Table 6: Evaluation Parameters of Transferosomal Gel

Parameter	Result	Inference
pH	6.3	Skin compatible
Spreadability	5.8	Good
Drug content	97.2%	Uniform
Viscosity	28,500 cps	Suitable
Irritation	None	Safe

Comparative In-vitro Drug Release Study

The comparative drug release study clearly demonstrates that the transferosomal gel (F6) exhibited significantly higher drug release compared to the marketed formulation (Table 7, Figure 7). At 9 hours, F6 showed 97.03% release, whereas the marketed gel showed only 49.30%, indicating nearly two-fold enhancement. The enhancement factor was highest at initial time points, suggesting rapid drug availability followed by sustained release. This improved performance is attributed to the deformable nature of transferosomes, which enhances skin penetration and drug diffusion.

Table 7: Comparative in-vitro drug release profile of Bifonazole transferosomal gel (F6) and marketed gel (Bi-fone)

Time (h)	Marketed Bifonazole Gel (%) (Bi-fone)	Transferosomal Gel F6 (%)	Enhancement Factor
1	9.20	42.01	4.57×
2	10.53	49.33	4.69×
3	13.45	51.55	3.83×
4	16.68	59.32	3.56×
5	22.39	62.77	2.81×
6	25.87	68.21	2.64×

7	30.70	79.27	2.58×
8	35.21	85.53	2.43×
9	49.30	97.03	1.97×

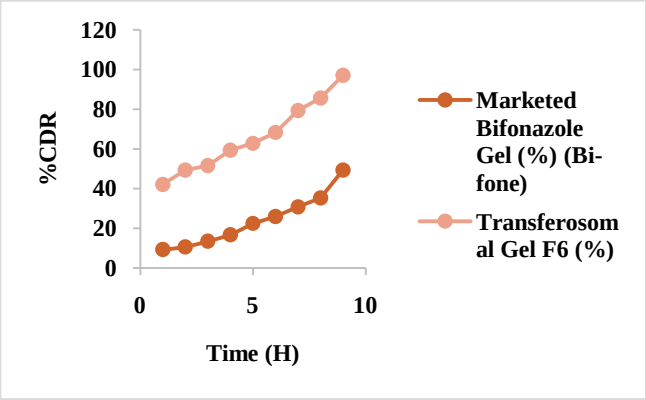

Figure 7: Comparative Drug Release Profile of Transferosomal Gel vs Marketed Gel

CONCLUSION

The present study successfully developed and evaluated a Bifonazole-loaded transferosomal topical gel for enhanced dermal drug delivery. Among all formulations, F6 was identified as the optimized formulation, showing highest entrapment efficiency (89.36%) and superior in-vitro drug release (86.23%). The optimized formulation exhibited nanosized vesicles (126.8 nm), low PDI (0.169), and good stability with a zeta potential of −32.0 mV. The transferosomal gel demonstrated significantly enhanced drug release (97.03%) compared to the marketed formulation (49.30%), confirming improved permeation and sustained release. Overall, the developed transferosomal gel offers a promising approach for effective management of tinea pedis and tinea corporis with improved therapeutic efficacy.

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AUTHOR CONTRIBUTIONS

B. Keerthi Reddy contributed to the experimental work, data collection, analysis, and manuscript preparation. A. Venkata Badarinath contributed to the study design, supervision, data interpretation, and critical revision of the manuscript. All authors have read and approved the final manuscript.

FUNDING

No

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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