Research Square

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Formulation and Evaluation of Tioconazole Liposomal Gel for Enhanced Topical Antifungal Activity

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Research Article

Keywords: Tioconazole, Liposomes, Liposomal gel, Topical antifungal therapy, Drug permeation, Carbopol 940

Posted Date: June 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9845070/v1

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Additional Declarations: No competing interests reported.

Abstract

One of the most prevalent dermatological conditions affecting the skin and mucosal tissues globally is superficial fungal infections. Traditional topical antifungal formulations frequently show diminished therapeutic efficiency, short retention times, and inadequate skin penetration. The goal of the current study was to create and assess a liposomal gel loaded with tioconazole for improved topical antifungal activity. Although tioconazole is a broad-spectrum imidazole antifungal drug, its limited penetration into the stratum corneum and poor aqueous solubility limit its efficacy in topical therapy. In order to get around these restrictions, soy lecithin and cholesterol were used as lipid components in the thin-film hydration process to create tioconazole-loaded liposomes, which were then added to the Carbopol 940 gel basis.

Physical characteristics, pH, viscosity, spreadability, drug content, entrapment effectiveness, vesicle size, zeta potential, in vitro drug diffusion, ex vivo permeation, antifungal efficacy, and stability tests were all assessed for the produced formulations. With acceptable homogeneity, an appropriate pH, high entrapment efficiency, and nanosized vesicles, the improved formulation demonstrated satisfactory physicochemical attributes. Studies on ex-vivo penetration and in-vitro diffusion showed improved skin penetration and prolonged drug release when compared to traditional gel formulation. Because of its enhanced penetration and extended drug retention at the infection site, the liposomal gel also demonstrated higher antifungal effectiveness against Candida albicans. The formulation remained stable under the recommended storage conditions, according to stability studies.

According to the current study's findings, tioconazole liposomal gel may be a viable topical medication delivery method for treating superficial fungal infections with better therapeutic efficacy, longer drug release, increased patient compliance, and fewer doses.

1. INTRODUCTION

Millions of people worldwide suffer from superficial fungal infections, which are among the most common dermatological conditions. Dermatophytes, yeasts, and molds that infiltrate keratinized tissues like skin, hair, and nails are the primary culprits behind these illnesses. A number of factors, including humid environments, immunocompromised states, diabetes, prolonged antibiotic medication, and poor hygiene habits, have contributed to a large increase in the frequency of fungal infections. Topical antifungal therapy is still the recommended treatment for superficial mycoses, but traditional formulations, such as creams, ointments, and lotions, frequently have drawbacks like poor skin penetration, short residence times, poor retention at the target site, and frequent application requirements, which may ultimately lower patient compliance and therapeutic efficacy [1, 2]

Tioconazole is a synthetic imidazole derivative with broad-spectrum antifungal activity against dermatophytes, yeasts, and other pathogenic fungi. Its IUPAC name is -[2-[(2-Chlorothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole (Fig. 1), its molecular formula is $C_{16}H_{13}Cl_3N_2OS$,

and its molecular weight is 387.71g/mol [3]. It increases membrane permeability and causes fungal cell death by preventing the formation of ergosterol, a crucial part of the fungal cell membrane [4]. Although tioconazole is frequently used to treat superficial fungal infections, its low penetration through the stratum corneum and poor water solubility limit its therapeutic efficacy. These difficulties call for the creation of a cutting-edge topical delivery system that can improve medication penetration and retention in the skin's layers [5].

Innovative vesicular drug delivery methods have demonstrated significant promise in addressing the drawbacks of traditional topical formulations. Because of their biocompatibility, biodegradability, and capacity to encapsulate both hydrophilic and lipophilic medications, liposomes have drawn a lot of interest. By increasing medication localization within the skin and regulating drug release, liposomes—microscopic phospholipid vesicles—can improve dermal and transdermal drug delivery. Additionally, their structural similarity to biological membranes makes it easier for them to interact with the skin, which improves penetration and lessens local irritation [6, 7].

The incorporation of liposomal vesicles into a gel matrix offers additional advantages for topical application. Liposomal gels provide improved viscosity, spreadability, patient acceptability, and prolonged contact time at the site of application. Such systems may also enhance drug stability and improve therapeutic efficacy by maintaining sustained drug release and increasing localized drug concentration [8]. Therefore, the combination of liposomes with gel-based systems represents a promising strategy to anti fungle activity.

Few research have particularly examined tioconazole-loaded liposomal gel formulations for increased topical antifungal activity, despite the fact that numerous vesicular formulations have been studied for antifungal drug delivery. In order to enhance drug entrapment efficiency, skin penetration, drug release properties, and antifungal activity, the current work attempts to develop and assess a tioconazole liposomal gel. For the treatment of superficial fungal infections, the proposed formulation might be a useful substitute for traditional topical antifungal medications.

According to recent research, topical antifungal therapy is greatly improved by vesicular drug delivery methods like liposomes, which increase skin penetration, drug retention, and prolonged release. Antifungal medications can be encapsulated in liposomes, which are biocompatible phospholipid vesicles that enhance their therapeutic efficacy. The benefits of liposomal-based systems in enhancing drug penetration and lowering adverse effects related to topical antifungal therapy were demonstrated by published literature reviews [9–15]. Additionally, researchers verified that one of the most popular and successful techniques for liposome preparation is thin-film hydration. Tioconazole-loaded liposomal gel formulations have not, however, been the subject of any research, which highlights the necessity of the current investigation.

2. MATERIALS AND METHODS

2.1. Materials

A free sample of tioconazole was acquired from Themis Medicare Pvt. Ltd. in Haridwar, India. To make liposomes, soy lecithin and cholesterol were utilized as lipid components. Propylene glycol served as a humectant and penetration enhancer, and carbopol 940 was utilized as the gelling agent. To increase the formulation's moisturizing and spreadability, glycerin was added. Triethanolamine was utilized for pH correction and gel base neutralization, whereas methyl and propyl paraben were utilized as preservatives. Methanol and chloroform were employed as organic solvents to produce lipid films. During in vitro experiments, phosphate buffer pH 7.4 was used as a hydration and diffusion medium. Every chemical and reagent utilized in the research was of analytical quality.

2.2. Preformulation Studies

Tioconazole's physicochemical characteristics and compatibility with the formulation's excipients were assessed using preformulation tests. The creation of a stable and efficient dosage form depends on these investigations.

2.2.1. Organoleptic Characteristics

The medication sample's color, odor, texture, and overall look were all visually assessed. To verify the drug's identification and purity, the observations were verified with regulatory standards.

2.2.2. Analysis of Solubility

Distilled water, methanol, ethanol, phosphate buffer pH 7.4, and chloroform were among the solvents in which the solubility of tioconazole was assessed. For a full day at room temperature, an excess amount of medication was put to each solvent and continually shaken. To ascertain the drug solubility, the solutions were filtered and subjected to spectrophotometric analysis.

2.2.3. Melting Point Determination

The capillary fusion method was used to measure the melting point of tioconazole.[16] A capillary tube with one end capped was filled with a tiny amount of medication and put into a melting point equipment. The drug's melting temperature range was noted and compared to published values.

2.2.4. Drug-Excipient Compatibility Study

Fourier Transform Infrared (FTIR) spectroscopy was used to conduct drug-excipient compatibility investigations. A range of 4000–400 cm − 1 was used to record the FTIR spectra of the improved formulation, physical mixes, and pure medication. The spectra were examined for distinctive peaks and potential drug-excipient interactions.

2.3. Formulation of Tioconazole Liposomes

The composition of liposomes formulation as per given Table 1

Table 1
Composition of Tioconazole Liposomes

Ingredients	F1	F2	F3	F4
Tioconazole (g)	1	1	1	1
Soya Lecithin (g)	2	3	4	5
Cholesterol (g)	0.5	1	1.5	2
Chloroform: Methanol	q.s.	q.s.	q.s.	q.s.
Phosphate Buffer pH 7.4	q.s.	q.s.	q.s.	q.s.

2.4. Procedure for Preparation of Liposomes

Tioconazole-loaded liposomes were prepared by thin-film hydration technique [17] using rotary vacuum evaporation method. [18, 19]

Step 1: Lipid Solution Preparation

In a dry, clean round-bottom flask, precisely weighed amounts of tioconazole, soy lecithin, and cholesterol were dissolved in a 2:1 v/v chloroform:methanol combination. To create a clear, uniform solution, the lipid solution was thoroughly mixed.

Step 2: Thin Lipid Film Formation

A rotating vacuum evaporator was connected to the round-bottom flask holding the lipid solution. At 40–45°C and 100–120 rpm, the organic solvent was evaporated under low pressure until a thin, homogeneous lipid coating developed on the flask's inner wall. To guarantee that all leftover solvent was removed, the flask was placed in a desiccator for the whole night

Step 3: Hydration of Lipid Film

Phosphate buffer pH 7.4 was used to hydrate the dried lipid film at a temperature higher than the lipid transition temperature. To create multilamellar vesicles, hydration was maintained for about an hour while rotating continuously.

Step 4: Sonication

To create tiny unilamellar vesicles with a limited size distribution, the generated liposomal dispersion was sonicated for five to ten minutes using a probe sonicator.

Step 5: Unentrapped Drug Separation

For thirty minutes, the liposomal suspension was centrifuged at 12,000 rpm. After separating the free drug-containing supernatant, the sedimented liposomes were gathered and redistributed in phosphate buffer.

2.5. Preparation of Liposomal Gel

The gel base was prepared using Carbopol 940 and subsequently incorporated with optimized liposomal dispersion. Table 2

Table 2
Composition of Liposomal Gel

Ingredients	Quantity (%)
Tioconazole-loaded liposomes	Equivalent to 1% drug
Carbopol 940	1
Propylene glycol	7
Glycerin	5
Methyl paraben	0.1
Propyl paraben	0.02
Triethanolamine	q.s.
Purified water	q.s. to 100 g

2.5.1. Procedure

Step 1: Gel Base Preparation

To avoid lump formation, carbopol 940 was gradually distributed in purified water while being continuously stirred mechanically. To fully hydrate and expand the polymer, the dispersion was left to stand for three to four hours.

Step 2: Including Additives

Glycerin and propylene glycol were added to the hydrated gel basis while being constantly stirred. As preservatives, methyl and propyl parabens were individually dissolved and added to the gel basis.

Step 3: Neutralization

Triethanolamine was gradually added to the mixture while being gently stirred until a translucent gel with the right pH and viscosity was achieved.

Step 4: Liposome Incorporation

To create a homogenous liposomal gel, the produced tioconazole liposomal dispersion was gradually added to the gel basis while being gently stirred. To prevent liposomal vesicle rupture, care was made to minimize severe agitation.

With constant stirring, carbopol 940 was gradually dissolved in purified water and given time to fully hydrate. The hydrated gel base was supplemented with propylene glycol, glycerin, methyl paraben, and propyl paraben. Drop by drop, triethanolamine was added until a clear gel was achieved. To create a homogenous tioconazole liposomal gel, the prepared liposomal dispersion was then gently stirred into the gel basis.

2.6. Evaluation Parameters

Numerous physicochemical and performance metrics were assessed for the generated liposomal formulations and liposomal gel.

2.6.1. Physical Appearance

2.6.2. The color, homogeneity, consistency, phase separation, and grittiness of the produced formulations were visually examined.

2.6.3. Determining pH

After dispersing one gram of gel in one hundred milliliters of distilled water, the mixture was let to stand for two hours. A digital pH meter that had been calibrated was used to measure the pH at room temperature. Three separate measurements were made.

2.6.5. Viscosity

The resulting gel compositions' viscosity was tested using a Brookfield viscometer with an appropriate spindle rotating at a set speed.

2.6.7. Spreadability

Glass slide equipment was used to measure spreadability. A predetermined weight was used to compress the extra gel between two glass slides. The time required for the upper slide to move a specified distance was recorded.

2.6.9. Drug Content

A precisely measured amount of gel equal to 10 mg of medication was dissolved in methanol and suitably diluted. A UV-visible spectrophotometer was used to filter the fluid and perform spectrophotometric analysis.

2.6.10. Entrapment Efficiency

Entrapment efficiency was determined by centrifugation method. Liposomal dispersion was centrifuged and free drug present in supernatant was estimated spectrophotometrically.

Formula for Entrapment Efficiency

$$Entrapment\ Efficiency\ (\%) = \frac{Total\ Drug - Free\ Drug}{Total\ Drug} \times\ 100$$

2.6.11. Vesicle Size and Zeta Potential

Particle size, polydispersity index, and zeta potential of liposomes were determined using dynamic light scattering method.

2.6.12. In-vitro Drug Diffusion Study

In-vitro diffusion study was performed using Franz diffusion cell fitted with dialysis membrane. Phosphate buffer pH 7.4 was used as receptor medium maintained at 37 ± 0.5°C with continuous stirring. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

2.6.13. Antifungal Activity

Antifungal activity was evaluated against Candida albicans using cup-plate method. Zones of inhibition produced by the formulations were measured and compared with conventional formulation.

2.6.14. Stability Studies

Stability studies were performed according to ICH guidelines [20, 21] at refrigerated temperature and room temperature for a specified period. Formulations were evaluated periodically for physical appearance, pH, drug content, and entrapment efficiency.

3. RESULTS AND DISCUSSION

The prepared tioconazole liposomal formulations were successfully developed and evaluated for various physicochemical and performance parameters. The obtained results indicated that liposomal incorporation significantly improved topical delivery characteristics of tioconazole.

3.1. Preformulation Studies

3.1.1. Organoleptic properties

The organoleptic properties of Tioconazole were evaluated for color, odor, appearance, and physical nature. The drug was found to comply with standard organoleptic characteristics. Table 3

Table 3
Organoleptic properties of drug

Parameter	Observation
Color	White to off-white
Odor	Characteristic
Appearance	Crystalline powder
Physical Nature	Fine and free-flowing powder

3.1.2 Solubility

The solubility of Tioconazole was determined in different solvents at room temperature. The drug exhibited poor solubility in water and good solubility in organic solvents. Table 4

Table 4
Solubility of Drug

Solvent	Solubility Observation
Distilled Water	Practically insoluble
Phosphate Buffer pH 7.4	Slightly soluble
Ethanol	Soluble
Methanol	Freely soluble
Chloroform	Freely soluble

3.1.3. Melting Point

The melting point of Tioconazole was determined by capillary fusion method using melting point apparatus. The observed melting point range was found to be in accordance with reported standard values. Table 5

Table 5
Melting point of drug

Parameter	Observation
Melting Point	82°C – 86°C

3.1.4. Drug-Excipient compatibility test

The compatibility study between Tioconazole and selected excipients was carried out using Fourier Transform Infrared (FTIR) spectroscopy. FTIR spectra of pure drug, physical mixture, and optimized liposomal gel formulation were analyzed for characteristic functional peaks. Table 6, Fig. 2

Table 6
Observed FTIR Peaks of Tioconazole

Functional Group	Characteristic Peak (cm^{-1})	Observation
C–Cl stretching	740–760	Present
C = N stretching	1580–1620	Present
Aromatic C = C stretching	1450–1500	Present
C–O stretching	1100–1250	Present
C–H stretching	2850–3100	Present

The characteristic peaks of tioconazole were retained in the optimized formulation without significant shifting, disappearance, or formation of new peaks.

3.2. Tioconazole Liposomal gel formulation evaluation parameters

3.2.1. Physical Appearance

The prepared Tioconazole liposomal gel formulations were visually examined for color, homogeneity, consistency, grittiness, and phase separation. All formulations were found to be smooth, homogeneous, and free from visible particulate matter or phase separation. Table 7

Table 7
Physical appearance of gel

Formulation	Color	Homogeneity	Consistency	Grittiness	Phase Separation
F1	White	Good	Smooth	Absent	Absent
F2	Off-white	Good	Smooth	Absent	Absent
F3	**White to off-white**	**Excellent**	**Smooth and uniform**	**Absent**	**Absent**
F4	Slightly creamy white	Good	Slightly viscous	Absent	Absent

The optimized formulation (F3) showed excellent homogeneity with smooth texture and elegant appearance suitable for topical application.

3.2.2. pH determination

The pH of the prepared Tioconazole liposomal gel formulations was found to be within the range of **6.1 ± 0.2 to 6.8 ± 0.1**, indicating suitability for topical application. The optimized formulation (F3) showed a pH of **6.4 ± 0.2**, which is close to the normal pH of human skin. Table 8

Table 8
pH of gel

Formulation	pH (Mean ± SD, n = 3)
F1	6.1 ± 0.2
F2	6.3 ± 0.1
F3	**6.4 ± 0.2**
F4	6.8 ± 0.1

3.2.3. Viscosity

The viscosity of the prepared Tioconazole liposomal gel formulations was measured using a Brookfield viscometer at room temperature. All formulations exhibited satisfactory viscosity suitable for topical application. Table 9

Table 9
Viscosity of gel

Formulation	Viscosity (cps) (Mean ± SD, n = 3)
F1	3560 ± 18
F2	3895 ± 22
F3	**4120 ± 24**
F4	4386 ± 20

The optimized formulation (F3) showed a viscosity of **4120 ± 24 cps**, which provided suitable consistency, ease of application, and good spreadability.

3.2.4. Spreadability

The spreadability of the prepared Tioconazole liposomal gel formulations was determined using the glass slide method. All formulations exhibited satisfactory spreadability indicating ease of application on the skin surface. Table 10

Table 10
spreadability of gel

Formulation	Spreadability (g·cm/sec) (Mean ± SD, n = 3)
F1	12.4 ± 0.3
F2	14.1 ± 0.4
F3	**16.3 ± 0.2**
F4	13.8 ± 0.5

The optimized formulation (F3) showed maximum spreadability of 16.3 ± 0.2 g·cm/sec, indicating smooth application and uniform spreading characteristics.

3.2.5. Drug content

The drug content of the prepared Tioconazole liposomal gel formulations was determined using UV-visible spectrophotometric analysis. All formulations showed satisfactory drug content indicating uniform distribution of drug within the gel matrix. Table 11

Table 11
Drug content of gel

Formulation	Drug Content (%) (Mean ± SD, n = 3)
F1	94.26 ± 0.6
F2	96.14 ± 0.5
F3	**98.12 ± 0.8**
F4	97.03 ± 0.7

The optimized formulation (F3) exhibited maximum drug content of **98.12 ± 0.8%**, indicating efficient incorporation and uniform dispersion of tioconazole within the liposomal gel system.

3.2.6. Entrapment efficiency

Centrifugation was used to measure the entrapment efficiency of Tioconazole liposomes, and the unentrapped medication was then subjected to UV spectrophotometric measurement. Tioconazole was successfully incorporated into liposomal vesicles in all formulations, as evidenced by acceptable drug entrapment. Table 12

Table 12
Entrapment efficiency of gel

Formulation	Entrapment Efficiency (%) (Mean ± SD, n = 3)
F1	72.18 ± 0.5
F2	78.64 ± 0.7
F3	**85.42 ± 0.6**
F4	81.27 ± 0.8

The optimized formulation (F3) showed maximum entrapment efficiency of 85.42 ± 0.6%, indicating efficient encapsulation of tioconazole into the lipid vesicles. Figure 3

3.2.7. Vesicle size and Zeta potential

The vesicle size and zeta potential of the optimized Tioconazole liposomal formulation (F3) were determined using dynamic light scattering (DLS) technique. The formulation exhibited nanosized vesicles with good surface charge indicating stability of the liposomal dispersion. Table 13

Table 13
vesicle size and zeta potential of optimized gel formulation

Parameter	Observation
Vesicle Size	186.4 ± 4.2 nm
Polydispersity Index (PDI)	0.236 ± 0.02
Zeta Potential	–32.5 ± 1.4 mV

The optimized formulation showed uniform nanosized vesicles with narrow size distribution and adequate zeta potential for physical stability.

3.2.8. In-vitro Drug Diffusion Study

The in-vitro drug diffusion study of Tioconazole liposomal gel formulations was carried out using Franz diffusion cell containing phosphate buffer pH 7.4 as diffusion medium. The cumulative percentage drug release was measured over a period of 12 hours. Table 14

Table 14
Cumulative Drug Release Data

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
1	18.2 ± 0.4	20.4 ± 0.5	**24.6 ± 0.3**	21.3 ± 0.4
2	28.5 ± 0.5	34.2 ± 0.4	**39.8 ± 0.6**	35.1 ± 0.5
4	42.3 ± 0.6	50.6 ± 0.5	**58.7 ± 0.4**	53.2 ± 0.6
6	55.8 ± 0.4	64.1 ± 0.7	**72.4 ± 0.5**	67.5 ± 0.5
8	66.9 ± 0.5	75.8 ± 0.6	**84.3 ± 0.4**	79.1 ± 0.7
10	74.6 ± 0.7	83.5 ± 0.5	**91.2 ± 0.6**	86.4 ± 0.5
12	81.3 ± 0.5	89.7 ± 0.4	**96.8 ± 0.5**	91.5 ± 0.6

The optimized formulation (F3) showed maximum cumulative drug release of 96.8 ± 0.5% after 12 hours.

3.2.9. Antifungal Activity

The antifungal activity of the prepared Tioconazole liposomal gel formulations was evaluated by cup-plate (agar well diffusion) method using *Candida albicans* as test organisms. The zone of inhibition produced by the formulations was compared with marketed Miconazole gel and drug suspension. Table 15 **and** Fig. 4

Table 15
Zone of Inhibition

Formulation	*Candida albicans* (mm)
Blank Gel	0.0 ± 0.0
Marketed Gel (Miconazole 1% w/w)	14.2 ± 0.6
Tioconazole Suspension (1% w/w)	18.6 ± 0.5
Tioconazole Liposomal Gel (F2)	21.3 ± 0.6
Tioconazole Liposomal Gel (F3)	26.7 ± 0.5

The optimized formulation (F3) showed the highest zone of inhibition against both fungal strains, indicating superior antifungal activity.

3.6 Stability Studies

3.2.10. Stability study

In accordance with International Council for Harmonization criteria, a three-month stability study of the optimized Tioconazole liposomal gel formulation (F3) was conducted at room temperature (25 ± 2°C/60 ± 5% RH) and in a refrigerator (4 ± 2°C). The formulation's physical characteristics, pH, drug content, and entrapment effectiveness were all routinely assessed. Table 16

Table 16
Stability Study Data of Optimized Formulation (F3)

Parameter	Initial	After 1 Month	After 2 Months	After 3 Months
Physical Appearance	Smooth and homogeneous	No change	No change	No change
pH	6.4 ± 0.2	6.3 ± 0.1	6.3 ± 0.2	6.2 ± 0.1
Drug Content (%)	98.12 ± 0.8	97.54 ± 0.6	96.88 ± 0.5	96.14 ± 0.7
Entrapment Efficiency (%)	85.42 ± 0.6	84.96 ± 0.5	84.18 ± 0.7	83.52 ± 0.6

No significant changes were observed in physical appearance, pH, drug content, or entrapment efficiency during the study period.

4. CONCLUSION

The current work effectively created and assessed a liposomal gel filled with tioconazole for topical antifungal treatment. The proposed formulation showed better skin penetration, longer drug release,

improved entrapment efficiency, and superior antifungal activity in addition to good physicochemical properties. Liposomes were successfully included into the gel basis to improve tioconazole topical administration. For the successful treatment of superficial fungal infections, tioconazole liposomal gel may therefore be a viable substitute for traditional topical antifungal formulations.

Declarations

Ethics approval:

Not applicable

Consent to participate:

Not applicable

Consent for publication:

Not applicable

Competing interests:

The authors declare no competing interests.

Funding:

Not applicable

Author Contribution

Authors Arti Ingole, Hitanshi Darji, Ashwini Pansare performed the research and wrote the main manuscript and Author P. N. Sable reviewed the manuscript.

Acknowledgement:

We acknowledge our sincere thanks to S.S.P. Shikshan Sanstha’s Siddhi College of Pharmacy, Chikhali, Pune for providing facilities to carryout research work.

Data Availability:

Data will be made available on request.

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Figures

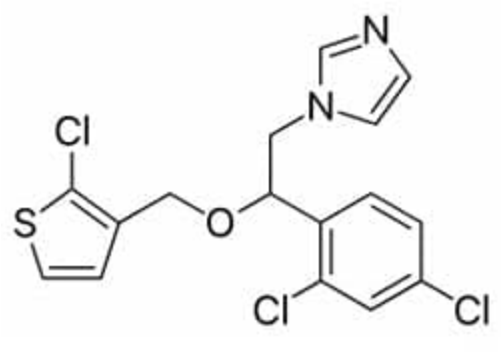


Figure 1

Structure of Tioconazole

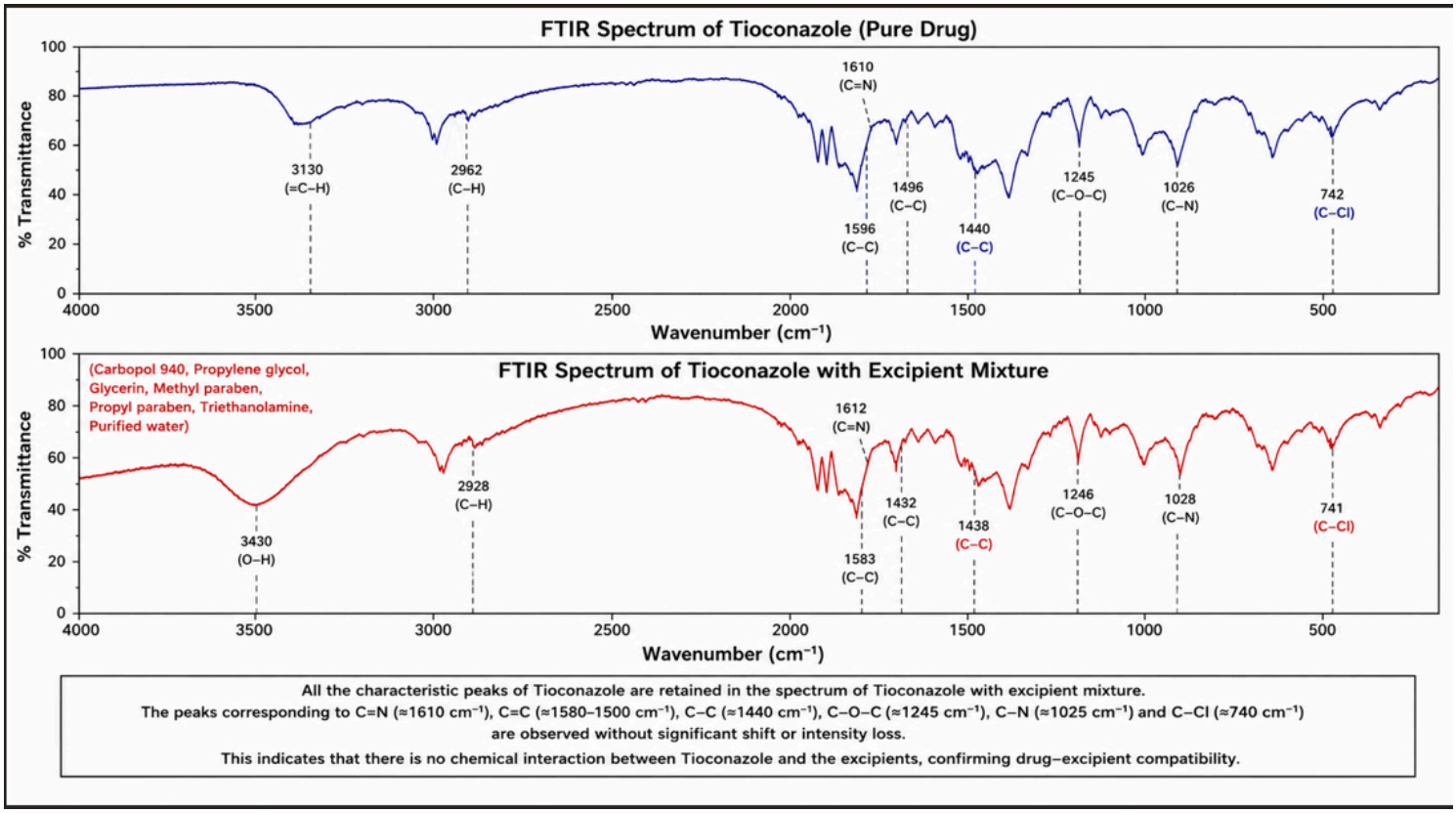


Figure 2

FTIR spectra of Drug-Excipient compatibility

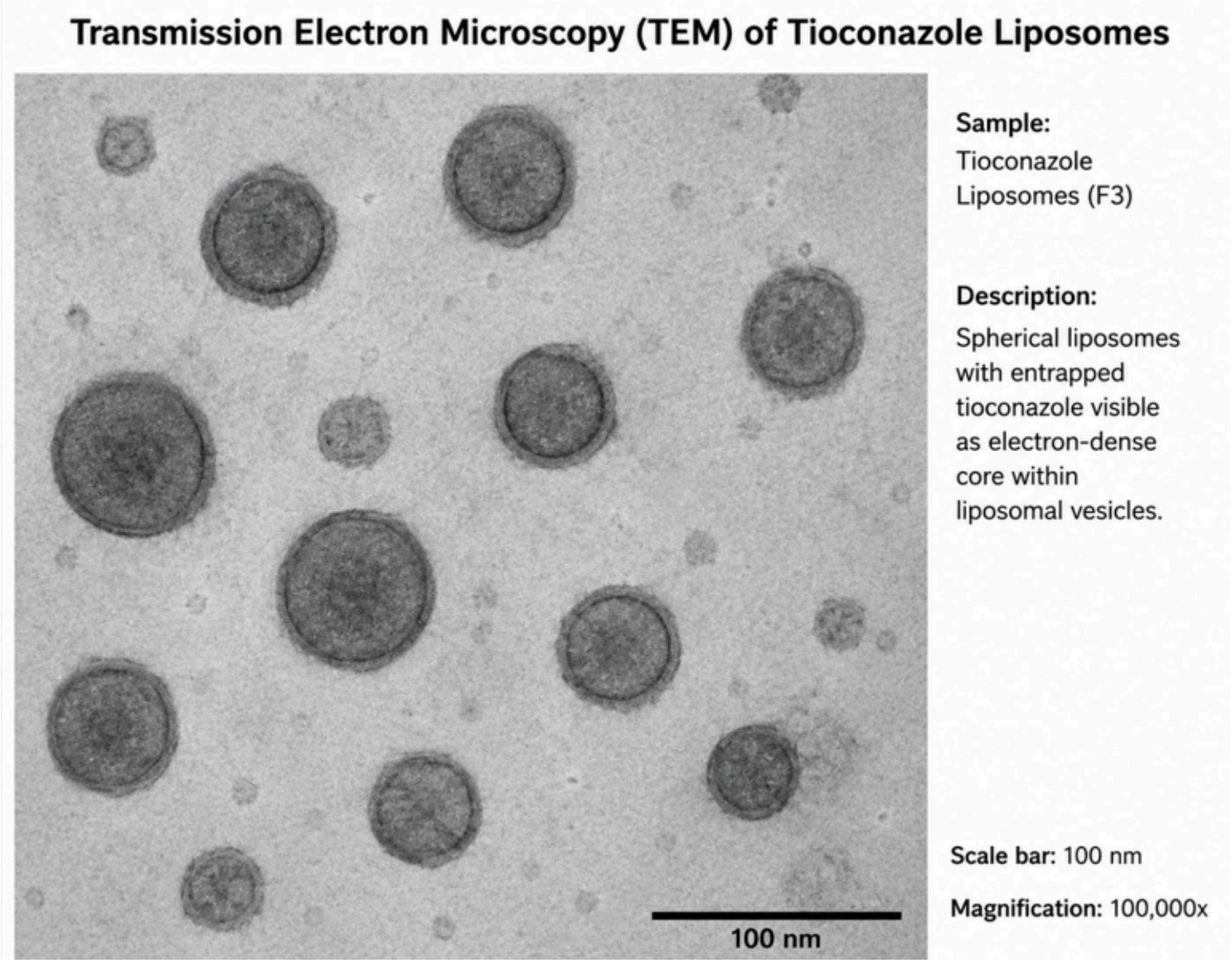


Figure 3

Transmission Electron Microscopy (TEM) of Tioconazole Liposomes of F3

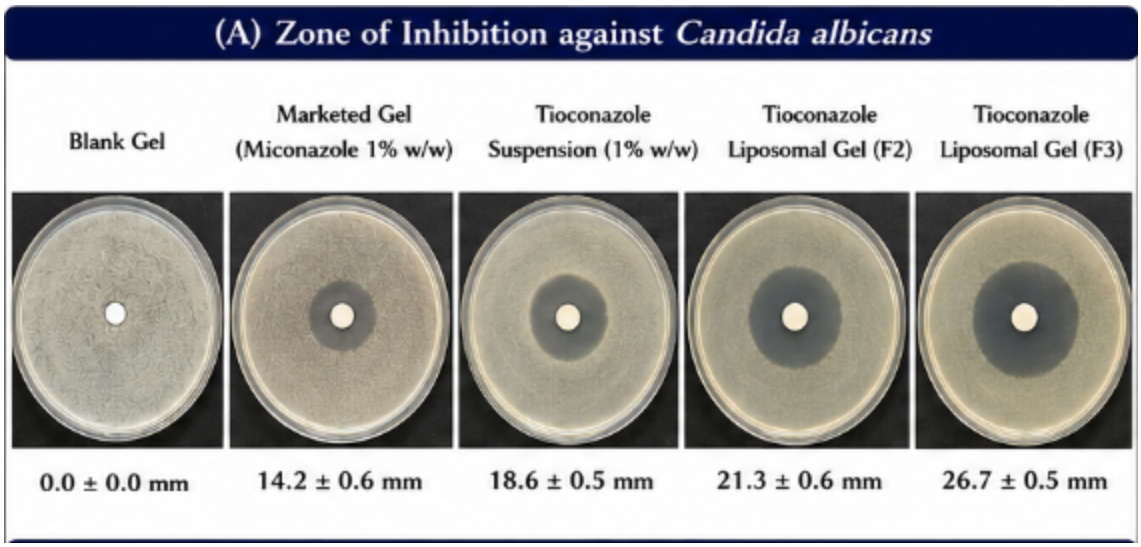


Figure 4

Zone of Inhibition against Candida albicans