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Formulation and Evaluation of Ketoconazole Loaded Ethosomal Gel for Antifungal Activity

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Abstract

Aim: Formulation and evolution of ketoconazole loaded ethosomal gel for Antifungal Activity.

Objectives: To formulate Ketoconazole-loaded ethosomal vesicles with enhanced skin penetration properties.

Methods: Ketoconazole-loaded ethosomes were created by employing the thin film hydration technique, which involved dissolving soya lecithin, cholesterol, and ketoconazole in a blend of ethanol and methanol, after which the solvent is evaporated to form a thin layer of lipid. After that, this film was rehydrated with various concentrations of hydromethanolic solution. and subjected to sonication to yield ethosomal vesicles. For later evaluation, the improved ethosomes were combined with a Carbopol 934 gel base. Carbopol was hydrated for a full night, and a W/V = 1% The suspension of ethosomes was thoroughly blended with the gel. Methyl paraben was included as a preservative finally, triethanolamine was employed to reduce the pH down to a range of 6-7.4.

Results: The ethosomal gel containing ketoconazole demonstrated nanosized vesicles with high entrapment efficiency and satisfactory physicochemical characteristics. The formulation displayed prolonged medication release and enhanced skin penetration. Enhanced antifungal effectiveness was verified by a greater inhibition zone when compared to the traditional gel.

Conclusion: The research effectively created an ethosomal gel loaded with ketoconazole that features enhanced entrapment efficiency, prolonged drug release, and appropriate physicochemical characteristics. The optimized formulation exhibited better skin penetration and greater antifungal efficacy when contrasted with traditional gels. In summary, the ethosomal gel offers a promising and efficient topical treatment for fungal infections, contributing to better patient adherence.

Keywords: Ethosome, Ketoconazole, Antifungal, Transdermal Enhancement.

INTRODUCTION

A recent report from the Disease Burden Worldwide indicates that fungal diseases of the skin rank as the fourth highest prevalent wellness issue, influencing around A billion individuals globally. There are three primary forms of fungal skin infections: dermatophytosis, pityriasis versicolor, and cutaneous candidiasis. Among these types, The most frequent source of superficial infections is dermatophytes. Additionally, it's important to recognize that any area of the skin may be susceptible to infection.

Fungal infections of the skin rank as the most prevalent type among fungal ailments, and the occurrence of superficial fungal infections has increased In the previous 20 years. Recently, there has been increased interest in discovering novel approaches to improve and simplify the treatment for patients with fungal infections. Administering medication to the skin seems to be the best choice for treating superficial fungal problems.[1] The epidermis serves as the primary location where pathogens gather and multiply. Treatment should involve appropriate topical formulations that can deliver an adequate quantity of the medication at therapeutic dosages and penetrate the upper layers of the skin, such as the stratum corneum, to ensure effective treatment. Recently, the science of nanomedicine has demonstrated significant potential in drug delivery by merging nanotechnology, pharmaceutical science, and biomedical applications through the use of nanoparticles.[1] Within the realm of nanoscale interactions, nanocarriers have exhibited remarkable capabilities by penetrating the skin's sub-atomic layers and effectively overcoming various barriers. Liposomes, recognized as the first nano-drug delivery system approved by the FDA, have proven highly effective due to their multifunctionality, safety profile, bio-compatibility, targeted delivery capabilities, substantial capacity, and ability to transport both hydrophilic and hydrophobic substances. [1,2]

Ethosomes: "Ethosomes are liposomes that contain ethanol." Ethosomes consist of soft vesicles of phospholipids that are either hydroalcoholic or hydroglycolic, characterized by a Comparatively high concentration of alcohols or their mixtures (ethanol and isopropyl). The unique aspect of the ethosomal system is the elevated level of ethanol. Ethosomes typically contain ethanol at concentrations ranging from 20% to 50%.[1]

Types of Ethosomal Systems:

Three types of ethosomal systems exist

1. Traditional Ethosomes: Water, phospholipids, and a significant quantity of ethanol (40%) make up classical ethosomes. Classical ethosomes can encapsulate medications with molecular weights between 130,077 Da and 24 kDa.[2]

2. Two-way ethosomes: Two-way ethosomes are developed by incorporating a different kind of alcohol into traditional ethosomes. The most often used types of alcohol in the formulation are propylene glycol and isopropyl alcohol.[2]

3. Interethosomes: These comprise these essential elements out of traditional ethosomes along with a penetration enhancer (surfactant). They have been designed to integrate the advantages of traditional ethosomes and interthosomes, resulting in interethosomes. Interethosomes are a more advanced form of ethosomes, combining the advantages of both classical ethosomes and transferosomes.[2]

MATERIALS AND METHODS:

Materials: The ketoconazole sample was obtained from Aurochem Drug Products in Palghar and is utilized as an active pharmaceutical ingredient in various formulations. Soya lecithin serves as the Cholesterol and phospholipid serve as stabilizers, The gelling agent is carbopol 934, while ethanol and methanol are employed as solvents. Triethanolamine is used to maintain the pH level, and methyl paraben serves as a preservative, all sourced from Research Lab Fine Chem Industries in Mumbai, India.

Ketoconazole-loaded ethosome preparation employing thin-film the hydration method

Ketoconazole-loaded in ethosomes created employing the thin-film hydration method. During this procedure, soya lecithin and cholesterol were combined in a solution of methanol, along with ketoconazole. The liquid solvent mixture was extracted using a rotary evaporator under reduced pressure, resulting in a thin layer of lipid on the interior of a round-bottom flask. After that, the film was rehydrated using hydromethanolic solution at different concentrations at 100rpm while continuously agitated, which led to the formation of ethosomal vesicles. The dispersion was then sonicated to decrease the size of the vesicles and kept for further assessment.[7]

Optimization Studies: In order to optimize the ethosomal formulation, 3^2 factorial design was employed by examining the impact of phospholipid concentration (X_1) and hydromethanol content (X_2) on entrapment effectiveness, zeta potential, and vesicle size. Design-Expert® software was used for

experimental design and statistical analysis, and the optimized model was evaluated using ANOVA while keeping other formulation variables constant.[7]

Table 1: Independent variable in 3^2 factorial designs

Independent Variables		Levels		
	Unit	Low	High	Medium
X_1 Concentration of Soya lecithin	mg	50	150	100
X_2 Concentration of Hydromethanol	%w/v (ml)	20	40	30

Formulation of Ketoconazole Ethosomes applying 3^2 factorial designs

Table 2: 3^2 full factorial design in ethosomes formulation using

Batch number	Drug (mg)	Soya lecithin(mg)	Hydromethanol (ml)	Cholestrol (mg)
1	25	100	30	5
2	25	50	30	5
3	25	150	20	5
4	25	150	40	5
5	25	100	40	5
6	25	50	20	5
7	25	100	20	5
8	25	50	40	5
9	25	150	30	5

Ketoconazole-loaded ethosomal gel preparation

A gel base was incorporated into the improved ethosomes in order to perform in vitro, ex vivo skin penetration tests, and in vivo evaluations. The hydrophilic qualities of linking together ability, and insolubility in water, Carbopol is ideal for the controlled release of the drug. Carbopol 934 was diffused in water and permitted to spend the night. The next day, to create a homogeneous dispersion, the fluid was agitated using a magnetic stirrer.. A 1% suspension w/v of Ketoconazole ethosomes was uniformly absorbed into the Carbopol dispersion. The introduction of methyl paraben as a preservative. Lastly Triethanolamine was added little by bit while being gently stirred to regulate the pH within the range of 6.5 to 7.4.[6,7]

Characterization of Ethosomes:

Morpholgy: The morphology of the ethosomal suspension was evaluated using SEM (JEOL JSM-6360, Japan) after platinum coating.[4]

Size distribution and Zeta Potential: The produced ethosomes were analyzed using dynamic light scattering with a computerized system to estimate the vesicle size, zeta potential, and Polydispersity Index values. The ethosome samples were diluted in order to prevent agglomeration and examined at consistent 90° angle. For each sample, the assessments were carried out in triplicate at a temperature of 25°C.[2]

Efficiency of entrapment: The entrapment efficiency of ketoconazole in ethosomes stored overnight at 4°C was evaluated using an ultracentrifugation technique. pH 7.4 Phosphate Buffer Solution (PBS) was combined with 1 ml of Ketoconazole-loaded ethosome formulation in Eppendorf tubes. The tubes were then put in a Beckman type cold centrifuge with a fixed angle rotor and spun for two hours at 15,000 rpm. A Shimadzu UV-V spectrophotometer was employed to quantify absorbance at a wavelength of 223 nm after PBS at pH 7.4 was used to dilute the highest transparent layer that separated. This is how the encapsulation efficiency (EE%) was determined:

EE (%) is equal to (T – C) x 100.

where C is the quantity of unentrapped ketoconazole in the supernatant of the unvortexed sample, and T is the total amount of ketoconazole from the supernatant layer. [7]

FTIR Analysis: An infrared spectrophotometer with Fourier transform was employed to obtain the ketoconazole infrared (IR) spectra and ketoconazole loaded ethosomes containing it. By examining the IR spectra, interactions between the medication and excipients were investigated.

Analysis of Differential Light Scattering Colorimeter: The compatibility between the drug

and excipients was confirmed by sample analysis conducted using a the transition temperature of lipids was also measured using a differential scanning calorimeter.

Evaluation of ethosomes integrated gel

pH of gel: A crucial factor pH is used in the formulation process. The pH of the ethosomes included gel should match the skin's pH to maintain stability at the desired pH level, avoiding any discomfort to the patient during topical usage. The pH of the ethosomal gel was determined using a digital pH meter.

Spreadability measurement:

Parallel-plate Methodology: The spreadability using the parallel-plate method.

To compute the spreadability, insert values into the following equation:

S equals M × L/T

In this case, S stands for spreadability, M for the weight fastened to the top slide, L for the glass slide's length, and T for the amount of time in seconds needed to travel a given distance. The gels' slip and drag properties were used to calculate the spreadability.

Viscosity determination: The ethosome gel's included viscosity was evaluated using a Brookfield viscometer with a sample adapter and spindle number 7. The viscosity was measured at 25 rpm at room temperature while the spindle was submerged in 50 g of ethosomal gel.

In vitro diffusion study: The drug release from the suspension of ketoconazole ethosomes was investigated using a dialysis membrane. The dialysis bag was filled with one milliliter of the optimal formulation containing ten milligrams of ethosomal gel, which was then submerged in one hundred milliliters of phosphate buffer (pH 7.4). The temperature was maintained at 37 ± 0.5 °C with constant stirring at 100 rpm. At predefined time intervals (1, 2, 3, 8, 12, and 24 hours), samples were removed and replaced with fresh buffer. The amount of drug released was measured using a UV spectrophotometer set to 244 nm. A Franz diffusion cell was utilized to test the ketoconazole-loaded ethosomal gel in vitro diffusion. Statistical analysis was performed using a one-way ANOVA, and results with $p < 0.05$ were declared significant.[7]

Antifungal activity by well method: Over the course of seven days, the zone of inhibition against Candida albicans was measured using the well diffusion method to evaluate the antifungal effects of ketoconazole. After allowing about 15 to 20 milliliters of molten potato dextrose agar to settle, wells were created on sterile petri plates. Following the creation of test, standard, and control groups on the agar plates, a suspension of Candida albicans was added. The inoculation after the wells were filled, the plates were incubated for seven days at 37°C with ethosomal suspension and a commercially available cream, Ketoconazole, at doses of 10, 50, and 100 µg/ml, respectively. The results of the standard product were compared to the diameter of the circular inhibitory zone (measured in millimeters) surrounding the well. The statistical significance was evaluated using a one-way ANOVA, with a p-value of less than 0.05 being deemed statistically significant. [5,6,7]

Stability study: In accordance with ICH recommendations, the ketoconazole ethosome solution and ketoconazole ethosomal gel were kept in a sealed glass container after undergoing three separate physical stability tests. The vials were stored at room temperature. (25 ± 2 °C) and ambient moisture content (4±2 °C). For three months, monthly inspections of the stored samples were conducted. While pH, % encapsulation efficiency, and viscosity were assessed for ketoconazole ethosomal gels, vesicle size, Encapsulation efficiency and zeta potential were assessed for ketoconazole suspensions.[5]

Kinetic investigations of drug release: Drug release kinetics can be investigated using a variety of mathematical models. taking into account the quantity of drug released between 0 and 8 hours. The following equations illustrate the models that were tested. Based on these estimates, suitable to characterize the dissolution profiles, mathematical models were used. Plots like this one were made: total proportion of medications.

RESULTS AND DISCUSSION:

Research on Preformulation:

Physicochemical properties of Ketoconazole: The color of the ketoconazole is white and the no characteristic odor, nature is amorphous.

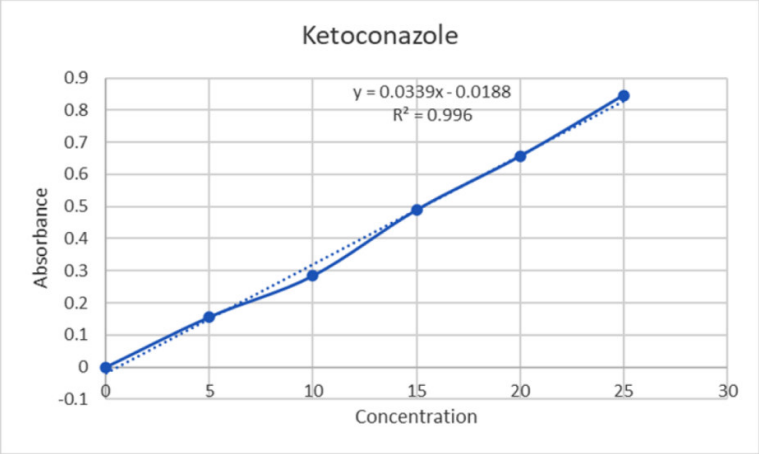
Solubility profile of Ketoconazole: A key objective of the pre-formulation process is to

assess the drug's stability and solubility in different solvents. The solubility of ketoconazole was evaluated using the shake-flask method. The solubility levels of ketoconazole across different solvents are presented in a table. It was observed that ketoconazole is soluble in methanol and ethanol, acetone, has limited solubility in pH 7.4 PBS, and is virtually insoluble in distilled water (0.056 mg/ml).

Log p value: The log p value of ketoconazole is 4.27.

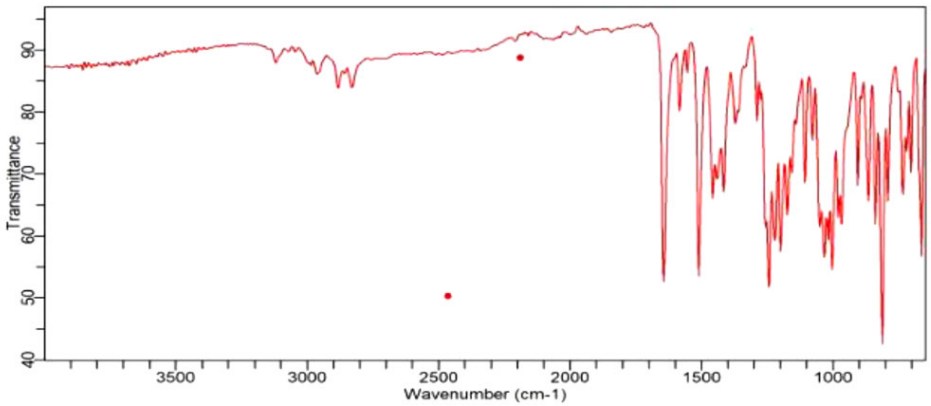
Determination of Melting point: The melting point was ascertained using a digital melting point apparatus of ketoconazole. Specifically, EQuiptronics EQ730. The process begins by filling a clean, Dry capillary tube with an approximate amount of Ketoconazole. This tube was then inserted into the melting point apparatus, which contains liquid paraffin. After securing the lid of the Apparatus, the desired temperature range is set. As the Ketoconazole was heated, its melting point was observed and subsequently recorded. It's found to be **149±1.0 °C**.

Ketoconazole calibration curve: The ketoconazole calibration curve was established utilizing a UV spectrophotometer with a wavelength of 244 nm, with methanol serving as the blank.The calibration curve was created by plotting the absorbance. versus drug concentrations. The data were evaluated using MS Excel 2010. The correlation value [R^2 = 0.996] in methanol, demonstrating a linear relationship.

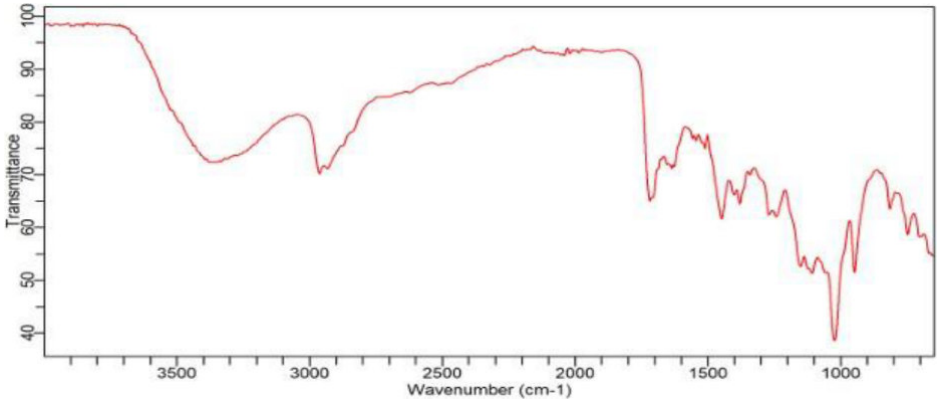


Graph 1: Standard calibration curve of Ketoconazole

Infrared spectroscopy using Fourier transform (FT-IR): IR spectroscopy was used to examine the drug-polymer interactions. To determine the compatibility of the drug Ketoconazole, excipient, physical mixture, and ideal formulation, an FT-IR investigation was carried out. It was discovered that no peaks appeared or vanished based on the spectrum measurements. The outcome showed that the medicine and the chosen polymers were compatible.



Graph 2: FTIR spectrum of Ketoconazole

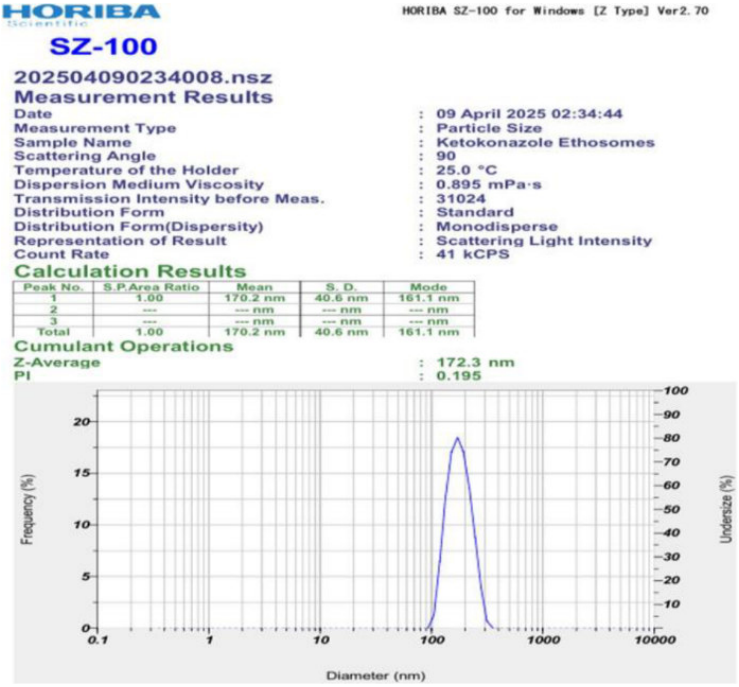


Graph 3: FTIR spectrum of Physical Mixture

Characterization of Ethosomes

Analysis of particle size:

The size of the ketoconazole ethosomes that were formed was determined. Ethosomes generated with a higher concentration had larger vesicle sizes, according to the observed data. The vesicle size for ketoconazole varied from 172 nm to 200 nm. The analysis of particle size results show that the generated Ketoconazole Ethosomes have a particle size of less than 200 nm, making them appropriate for transdermal applications.

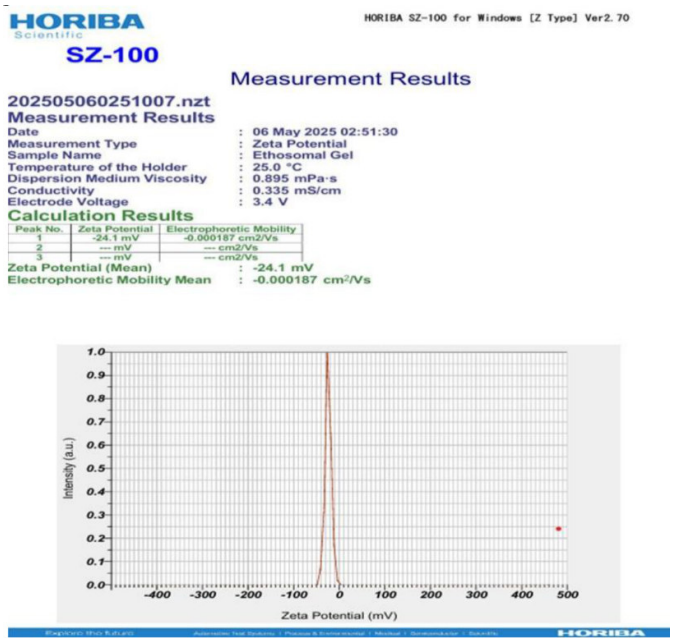


Graph 4: Particle Size Analysis

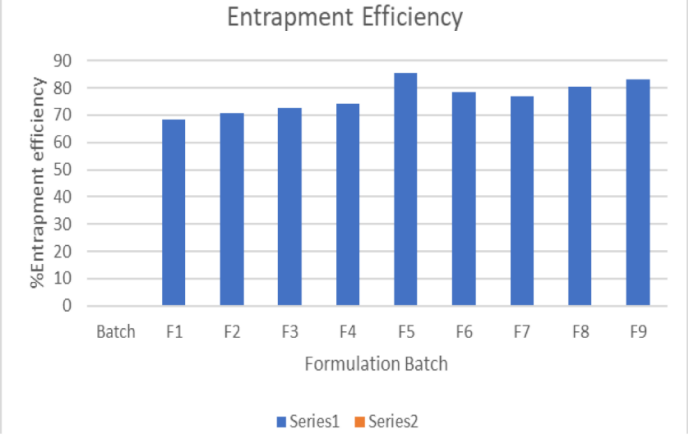
Zeta potential:

Zeta potential is a word used to describe how stable samples are for sufficiently small particles and molecules; stability will be provided by a strong zeta potential, meaning it will prevent aggregation. Here, it was discovered that the ethosomal gel's zeta potential was -24.1 V, which would prevent aggregation.

Entrapment Efficiency of Ketoconazole Ethosome: The results indicated that the formulated Ketoconazole ethosomes had a favorable entrapment efficiency (EE%) percentage, with values varying from (68.2±0.045%) for the Ketoconazole ethosomes to (85.3±0.060%) for the Ketoconazole ethosomes - F5.



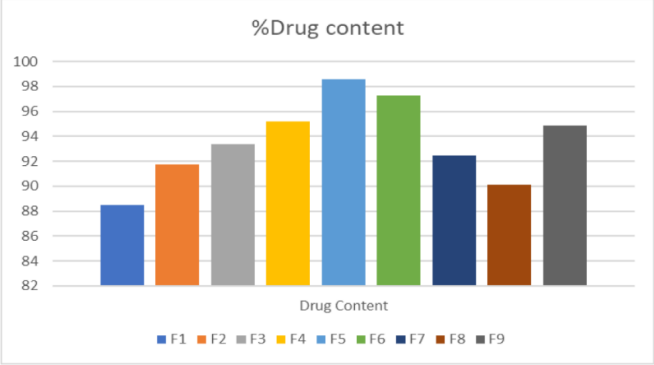
Graph 5: Zeta potential of Ethosomal Gel



Graph 6: Entrapment Efficiency of Ethosomes

Drug content:

Every formulation's drug content was discovered to be between**88.52±0.085** to **98.6±0.065** % w/w, which represents good content uniformity.

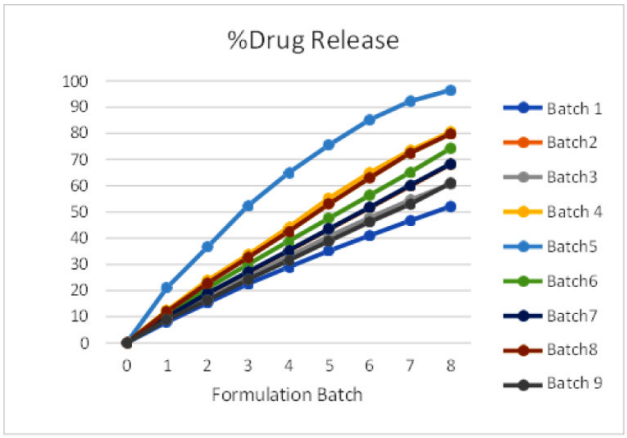


Graph 7: % Drug Content of Ethosomes

Drug release studies *In vitro*:

Using the *In vitro* drug release of a Franz diffusion cell each ethosomal gel and control gel was assessed during a 12-hour period. The ethosomal gel showed controlled and sustained release of ketoconazole in contrast to the formulation for control. The F-5 batch was found to be optimized at 96.48.

Surface morphology of Ethosomes: The vesicular properties were assessed through optical and scanning electron microscopy (SEM).. SEM analysis offered a clear view of the morphology and structural characteristics of the created ethosomal vesicles.



Graph 8: % Drug release of Ethosomes

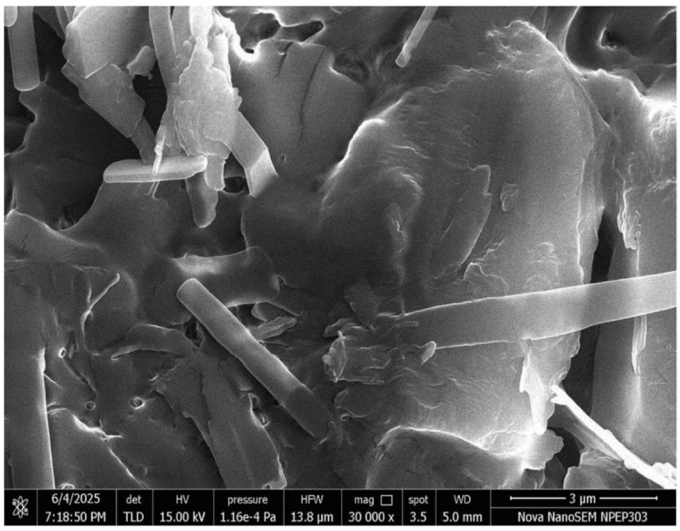


Fig 1. SEM analysis of Ketoconazole loaded ethosomes

Table 3: Ethosome optimization utilizing a 3^2 level complete factorial design

Batch No	Factor 1 Soya Lecithin (mg)	Factor 2 Hydromethanol (ml)	Response 1 Entrapment Efficiency %	Response 2 %Drug release
F1	100	30	68.2	52.1
F2	50	30	70.8	68.2
F3	150	20	72.5	60.7
F4	150	40	74.3	80.50
F5	100	40	85.3	96.48
F6	50	20	78.5	74.30
F7	100	20	76.8	68.3
F8	50	40	80.2	79.80
F9	150	30	83.1	61.0

Axes:

X-axis (A): Soya lecithin (mg)
Y-axis (B): Hydromethanol (ml)
Z-axis: Entrapment efficiency (%)

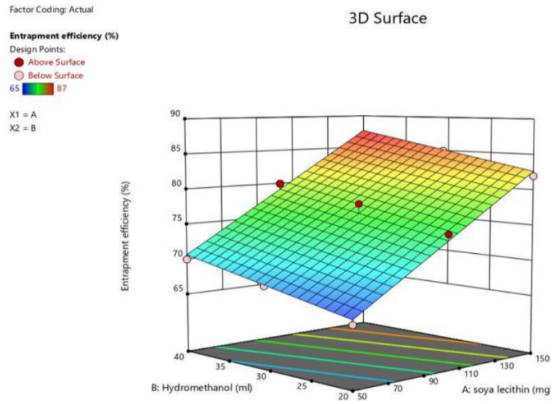


Fig 2: Plot Response in 3D Surface plot illustrating how medication release is affected by polymer content

ANOVA for Linear model Response 1:

Table 4: ANOVA for linear model

	Sum of Squares	df	Mean Square	F- value	p-value	
Model	471.00	2	235.50	282.60	< 0.0001	significant
A-soya lecithin	433.50	1	433.50	520.20	< 0.0001	
B-Hydromethanol	37.50	1	37.50	45.00	0.0005	
Residual	5.00	6	0.8333			
Cor Total	476.00	8				

EVALUTION OF KETOCONAZOLE LOADED ETHOSOMAL GEL:

Uniformity:

A visual test for pharmacological product homogeneity may be useful, at least for an initial batch, to ensure there is no phase separation, no synersis (water extrusion from a gel), and no foreign matter. Every batch of ethosomal gel injected with ketoconazole was uniformly smooth.

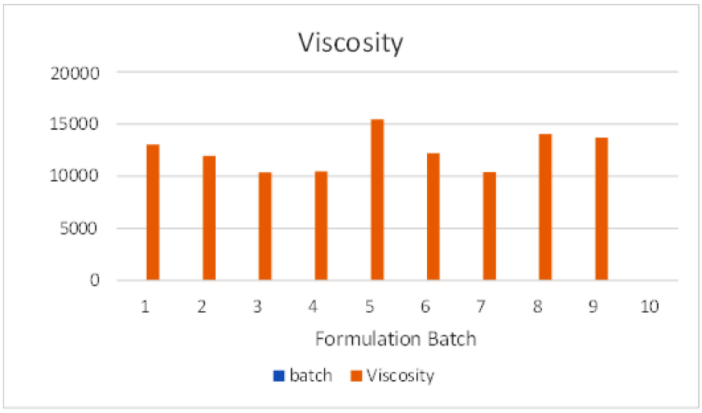
Determination of pH: The prepared substance's pH Ethosomal Gels was discovered to be in bounds of 5.41to 6.72 at 25^{0}C, which were considered. within the normal range of pH for Topical preparations.

Viscosity: The ethosomal gel loaded with ketoconazole was found to have a viscosity between 10356-15455cps at 25 rpm.

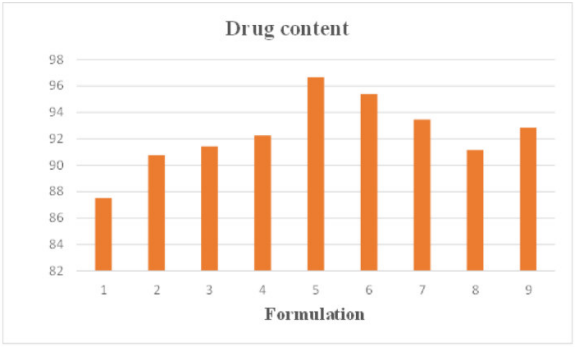
Drug content estimation: A UV spectrophotometer was used to determine the drug content. Each formulation's drug content ranged from 87.84±91 to 96.24±55 % w/w, which demonstrates good content uniformity.

Spreadability: The spreadability was determined to be between 11.18 and 14.98 g.cm/sec based on the gels' properties of drag and sliding indicating that they can be spared on skin surfaces with minimal stress.

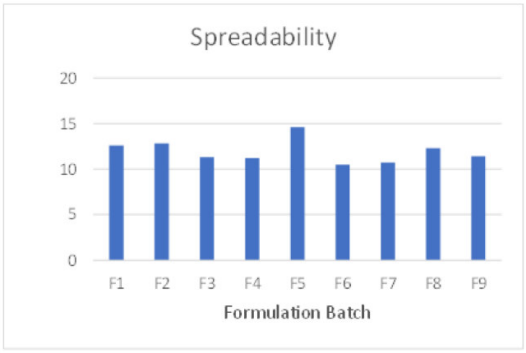
Entrapment Efficiency of Ketoconazole Ethosomes gel: It was found that the prepared Ketoconazole ethosomes showed a respectable percentage of entrapment (EE%), with values between **(66.1±0.020%)** for Ketoconazole ethosomes to **(80.1±0.054%)** for Ketoconazole ethosomes -F5.



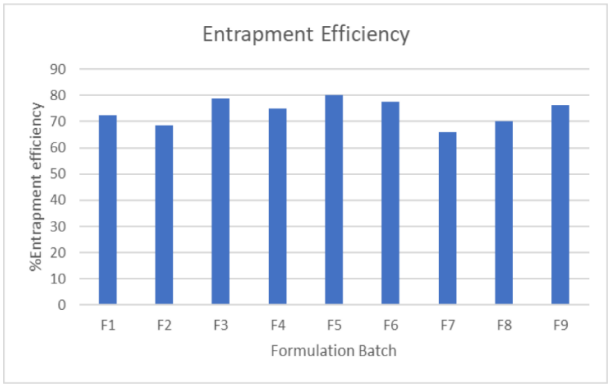
Graph 9: Rheological profile of ketoconazole Loaded ethosomal gel



Graph 10: Drug content of Ethosomal gel



Graph 11: Spreadability of Ethosomal Gel

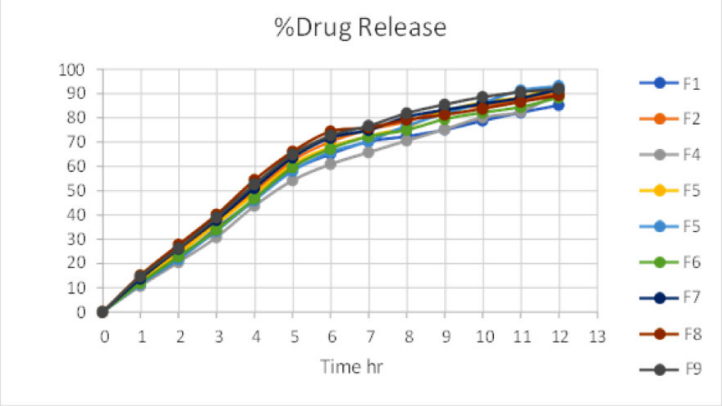


Graph 12: % Entrapment Efficiency of Ethosomal gel

Drug release studies *In vitro* ethosomal gel: A Franz diffusion cell was utilized in 12-hour drug release *In vitro* tests for each gel formulation and the control gel. In contrast to the control formulation, the ethosomal gel demonstrated a regulated and prolonged release of ketoconazole.

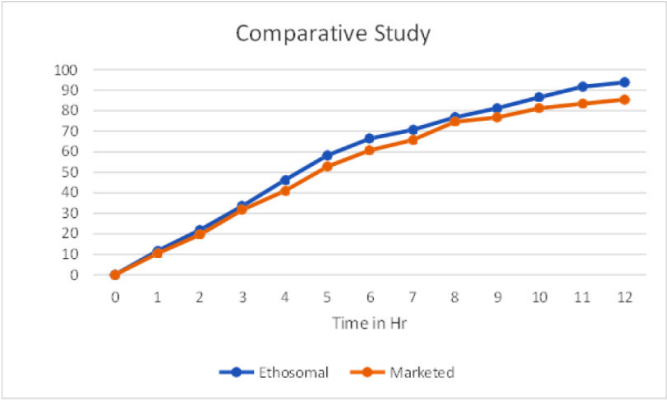
Table 5*: In-vitro* release data of Ketoconazole Ethosomal gel

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.5	14.2	10.8	13.1	11.6	12.0	13.8	15.2	14.7
2	22.3	25.4	20.6	24.2	21.8	22.9	26.1	27.8	26.3
3	34.6	37.1	30.9	36.3	33.5	34.0	38.0	40.2	39.0
4	46.5	50.0	43.8	48.7	46.1	46.9	51.2	54.5	52.7
5	58.4	62.5	54.3	60.9	58.2	59.7	63.8	66.2	64.9
6	65.2	70.3	61.0	68.1	66.0	67.4	71.9	74.5	72.8
7	70.3	75.2	65.9	72.6	70.6	72.4	75.1	76.1	76.8
8	72.5	78.6	70.7	76.3	76.8	75.1	80.5	79.3	82.0
9	75.2	83.4	75.4	82.8	81.9	79.6	83.4	81.4	85.6
10	78.9	85.1	80.3	86.5	86.4	82.3	85.9	83.9	88.7
11	82.3	87.6	82.7	88.6	91.4	84.6	88.3	86.7	90.7
12	85.3	90.4	90.2	92.7	93.2	88.5	91.8	89.4	92.1



Graph 13: Invitro drug release profile of different formulations

Comparative assessment of marketed Ketoconazole Cream: The marketed formulation used for comparison was Ketoconazole cream manufactured by Primus Pharmaceuticals Ltd. The 30 mg cream is priced at ₹190.00 (Batch No. 273), with a mfg date of October 2023 and an exp date of sep 2026.



Graph 14: Comparative Study of Ethosomal and Marketed Formulation

Antifungal Study: Using the agar well diffusion method, the improved ketoconazole-loaded ethosomal gel's antifungal activity was assessed against Candida albicans and contrasted with traditional ketoconazole gel. The optimized ethosomal formulation showed a greater zone of inhibition, signifying enhanced antifungal efficacy. Sabouraud dextrose agar was prepared, sterilized, inoculated

with *Candida albicans*, and wells were filled with the test formulations for evaluation. The diameter of inhibition of zone was evaluated after the assay plates were incubated for 24 hours at 37ºC.

Table 6: Antifungal Properties Against Candida albicans

Well Nos	Inhibition Zone
1	9mm
2	12mm
3	9mm

Fig 10: Antifungal Activity Against Candida Albicans

Stability Study: Formulation F5 was the subject of a three-month stability investigation. The stability study's results indicate because nothing seemed to have changed in physical appearance, entrapment efficiency, and the in vitro drug release study also demonstrated that there was no change in medication release profile. The comparison of the parameters before and after stability studies was shown in the table. It demonstrates the stability and reproducibility of the chosen batch F5.

Table 7: Stability study of formulation batch no. F5

Parameter	Before Stability Studies	After month Stability Studies	After three month Stability Studies
Appearance	Transparent and Homogeneous	Transparent and Homogeneous	Transparent and Homogeneous
pH	6.2	6.1	6.1
Drug release	93.2	93.0	93
Viscosity	15455	15450	15450
Drug Content	96.67	96.65	96.65
Entrapment efficiency	80.1	80	80

CONCLUSION: The research effectively created an ethosomal gel filled with ketoconazole using improved entrapment efficiency, sustained drug release, and suitable physicochemical properties. The improved formulation revealed greater skin penetration and higher antifungal effectiveness compared to traditional cream. Overall, the ethosomal gel offers a promising and effective topical therapy for fungal infections with improved patient compliance.

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