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FORMULATION AND EVALUATION OF ITRACONAZOLE LOADED TRANSFEROSOMAL GEL FOR IMPROVED SKIN PERMEATION

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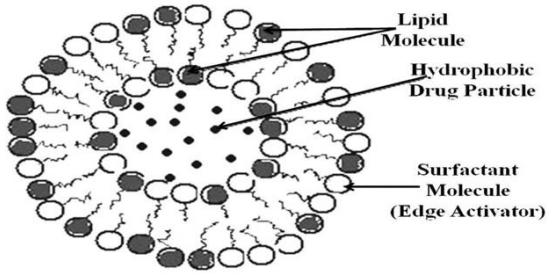
Abstract: Itraconazole is a broad-spectrum antifungal drug widely used in the treatment of various fungal infections. However, its poor aqueous solubility and limited skin permeation can reduce its therapeutic effectiveness when administered through conventional dosage forms. Transferosomes were prepared by the thin-film hydration method using soya lecithin, cholesterol, and Span 80, and subsequently incorporated into Carbopol 940 gel. The prepared formulations were evaluated for vesicle size, zeta potential, entrapment efficiency, surface morphology by scanning electron microscopy (SEM), pH, viscosity, in vitro drug release, and stability studies. The prepared transferosomes exhibited particle sizes ranging from 112 to 137 nm and zeta potential values ranging from −19 to −30 mV, indicating good vesicular stability. SEM analysis confirmed the formation of spherical and uniformly distributed vesicles without aggregation. Among all formulations, F3 was found to be the optimized formulation with a particle size of 112 nm, zeta potential of −30 mV, and entrapment efficiency of 85.78%. The transferosomal gel showed suitable pH and viscosity for topical application. In vitro drug release studies demonstrated a maximum cumulative drug release of 98.84% from formulation F3 within 8 hours. Stability studies carried out for three months under different storage conditions revealed no significant changes in physical appearance or drug release characteristics, confirming the stability of the formulation. The results indicate that Itraconazole-loaded transferosomal gel is a promising topical drug delivery system capable of improving drug release, stability, and skin permeation. The developed formulation may offer enhanced therapeutic efficacy in the treatment of fungal infections.

Keywords: Itraconazole, Transferosomes, Transferosomal Gel, Skin Permeation, Controlled Release, Transdermal Drug Delivery.

INTRODUCTION

Transferosomes

Transfersomes consist of a phospholipids component along with a surfactant mixture. The ratio of individual surfactants and total amount of surfactants control the flexibility of the vesicle. The uniqueness of this type of drug carrier system lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic to drugs.20 Transfersomes are applied in a non- occluded method to the skin and have been shown permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. Transfersomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller.



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Fig-1: Structure of transfersomes

Advantages of transfersomes

Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.

1. They have high entrapment efficiency, in case of lipophilic drug near to 90%.
2. This high deformability gives better penetration of intact vesicles.
3. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
4. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
5. They act as depot, releasing their contents slowly and gradually.
6. They can be used for both systemic as well as topical delivery of drug.
7. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
8. They protect the encapsulated drug from metabolic degradation.
9. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.

Limitations of transfersomes

1. Transfersomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criterion militating against adoption of transfersomes as drug delivery vehicles.
3. Transfersomes formulations are expensive.

MATERIALS

Itraconazole was procured from Synpharma Research Labs, Hyd, Cholesterol, Carbopol 940, Span 80 and Lecithin were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Fourier transform infrared spectroscopy:

Fourier transform IR spectra were obtained on Shimadzu FT-IR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 450-4000 cm-1 and the resolution was 4 cm-1.

Formulation development

Table-1: Formulation table of Itraconazole

Ingredients (mg)	F1	F2	F3	F4
Itraconazole	100	100	100	100
Soya lecithin	100	125	150	175
Cholesterol	50	50	50	50
Span 80 (ml)	0.1	0.2	0.3	0.4
Chloroform (ml)	3	3	3	3
Methanol (ml)	1	1	1	1

Preparation method of Transferosomes

A thin-film hydration technique was employed to form transferosomes. Specific amounts of lipids were dissolved in a mixture of organic solvents consisting of methanol and chloroform (1:2) in a dry round-bottom flask. The evaporation of organic solvents was performed under vacuum using a rotary evaporator at 100 rpm, at 48-50 °C. The thin lipid film thus obtained was then hydrated using water containing surfactant and drug by rotation for 1 hour at 50 °C. Each formulation was placed in a bath sonicator at 150 W for 20 seconds. A dialysis bag was used to remove the free drug, and the final formulation was stored at 4 °C for further use. Blank transfersomes were prepared using the same method for each formulation.

Incorporation into gel base (Carbopol gel)

Table-2: Formulation development of transferosomal gel

Ingredients	F1	F2	F3	F4
Transferosomes (ml)	5	5	5	5
Carbopol 940 (mg)	100	200	300	400
Triethanolamine (ml)	0.01	0.01	0.01	0.01
Glycerine (ml)	1	1	1	1
Water	q.s	q.s	q.s	q. s

Preparation of Topical Transferosomal gel:

As a vehicle for incorporation of transferosomes for topical delivery, Carbopol gels were prepared. Transfersomes aqueous dispersion was utilized for the formulation of topical gel. Gel polymer such as Carbopol 940 was utilized to prepare transfersome gel. Various quantities of Carbopol- 940 powder

were dispersed into vigorously stirred (stirred by magnetic stirrer Remi 5MLH) distilled water (taking care to avoid the formation of in dispersible lumps) and allowed to hydrate for 24 hrs. The dispersion was neutralized with triethanolamine to adjust the pH 7.4.

Characterization

Vesicle size

Transferosomes vesicles can be visualized by SEM and optical microscope. The Morphological characterization of transferosome vesicle such as shape and surface feature was projected by using optical microscope and SEM.

SEM Analysis

The shape, surface characteristics, and size of the Transferosomes were observed by scanning electron microscopy. Once again, 0.2 g of the Transferosomes in a glass tube was diluted with 10 ml of pH 7.4 phosphate buffer. The Transferosomes were mounted on an aluminum stub using double-sided adhesive carbon tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Hitachi 3700N, Germany) equipped with a digital camera, at 10 kV accelerating voltage.

Zeta-potential:

The sample was diluted with distilled water (1:100 (V/V)) and zeta potential was determined using Malvern zetasizer (Nano ZS, Malvern Instruments, United Kingdom). Measurement was based on the electrophoretic mobility of the particles, which was converted to the zeta potential by inbuilt software based on the Helmholtz-Smoluchowski equation.

Determination of entrapment efficiency percentage:

The entrapment efficiency of Itraconazole-loaded transferosomes was determined by the centrifugation method. An aliquot of the transferosomal dispersion was taken and centrifuged at 14,000 rpm for 30 minutes. The supernatant containing the unentrapped (free) drug was collected and analyzed spectrophotometrically at 262 nm using a UV-Visible spectrophotometer. The amount of entrapped drug was calculated by subtracting the amount of free drug from the total amount of drug added during formulation.

$$\% \text{ Entrapment} = \frac{\text{Total drug} - \text{Entrapped drug}}{\text{Total drug}} \times 100$$

Evaluation Parameters of Transferosomal Gel

Determination of pH:

The pH of the prepared transferosomal gel was measured using a calibrated digital pH meter at room temperature. Measurements were performed in triplicate and the average value was recorded.

Determination of viscosity:

The viscosity measurement of Transferosomal gels was determined by using a Brookfield viscometer. 10gm of gel preparation was kept in 50ml beaker, set at room temperature and spindle at 5, 10, 20, 50, and 100rpm.

In-vitro drug release studies

Modified Franz diffusion cell with a receiver compartment volume of 10ml and effective diffusion area of 2cm2 was used for this study. In-vitro drug study was performed by using dialysis membrane in phosphate buffer solution (pH 7.4). To perform in-vitro drug release study, dialysis membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2cm2 and capacity of receptor compartment was 10ml. The receptor compartment was filled with 10ml of phosphate buffer (pH 7.4) maintained at 37± 0.50C and stirred by a magnetic bar at 100rpm. Transfersomal gel formulation equivalent to 10mg drug was placed on the cellophane membrane and the top of the diffusion cell was covered. At appropriate time intervals 1 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 7.4) to maintain sink conditions. The samples were analyzed spectrophotometrically at λ max 262 nm.

Stability Studies of transfersomal gel

The optimized transfersomal gel formulation of Itraconazole was subjected to accelerated stability studies to evaluate its physical and chemical stability. The prepared transfersomal gel was wrapped in aluminium foil and packed in airtight glass vials to protect them from light and environmental factors. The samples were stored in a stability chamber maintained at 25 ±

2°C / 60 ± 5% RH, 300C/75% RH and 40 ± 2°C / 75 ± 5% RH for a period of 3 months as per ICH guidelines. During the stability study, samples were withdrawn at predetermined time intervals (0, 1, 2, and 3 months) and evaluated for changes in physical appearance and in-vitro drug release.

RESULTS & DISCUSSION

FT-IR Spectrum of Itraconazole

FT-IR Spectra of Itraconazole and F3 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between drug and excipients.

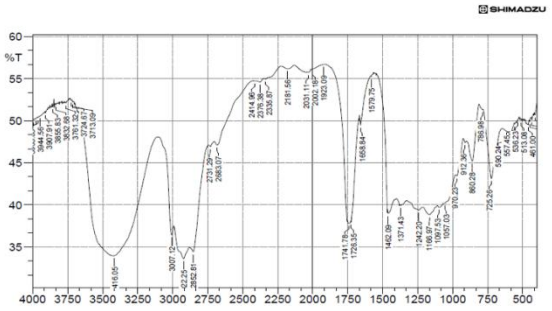


Fig-2: FTIR Studies of Itraconazole

Table-3: Characteristic Peaks for Itraconazole

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH Bending	4000-3500	3907.91
2	C-H stretching	2500-2000	2414.96
3	C=O stretching	1500-1000	1371.43

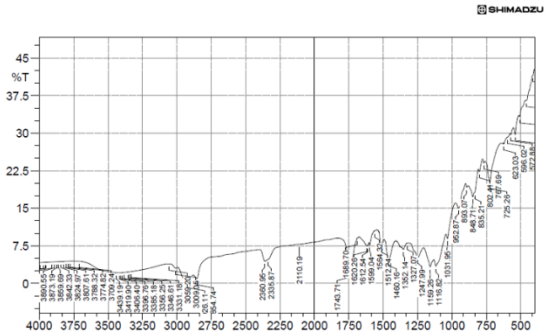


Fig-3: FTIR Studies of physical mixture of drug and excipients

Table-4: Characteristic Peaks for drug and excipients

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3842.33
2	OH Bending	2500-2000	2360.95
3	C=O stretching	1500-1000	1352.14

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients. The compatibility between the drug and the selected polymer and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer and other ingredients used.

EVALUATION PARAMETERS:

Particle size of Transferosomes

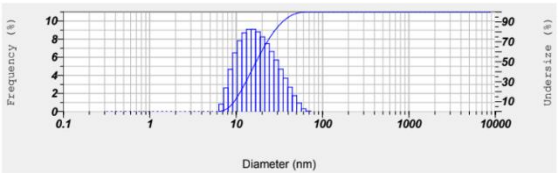


Fig-4: Particle size of Optimized formulation

Discussion: Particle size analysis revealed that all transferosomal formulations were within the nanometer range. The particle size of the prepared transferosomes varied from 112 nm to 137 nm. Among all formulations, F3 exhibited the smallest vesicle size of 112 nm, which may facilitate enhanced skin permeation and improved drug delivery. The reduction in vesicle size may be attributed to the optimal concentration of soya lecithin and Span 80 used in the formulation.

SEM Analysis

Scanning electron microscopy (SEM) revealed that the Itraconazole transferosome's were smooth and spherical without any aggregation.

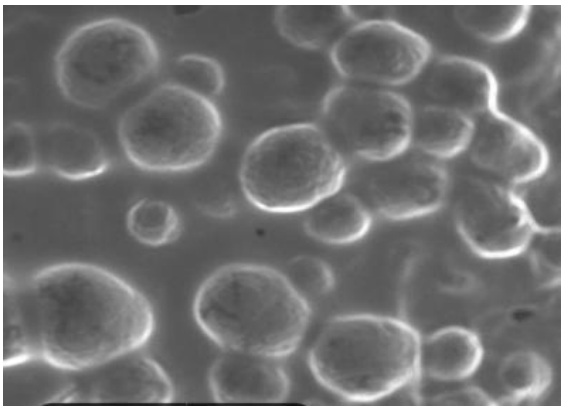


Fig-5: SEM Analysis of Transferosomes

Discussion: Scanning electron microscopy (SEM) revealed that the prepared transferosomes were spherical in shape with smooth surface morphology and showed no evidence of aggregation. The vesicles appeared discrete and uniformly distributed, indicating successful formation of transferosomes. The absence of aggregation suggests good physical stability of the vesicular system.

Zeta potential

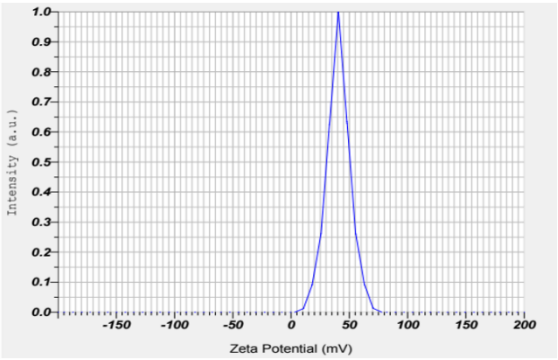


Fig-6: Zeta potential of Transferosomes

Discussion: The zeta potential values varied from –19 mV to –30 mV, indicating a sufficiently high negative surface charge to confer electrostatic repulsion between vesicles and thereby good physical stability of the dispersions. Among the batches, F3 (–30 mV) exhibited the highest absolute zeta potential, supporting better stability against aggregation.

Table-5: Evaluation Studies of particle size and Zeta potential Transferosomes

F. No	Particle size	Zeta potential
F1	132	-19
F2	137	-23
F3	112	-30
F4	123	-22

Entrapment efficiency

Table-6: Percentage entrapment efficiency

F. No	% EE
F1	79.63
F2	81.23
F3	85.78
F4	84.20

Discussion: The entrapment efficiency of all formulations was determined to evaluate the drug-loading capacity of transferosomes. The percentage entrapment efficiency ranged from 79.63% to 85.78%. Among all formulations, F3 showed the highest entrapment efficiency of 85.78%, indicating efficient incorporation of Itraconazole within the vesicular structure. The increased entrapment efficiency may be due to the optimum lipid concentration and vesicle composition.

pH value and Viscosity of transfersomal gel:

Table-7: pH and Viscosity values of all formulations

F. No	pH	Viscosity (cps)
F1	6.4	175
F2	7.2	169
F3	6.6	176
F4	6.8	158

Discussion: The pH of all transferosomal gel formulations was found to be in the range of 6.4–7.2, which is suitable for topical application and compatible with skin pH. The viscosity values ranged from 158 to 176 cps, indicating acceptable consistency and spread ability of the gel formulations. Formulation F3 exhibited a pH of 6.6 and viscosity of 176 cps, suggesting good suitability for topical administration.

In vitro drug release studies

Table-8: Diffusion st

udies of Transfersomal gel

Time	F1	F2	F3	F4
0	0	0	0	0
1	17.19	16.42	21.63	16.93
2	27.10	24.60	30.25	27.46
3	35.13	32.99	42.16	36.82
4	45.32	55.37	49.80	55.34
6	83.69	84.56	88.96	84.23
8	94.50	95.69	98.84	93.52

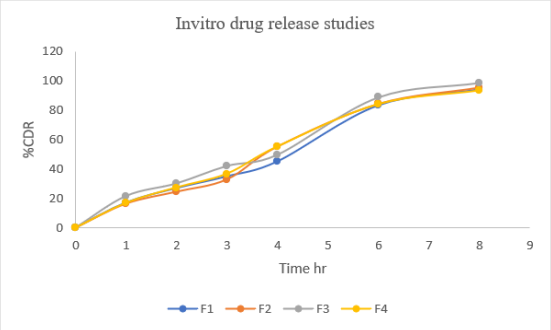


Fig-7: Diffusion studies of Transfersomes (F1-F4)

Discussion: In vitro drug release studies were carried out using a Franz diffusion cell containing phosphate buffer pH 7.4 as the diffusion medium. All formulations exhibited a gradual increase in drug release over the study period. Among the formulations, F3 showed the highest cumulative drug release of 98.84% at the end of 8 hours, whereas F1, F2, and F4 exhibited drug releases of 94.50%, 95.69%, and 93.52%, respectively. The enhanced drug release from F3 may be attributed to its smaller vesicle size and higher entrapment efficiency, making it the optimized formulation.

Stability studies:

There was no significant change in physical and chemical properties of the transferosomal gel formulation F3 after 3 months. Parameters quantified at various time intervals were shown.

Table-9: Results of stability studies of optimized formulation F-3, Temperature 25°C/60% RH, 30°C/75% RH, 40°C/75% RH

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	250C/60%RH % Release	98.84	97.57	96.60	95.55	Not less than 85 %
F-3	300C/75% RH % Release	98.84	97.69	96.57	95.50	Not less than 85 %
F-3	400C/75% RH % Release	98.84	97.25	96.16	95.12	Not less than 85 %

Discussion: Stability studies of the optimized formulation F3 were carried out under different storage conditions for a period of three months. The formulation showed no significant changes in physical appearance or drug release characteristics during the study period. The cumulative drug release remained above 95% under all storage conditions, demonstrating good stability of the transferosomal gel. These results indicate that formulation F3 retained its physicochemical properties and remained stable throughout the storage period.

CONCLUSION

The present study was successfully carried out to formulate and evaluate Itraconazole-loaded transferosomal gel for enhanced topical drug delivery. Preformulation studies confirmed the identity, purity, and suitability of Itraconazole for formulation development. FTIR compatibility studies demonstrated the absence of any significant interaction between the drug and the selected excipients, indicating good compatibility. Transferosomes were successfully prepared by the thin-film hydration technique and incorporated into Carbopol 940 gel. The prepared transferosomes exhibited nanosized vesicles with particle sizes ranging from 112 to 137 nm and showed spherical morphology without aggregation as confirmed by SEM analysis. The zeta potential values indicated good physical stability of the vesicular system. Among all formulations, F3 was identified as the optimized formulation due to its smallest vesicle size (112 nm), highest entrapment efficiency (85.78%), highest zeta potential (–30 mV), and maximum cumulative drug release (98.84% at 8 hours). The pH and viscosity of the transferosomal gel were found to be suitable for topical application and skin compatibility. Stability studies conducted for three months under different storage conditions revealed no significant changes in the physical appearance or drug release characteristics of the optimized formulation. The cumulative drug release remained above 95%, indicating excellent stability of the transferosomal gel. Therefore, it can be concluded that the developed Itraconazole-loaded transferosomal gel is a promising topical drug delivery system with improved drug entrapment, enhanced drug release, good stability, and potential for effective treatment of fungal infections. Further in vivo and clinical studies may be carried out to establish its therapeutic efficacy.

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