

Characterization & Optimization Itraconazole Loaded Deformable Lipid Vesicles: A Novel Approach Antifungal Management

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Abstract

Background: Itraconazole is a lipophilic antifungal drug with limited aqueous solubility, which may restrict its effective delivery across biological membranes. The present study was undertaken to develop an ultra-deformable lipid-based vesicular system of Itraconazole and incorporate the selected ethosomal formulation into a polymeric gel to improve drug permeation.

Methods: Itraconazole was subjected to preformulation studies including UV spectrophotometric identification, FTIR analysis, solubility studies and partition coefficient determination. Ethosomal formulations were prepared by the cold method using different concentrations and combinations of ethanol, phospholipid, surfactants, co-solvents and oil phases. The formulations were screened on the basis of clarity, phase separation, microscopic appearance and stress stability. Selected ethosomal formulations were incorporated into Carbopol 980 NF, HPMC 15000 cps and Xanthan gum gel bases. The prepared formulations were evaluated for vesicle size, polydispersity index, entrapment efficiency, drug content, physical characteristics and in-vitro drug permeation using a Franz diffusion cell.

Results: Itraconazole showed a λ_{max} of 264 nm and exhibited a partition coefficient of 5.67, indicating its lipophilic nature. Among the screened ethosomal formulations, F20, F21 and F22 showed satisfactory physical characteristics and stability. F22 exhibited the smallest mean vesicle size of 171.8 ± 4.37 nm, lowest PDI of 0.196 ± 0.010 , highest entrapment efficiency of $89.30 \pm 1.05\%$ and highest drug content of $98.10 \pm 0.64\%$. These formulations were incorporated into three polymeric gel bases. Among the developed gels, the Carbopol 980 NF-based formulations showed comparatively higher drug permeation. The optimized formulation C22, containing F22 ethosomes in 1.5% w/w Carbopol 980 NF gel, showed 64.83 mg cumulative drug permeation and 86.44% drug permeation at 12 h.

Conclusion: The study demonstrated that an ultra-deformable Itraconazole ethosomal gel can be successfully developed using Carbopol 980 NF as the polymeric gel base. Formulation C22 showed satisfactory vesicular characteristics, drug entrapment, drug content and in-vitro permeation, and maintained acceptable physical and performance characteristics during three months of stability evaluation.

Keywords: Itraconazole; Ethosomes; Ultra-deformable vesicles; Ethosomal gel; Carbopol 980 NF; Drug permeation.

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Introduction

Fungal infections are common infectious diseases caused by pathogenic fungi and may affect the skin, nails, mucosal surfaces and other parts of the body. Superficial and cutaneous fungal infections are particularly common and can cause itching, redness, irritation, scaling and discomfort. The treatment of fungal infections mainly depends on antifungal drugs, and the choice of drug and dosage form depends on the site and severity of infection. Although several antifungal agents are available, effective delivery of these drugs to the required site remains an important consideration in formulation

development. Itraconazole is a broad-spectrum triazole antifungal drug used for the treatment of various fungal infections. It acts mainly by inhibiting the synthesis of ergosterol, an important component of the fungal cell membrane. Itraconazole has activity against a wide range of pathogenic fungi and is therefore considered an important antifungal agent. However, its physicochemical properties present challenges during formulation development. The drug is poorly water soluble and shows a lipophilic nature, which can affect its dissolution and movement

through aqueous biological environments. The development of suitable drug delivery systems can help overcome some of these limitations. Vesicular drug delivery systems have received considerable attention because they can improve drug incorporation and facilitate drug transport across biological membranes.

Ethosomes are lipid-based vesicular systems containing a relatively high concentration of ethanol along with phospholipids and other formulation components. The presence of ethanol provides flexibility to the vesicles and allows them to deform and pass through narrow pathways in biological membranes.

This property makes ethosomes useful for improving the delivery and permeation of drugs across the skin and other biological barriers.

Aim and Objectives

Aim: To develop and evaluate an Itraconazole-loaded ultra-deformable ethosomal gel for enhanced drug permeation.

Objectives

- To perform preformulation studies of Itraconazole.
- To develop and screen Itraconazole-loaded ethosomal formulations.
- To incorporate the selected ethosomes into different polymeric gel bases.

- To evaluate the formulations for vesicle size, entrapment efficiency, drug content and in-vitro drug permeation.
- To select and evaluate the optimized ethosomal gel formulation for stability.

Materials and Methods

Materials: Itraconazole, ethanol, lecithin, Span 20, Span 80, Tween 20, lactic acid, oleic acid, DMSO, benzyl alcohol, propylene glycol, sodium benzoate, Carbopol 980 NF, HPMC 15000 cps and Xanthan gum were used for formulation development.

Methods

Preformulation Studies: Itraconazole was evaluated for UV absorption, FTIR, solubility and partition coefficient. The λ_{max} of the drug was determined by UV spectroscopy and found to be 264 nm.

Preparation of Ethosomes: Itraconazole-loaded ultra-deformable vesicles were prepared by the cold method. Phospholipid was dissolved in ethanol and stirred. Itraconazole was dissolved separately in the selected oil phase and surfactant and then added to the ethanolic solution. Water maintained at 30°C was added gradually and the mixture was stirred for 5 min. The prepared vesicular dispersion was sonicated using a probe sonicator to reduce vesicle size.

Table 1: Formulation of Itraconazole Ethosomal Preparations

Formulation	Drug	Ethanol (mL)	Oil/Co-solvent (mL)	Surfactant (mL)	Phospholipid	Water
F1	10 mg	1.07	Oleic acid 0.28 + Lactic acid 0.28	Span 80 0.14 + Span 20 0.15	Lecithin 35 (0.08)	1:1
F2	10 mg	1.36	Lactic acid 0.36	Span 20 0.19	Lecithin 70 (0.09)	1:1
F3	10 mg	1.08	Ethyl oleate 0.28 + Lactic acid 0.28	Span 20 0.14 + Span 80 0.14	Lecithin 35 (0.08)	1:1
F4	10 mg	1.27	Benzyl benzoate 0.09 + Benzyl alcohol 0.09 + Lactic acid 0.37	Span 20 0.18	—	1:1
F5	10 mg	1.07	Octanol 0.28 + Oleic acid 0.28 + Lactic acid 0.28	—	Lecithin 35 (0.09)	1:1
F6	10 mg	1.50	Lactic acid 0.20	Span 80 0.20	Lecithin 35 (0.10)	1:1
F7	10 mg	1.36	Oleic acid 0.18 + Lactic acid 0.18	Span 80 0.18	Lecithin 35 (0.10)	1:1
F8	10 mg	1.27	DMSO 0.09 + Lactic acid 0.36	Span 20 0.18	Lecithin 35 (0.10)	1:1
F9	10 mg	1.07	DMSO 0.08 + Ethyl oleate 0.16 + Oleic acid 0.23 + Lactic acid 0.30	Span 20 0.16	—	1:1
F10	10 mg	1.17	Benzyl benzoate 0.09 + Benzyl alcohol 0.09 +	Span 65 0.16	Lecithin 35 (0.09)	1:1

			Oleic acid 0.16 + Lactic acid 0.10			
F11	10 mg	1.08	Isopropyl myristate 0.28 + Oleic acid 0.28 + Lactic acid 0.28	—	Lecithin 35 (0.08)	1:1
F12	10 mg	1.50	Oleic acid 0.20 + Lactic acid 0.20	—	Lecithin 35 (0.10)	1:1
F13	10 mg	1.04	Lauryl alcohol 0.46 + Oleic acid 0.20 + Lactic acid 0.20	—	Lecithin 35 (0.10)	1:1
F14	10 mg	1.07	Octanol 0.15 + Isopropyl myristate 0.15 + Oleic acid 0.28 + Lactic acid 0.28	Lecithin 70 (0.09)	—	1:1
F15	10 mg	0.74	Lauryl alcohol 0.32 + Octanol 0.15 + Isopropyl myristate 0.15 + Oleic acid 0.28 + Lactic acid 0.28	—	Lecithin 35 (0.08)	1:1
F16	10 mg	1.00	Lactic acid 0.60	Span 20 0.40	—	1:1
F17	10 mg	0.90	Lactic acid 0.60	Span 20 0.50	—	1:1
F18	10 mg	0.80	Lactic acid 0.40	Span 20 0.40	Lecithin 35 (0.40)	1:1
F19	10 mg	0.90	Lactic acid 0.50	Span 20 0.60	—	1:1
F20	10 mg	Ethanol (0.8)	Lactic acid (0.4)	Span 20 (0.4)	Lacivia 70 (0.4)	(1:1)
F21	10 mg	Ethanol (0.96)	Oleic acid (0.2)	Span 80 (0.18), Tween 20(0.19)	Lacivia 70 (0.47)	(1:1)
F22	10 mg	Ethanol (1ml)	Lactic acid (0.4)	-	Lacivia 70 (0.6)	(1:1)

Screening of Ethosomal Formulations: The formulations were screened for clarity, phase separation, microscopy and stress stability. Based on these parameters, F20, F21 and F22 were selected for further formulation development.

three polymeric gel bases: Carbopol 980 NF (1.5% w/w), HPMC 15000 cps (4% w/w) and Xanthan gum (2.5% w/w). The ethosomal dispersions were incorporated by gentle stirring to obtain a final Itraconazole concentration of 2% w/w.

Preparation of Ethosomal Gel: The selected ethosomal formulations were incorporated into

Table 2: Formulation Coding of Itraconazole Ethosomal Gels

Formulation Code	Ethosomal Batch	Gelling Polymer	Polymer Concentration
C20	F20	Carbopol 980 NF	1.5% w/w
H20	F20	HPMC 15000 cps	4% w/w
X20	F20	Xanthan gum	2.5% w/w
C21	F21	Carbopol 980 NF	1.5% w/w
H21	F21	HPMC 15000 cps	4% w/w
X21	F21	Xanthan gum	2.5% w/w
C22	F22	Carbopol 980 NF	1.5% w/w
H22	F22	HPMC 15000 cps	4% w/w
X22	F22	Xanthan gum	2.5% w/w

Evaluation of Formulations: The prepared formulations were evaluated for vesicle size, PDI, entrapment efficiency, drug content and in-vitro drug permeation.

In-Vitro Drug Permeation Study: In-vitro drug permeation was performed using a Franz diffusion cell with egg membrane. Phosphate buffer pH 6.8 containing 30% ethanol was used as receptor medium and maintained at $37 \pm 2^\circ\text{C}$. Samples were

withdrawn at predetermined intervals and analysed by UV spectroscopy at 264 nm.

Results And Discussion

Preformulation Studies: Itraconazole showed maximum absorbance at 264 nm. The calibration curves in 0.1 N HCl and pH 6.8 phosphate buffer showed good linearity in the concentration range of

1–10 $\mu\text{g/mL}$, with R^2 values of 0.9999978 and 0.9999981, respectively. The highest solubility of Itraconazole was observed in Transcutol P (6.15 mg/mL), followed by Tween 80 (5.42 mg/mL) and Cremophor RH 40 (4.68 mg/mL). The partition coefficient was 5.67, with log $K_{\text{o/w}}$ of 0.75, indicating the lipophilic nature of the drug.

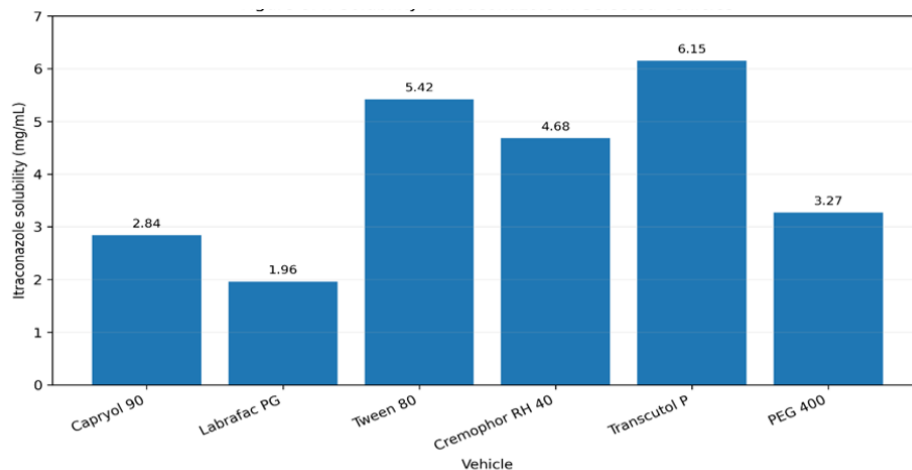


Figure 1: Solubility of Itraconazole in Selected Vehicles

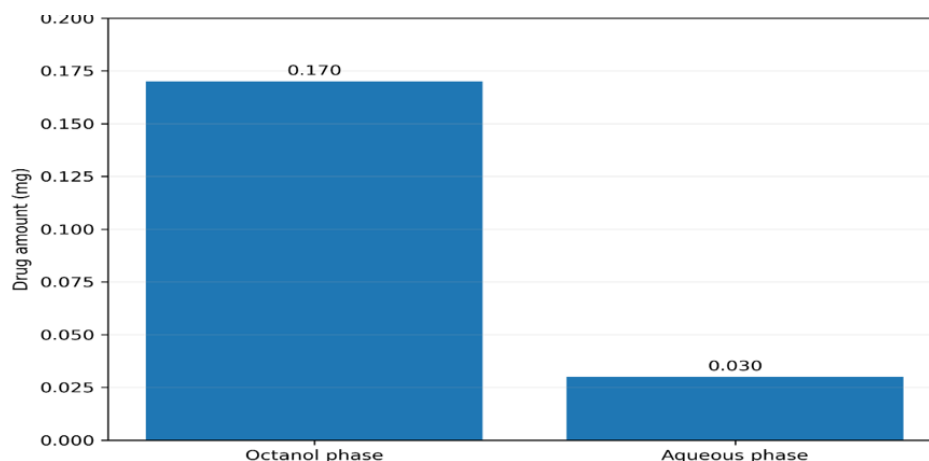


Figure 2: Distribution of Itraconazole between Octanol and Aqueous Phases

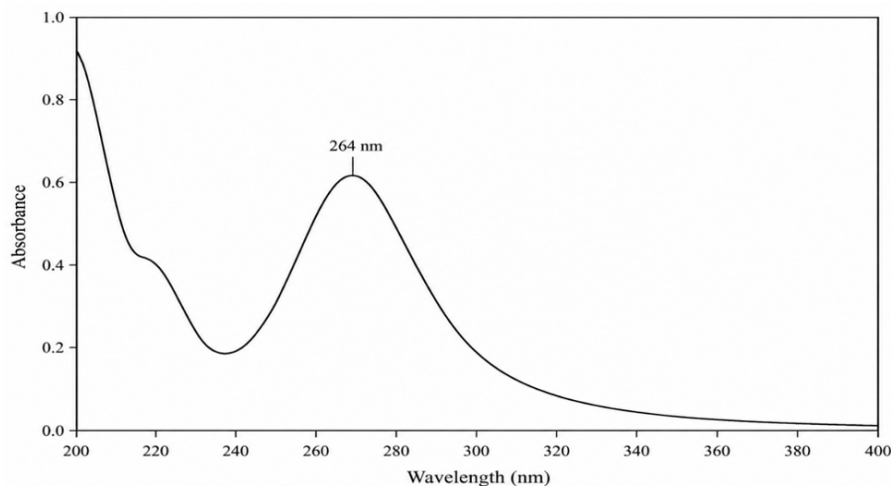
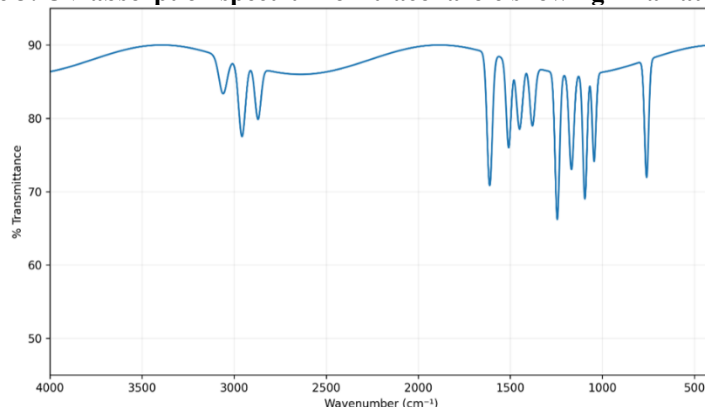


Figure 3: UV absorption spectrum of Itraconazole showing λ_{max} at 264 nm**Figure 4: FTIR Spectrum of Itraconazole**

Screening of Ethosomal Formulations: The prepared ethosomal formulations were screened for clarity, phase separation, microscopic characteristics and stress stability. Based on these studies, F20, F21 and F22 were selected for further evaluation.

Table3: Evaluation of Selected Ethosomal Formulations

Parameter	F20	F21	F22
Vesicle size (nm)	184.6 $\pm$ 4.82	207.3 $\pm$ 5.16	171.8 $\pm$ 4.37
PDI	0.214 $\pm$ 0.012	0.238 $\pm$ 0.015	0.196 $\pm$ 0.010
Entrapment efficiency (%)	84.60 $\pm$ 1.24	87.10 $\pm$ 1.18	89.30 $\pm$ 1.05
Drug content (%)	96.20 $\pm$ 0.86	97.40 $\pm$ 0.72	98.10 $\pm$ 0.64

F22 showed the smallest vesicle size and PDI, along with the highest entrapment efficiency and drug content. Therefore, F22 was considered the best among the selected ethosomal formulations.

all nine ethosomal gel formulations. At 12 h, C22 showed the highest drug permeation of 64.83 mg (86.44%), followed by X22 with 60.42 mg (80.56%) and C21 with 57.92 mg (77.23%).

In-Vitro Drug Permeation Study: Drug permeation increased progressively with time for

Table4: In-Vitro Drug Permeation Study

Formulation	Drug permeation at 12 h (%)
C20	69.97
H20	63.13
X20	67.52
C21	77.23
H21	68.35
X21	73.52
C22	86.44
H22	74.49
X22	80.56

Optimized Formulation: Based on the permeation results, C22 was selected as the optimized formulation. It contained F22 ethosomes incorporated into 1.5% w/w Carbopol 980 NF gel and showed 86.44% drug permeation at 12 h.

Stability Study: After three months, C22 showed only minor changes. Vesicle size increased from 171.8 $\pm$ 4.37 to 176.4 $\pm$ 4.72 nm, entrapment efficiency decreased from 89.30 $\pm$ 1.05 to 87.58 $\pm$ 1.16%, and drug content decreased from 98.10 $\pm$ 0.64 to 96.91 $\pm$ 0.75%. Drug permeation decreased

from 86.44% to 83.92% at 12 h. No visible phase separation was observed.

Summary and Conclusion

Summary: The present study was carried out to develop an Itraconazole-loaded ultra-deformable ethosomal gel for improved drug permeation.

Preformulation studies confirmed the suitability of Itraconazole for formulation development. Different ethosomal formulations were prepared and screened, from which F20, F21 and F22 were

selected for further evaluation. Among the selected formulations, F22 showed the best vesicle characteristics, with a vesicle size of 171.8 ± 4.37 nm, PDI of 0.196 ± 0.010 , entrapment efficiency of $89.30 \pm 1.05\%$ and drug content of $98.10 \pm 0.64\%$. The selected ethosomes were incorporated into Carbopol 980 NF, HPMC and Xanthan gum gels. Among all gel formulations, C22 showed the highest drug permeation of 86.44% at 12 h and was selected as the optimized formulation.

Conclusion

The study concluded that C22, containing F22 ethosomes in Carbopol 980 NF gel, was the optimized formulation. It provided improved in-vitro drug permeation and showed satisfactory stability during the study period. Thus, the developed ultra-deformable ethosomal gel can be considered a promising approach for enhanced in-vitro drug permeation of Itraconazole.

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