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Formulation, Development And Evaluation Of Econazole Nitrate Emulgel

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Abstract:
Objective*: The aim of the present study was to develop a stable and effective emulgel formulation containing econazole nitrate for topical antifungal application.*
Methods: *UV–visible spectrophotometric analysis was performed. A stock solution was prepared by dissolving 10 mg of econazole in 10 ml of methanol to obtain a concentration of 1000 µg/ml. From this solution, 0.2 ml was withdrawn and diluted to 10 ml with methanol to obtain a 20 µg/ml solution, which was subjected to spectral analysis.*
Results: *Characterization of the drug sample indicated that econazole nitrate was white in colour, odourless, and crystalline in appearance. Solubility testing revealed solubility in methanol, ethanol (95%), and dimethyl sulfoxide (DMSO), while the drug was insoluble in water.*
Conclusion: *The development of econazole nitrate emulgel offers a promising therapeutic option for the management of superficial fungal infections, combining antifungal efficacy with a convenient and patient-friendly dosage form.*
Keywords: *Econazole nitrate, emulgel, antifungal.*

INTRODUCTION:

The design and characterization of antibiotic-loaded emulgels for topical administration has gained significant attention in recent years. Emulgels are biphasic systems in which an emulsion - either oil dispersed in water (O/W) or water dispersed in oil (W/O) - is incorporated into a gel base using suitable gelling agents. This combination of emulsion and gel provides a promising drug delivery system, particularly for hydrophobic drugs that have limited solubility in conventional formulations.

Emulgels serve as versatile carriers for a wide range of therapeutic agents, including analgesics, anti-inflammatory drugs, antifungal agents, anti-acne medications, and cosmetic products. The formulation process generally involves the preparation of a primary emulsion containing the oil and aqueous phases, which is subsequently incorporated into a gel matrix to form the final emulgel. The emulsion component functions as a vehicle for dissolving the drug, while the gel base improves consistency, spreadability, and patient acceptability.

Conventional topical dosage forms such as lotions, suspensions, ointments, and creams often present drawbacks, including greasiness, poor aesthetic appeal, and reduced patient compliance. Transparent gels, on the other hand, are non-greasy, easily spreadable, and cosmetically elegant, making them highly suitable for pharmaceutical as well as cosmetic applications [1,2].

Advantages of Emulgels:

- Improved stability.
- Effective incorporation of hydrophobic drugs using O/W or W/O emulsions.
- Simple production process with low preparation cost.

- Potential for controlled and sustained drug release, particularly beneficial for drugs with a short half-life.
- No requirement for extensive sonication during formulation.

Method of Preparation of Emulgel [3]

1. Formulation of emulsion (O/W or W/O).
2. Preparation of aqueous phase.
3. Development of gel base.
4. Emulsification under homogenization.
5. Incorporation of the emulsion into the gel base with continuous stirring or homogenization.

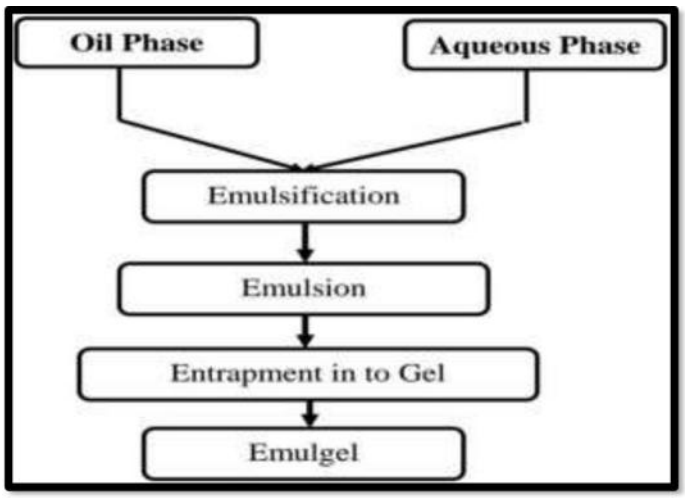

Figure 1: Method of preparation of Emulgel

Treatment of Econazole for Fungal Infections

Ergosterol is an essential component of the fungal cell membrane, and antifungal agents act by disrupting its synthesis, thereby inhibiting fungal growth and replication. Econazole, an imidazole derivative, is widely used in the clinical management of superficial fungal infections [1].

The objective of the present work was to develop a novel topical gel formulation of econazole nitrate that can be conveniently scaled up using a one-pot process, aimed at improving therapeutic efficacy against fungal and yeast infections. Econazole nitrate is commonly prescribed for conditions such as tinea versicolor, tinea pedis, and tinea cruris.

Compared with conventional topical dosage forms like creams or ointments, gel-based formulations offer several advantages, including improved patient compliance, non-greasy texture, enhanced spreadability, and faster drug release at the site of infection. For this study, econazole nitrate was incorporated into optimized Carbopol gel bases, prepared using a viscous mixture of propylene glycol along with suitable preservatives such as methyl and propyl paraben [4].

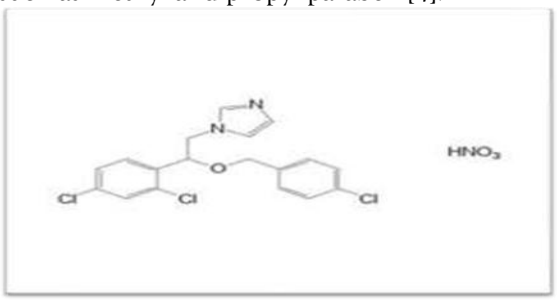

Figure 2: Structure of Econazole Nitrate

MATERIALS AND METHOD:

Preformulation Study:

FTIR Study: FTIR Study was carried out to determine drug and excipients compatibility study.
Melting Point:
Solubility Study: Solubility study of drug was carried out in different solvents like methanol, ethanol, DMSO (Dimethyl Sulfoxide), and water.

Formulation of Emulgel:

In order to formulate stable emulgel, 3^2 full factorial design was applied to the formulation that showed the satisfactory results to see the effect of varying the concentrations of variables such as Carbopol 940 (X1) and Span 80 (X2) on responses like viscosity and diffusion. The levels of two factors were selected on the basis of studies carried out before implementing the experimental design. Table summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study [5].

Factorial design model parameters

Table 1: Factorial design model for Emulgel

Independent Variables			Level		
			Low	Medium	High
X1	Carbopol 940	%	2	3	4
X2	Span 80	%	1	2	3

Formulation of Econazole Nitrate Emulgel [6,7]

Table 2: Formulation of Econazole Emulsion

Sr. No.	Ingredients	Quantity (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Econazole nitrate	1	1	1	1	1	1	1	1	1
2.	Carbopol 940	2	2	2	3	3	3	4	4	4
3.	Span 80	1	2	3	1	2	3	1	2	3
4.	Tween 80	1	1	1	1	1	1	1	1	1
5.	Propylene glycol	5	5	5	5	5	5	5	5	5
6.	Light liquid paraffin	7	7	7	7	7	7	7	7	7
7.	Cetosteryl alcohol	3	3	3	3	3	3	3	3	3
8.	Isopropyl myristate	7	7	7	7	7	7	7	7	7
9.	Methanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10.	Water	q. s	q. s	q. s	q. s	q. s 10gm	q. s	q. s	q. s	q. s
Total		10gm								

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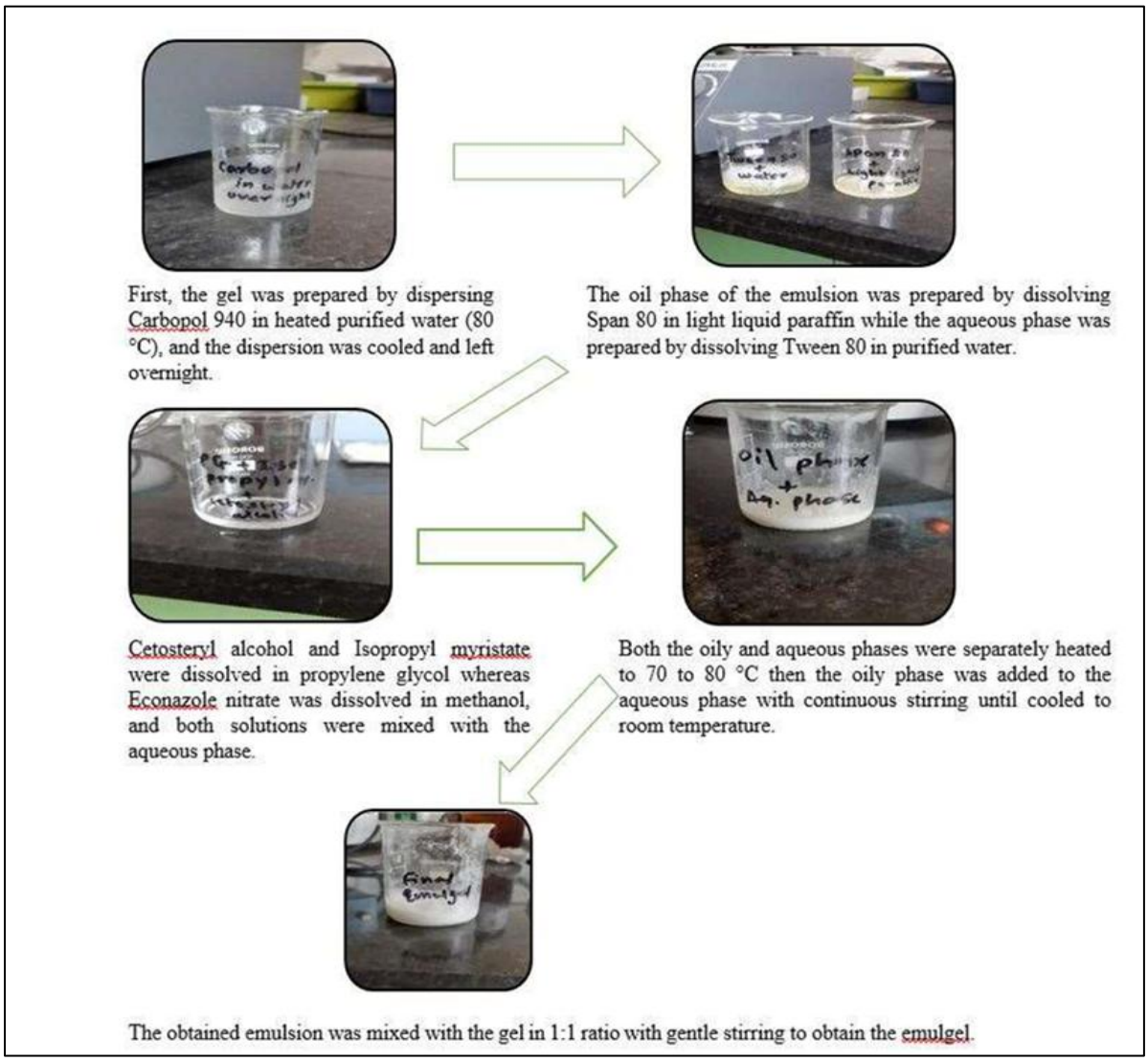

Figure 3: Preparation of Emulgel

Evaluation Tests of Emulgel Formulation [8,9]:

Physical examination:

The formulations were inspected for their colour, odour and appearance.

Colour: A little amount of emulgel was taken on a glass slide and examined in well lighted area. **Odour**: Adequate quantity of emulgel was smelled to get the odour.

Appearance: A pinch of emulgel was taken in between two fingers and appearance was experienced.

pH

The pH meter (Labman pH system LMPH-10) was calibrated using standard buffer solutions of pH 4, 7 and 9. About 0.5gm of the Emulgel was weighed and dissolved in 50.0 ml of distilled water and its pH was measured.

Viscosity

Viscosity of the emulgel was determined by Brookfield Viscometer (Amtech Model Number. LVDVE) at different rpm, using spindle number-64. The spindle was rotated at 10, 50, 60, 100 rpm and viscosity (cP) and Torque (%) was measured. Lesser the torque better will be viscosity.

Spreadability test

500 mg of the emulgel was sandwiched between 2 slides. A weight of 100gm was placed on upper slide. The weight was removed and extra formulation was scrapped off. The lower slide was fixed on board of apparatus and upper slide was fixed with non-flexible string on which 20gm load was applied. Time taken by upper slide to slip off was noted down.

S=ML/T

Whuere,

S= Spreadability

M= Weight on upper slide

L= Length moved on glass slide

Drug content:

Emulgel equivalent to 10 mg of Econazole nitrate (1000 mg emulgel) was taken in a 10 ml volumetric flask containing 5 ml solvent (methanol) and the volume was made up to mark with solvent (methanol) to get a concentration of 1000µg/ml. An aliquot of 1ml was transferred to a 10ml volumetric flask and volume was made up with solvent (methanol). The absorbance of prepared solution was measured at λ max 220 nm by using UV visible spectrophotometer.

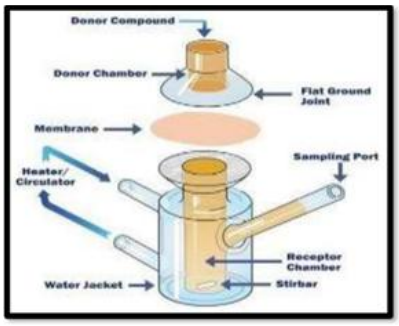

Figure 4: Franz diffusion cell assembly

In-vitro diffusion test: Laboratory-assembled apparatus resembling a Franz diffusion cell was used to determine the release profile of drug from emulgel. The cell consisted of two chambers, the donor and the receptor compartment between which a diffusion membrane (Cellophane membrane) was mounted. The donor compartment, with inner diameter 24 mm, was open i.e., exposed to the atmosphere at one end and the receptor compartment was such that it permitted sampling. The diffusion medium used was phosphate buffer solution pH 5.8 (PBS). 10mg equivalent drug containing emulgel was placed in the donor compartment over the drug release membrane and was separated from the receptor compartment by the cellophane membrane [10,11]. The cellophane membrane was previously soaked for 24 hr. in PBS. The donor and receptor compartments were held together using a clamp. The position of the donor compartment was adjusted so that cellophane membrane just touches the diffusion medium. The whole assembly was fixed on a magnetic stirrer. The receptor compartment with 25 ml of PBS was placed on a thermostatically controlled magnetic stirrer. It was maintained at 37 ± 0.50C and stirred constantly at 50 rpm. Samples of 1 ml were collected at predetermined time intervals and further diluted with solvent (methanol) analysed for drug content by UV spectrophotometer at λ max 220 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal [12].

Antifungal test:

Step 1: Media preparation:

Prepared plates of Mueller Hinton Agar for use in the Kirby Bauer method for rapidly growing aerobic organisms. For fastidious organisms such as Aspergillus niger and Candida albicans Mueller Hinton Agar is supplemented with 5% sterile defibrinated blood. For Fungal cultures used Mueller Hinton Agar (M173) + 2% Glucose + 0.5mcg/ml Methylene Blue Dye (GMB medium), The medium in the plates should be sterile and have a depth of about 4-5mm [13].

Step 2: Inoculum Preparation:
For fungal cultures inoculum was prepared by picking five distinct colonies of approximately 1mm from 24 hours old culture grown on Sabouraud Dextrose Agar (M063) and incubated at 35±2°c.
Step 3: Test procedure:
Using a wooden applicator, dipped a sterile non-toxic cotton swab into the standardized inoculum (turbidity adjusted to achieve confluent growth on the petri plate) and firmly rotated the soaked swab against the upper inside wall of the tube to express surplus fluid. Three times using the swab, streak the entire agar surface of the plate, turning the plate at a 60° angle between each streaking [14].
Allowed the inoculum to dry for 5-15 minutes with lid in place. Applied the discs using aseptic technique. Deposited the discs with centres at least 24 mm apart. For fastidious organisms and for Penicillin's and Cephalosporin's, the discs should preferably be deposited with centres 30mm apart. For fungal cultures incubated immediately at 35±2°c and examined each plate after 20-24 hours of incubation. The ensuing zones of inhibition will be evenly round and there will be a semi- confluent lawn of growth provided the plate was streaked correctly. Only read at 48 hours if there isn't enough growth after 24 hours of incubation [15,16].

RESULTS AND DISCUSSION

Preformulation study:
Drug Characterization:
Drug characterization parameters such as colour, odour and appearance were analysed for the procured drug samples and the results were shown in Table 3.
Table 3: Drug characterization parameters

Colour	White
Odour	Odourless
Appearance	Crystalline

Determination of melting point:
The melting point of Econazole nitrate was found in the range of 160-162^{0}C which comply with reported melting point of Econazole nitrate.
Solubility study:
The solubility study of Econazole nitrate was carried out by using different solvent systems as per the literature. The solubility results were shown in Table 4.
Table 4: Result of Solubility Study

Sr.No	Solvent	Observation
1.	Methanol	Soluble
2.	Ethanol (95%)	Soluble
3.	Dimethyl sulfoxide (DMSO)	Soluble
4.	Water	Insoluble

UV-visible spectrophotometric analysis:
The UV-visible spectrophotometric analysis was carried out by using Jasco Corporation, Japan V 550 Spectrophotometer and spectra manager software was used for analysis. Methanol was used as solvent system

for blank as well as sample preparation. 20 µg/ml of Econazole nitrate was used and λ max was found as 220 nm. The spectra for results were expressed in Figure 5 and 6.

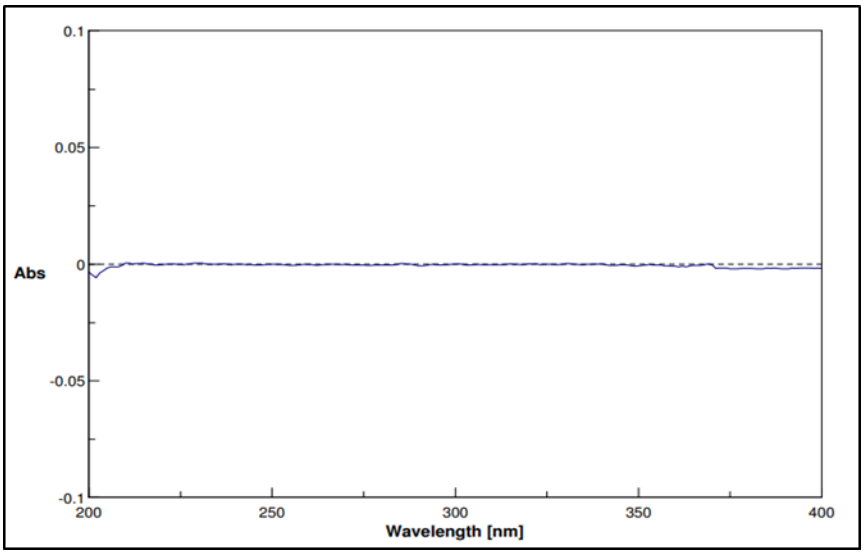

Figure 5: Blank in Methanol

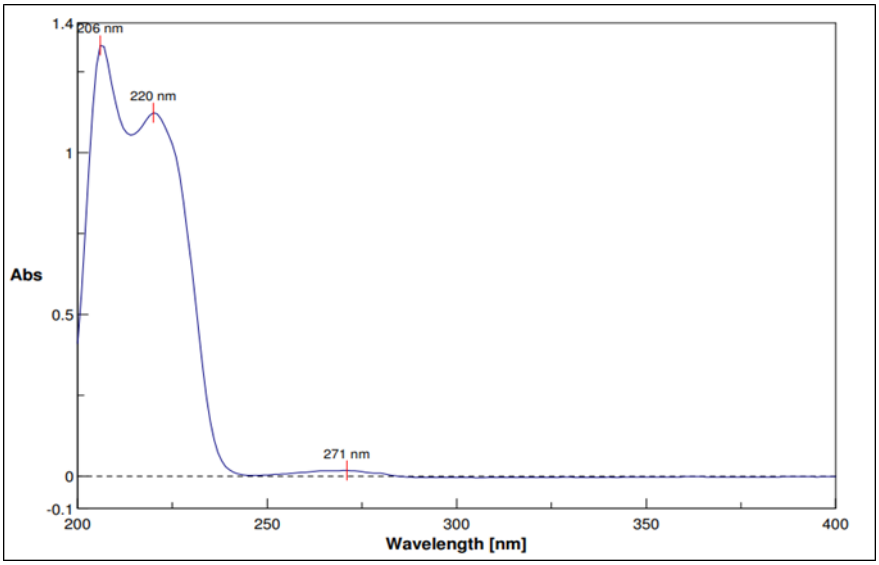

Figure 6: Econazole nitrate in Methanol

Preparation of Calibration curve for Econazole nitrate:

The calibration curve of Econazole nitrate was drawn by measuring the absorbance of different concentrations in methanol at 220 nm. The calibration curve obtained was shown in Table 5 and Figure 7.

Table 5: Calibration curve for Econazole nitrate

Sr.No.	Concentration (ppm)	Absorbance
1.	5	0.3054
2.	10	0.6145
3.	15	0.8129

4.	20	1.0346
5.	25	1.3611

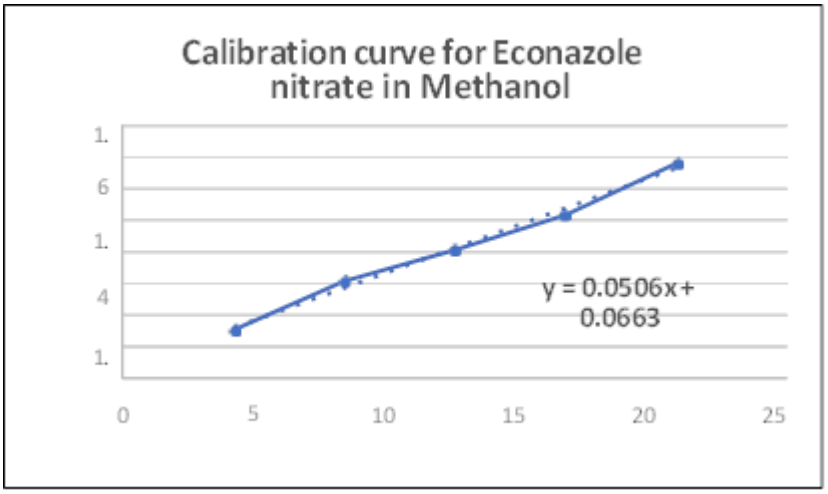

Figure 7: Calibration Curve of Econazole Nitrate

The calibration curve for Econazole nitrate were linear and obeyed Beer-Lambert's law in the concentration range 5-25 µg/ml. The correlation coefficient values were 0.9924 indicating excellent linearity of the data.

FT-IR of Econazole nitrate:

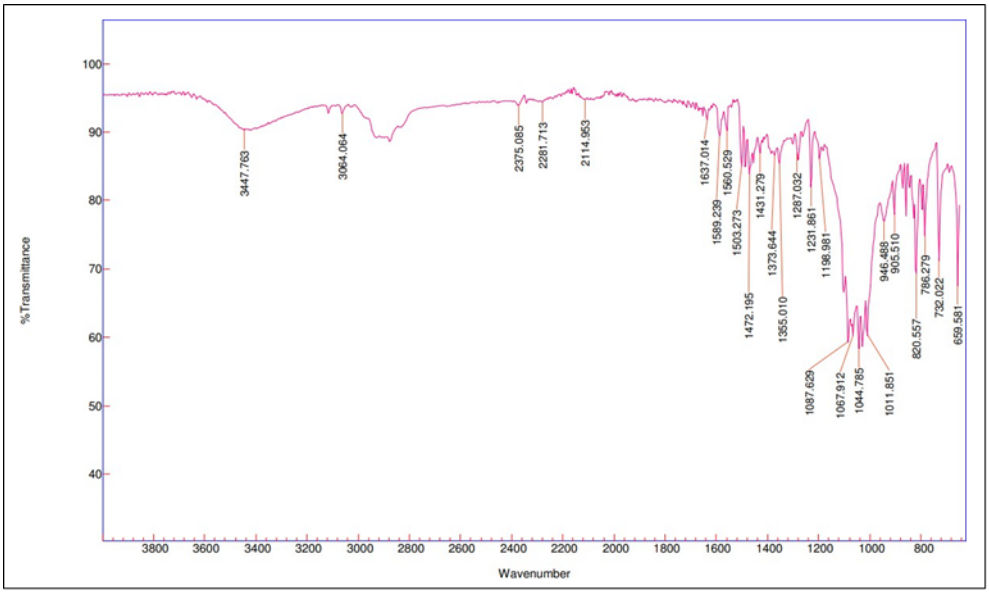

Figure 8 : IR of Econazole nitrate

Table 6. IR frequencies of Econazole nitrate functional group

Functional group	Observed Frequency	Reported Frequency
N–H stretching (Amine group)	3447.76	3500-3400

C-H Stretching (Aliphatic Alkane)	3064.06	3100-2900
C=C stretching (Conjugated alkene)	1637.01	1650-1600
C-H bending (Methyl group)	1472.19	1465
C-N stretching (Aromatic amine)	1287.03	1342-1266
C-Cl stretching (Halo compound)	820.55	850-550

Drug excipient compatibility study:

The FTIR Spectra of Econazole nitrate in pure form and their physical mixture was observed, the result showed that there is no interaction between drug, polymer and excipients. IR spectra for compatibility study were shown in Figure 9 and 10.

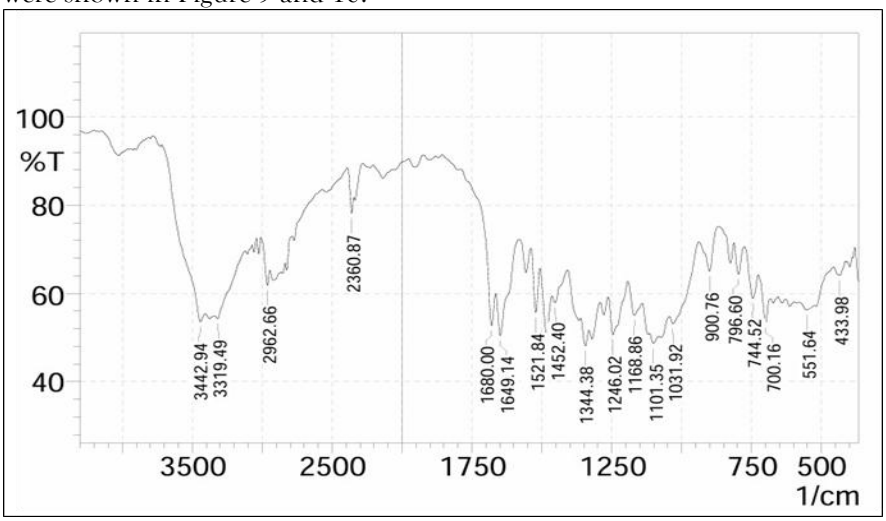

Figure 9: IR of Econazole nitrate: Carbopol 940

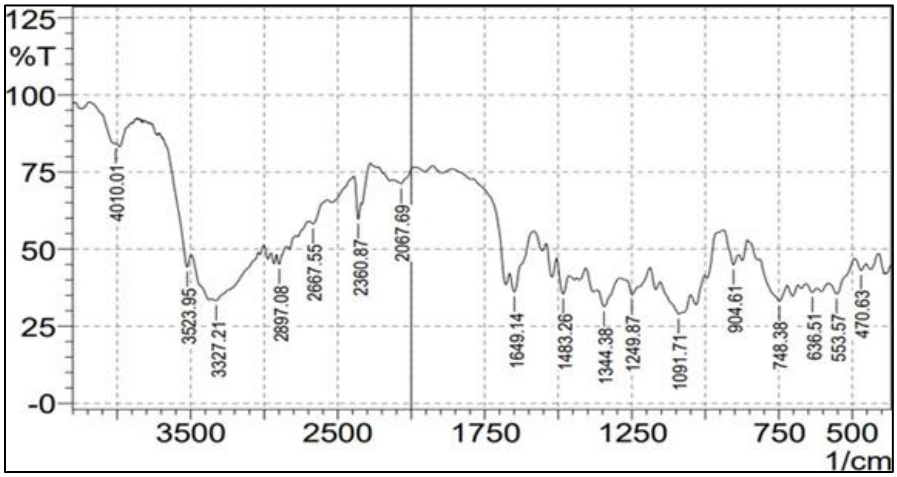

Figure 10: IR of Econazole nitrate: Span 80

EVALUATION OF FORMULATED BATCHES:

A. Physical evaluation:

Some batches showed smooth and grease free appearance whereas, some were viscous in nature. Colour difference was not observed in between any batch as all were white in colour. Also, there was no odour difference in between any batch as all batches were odourless. Results were expressed in table 7.

Table 7: Physical characteristics of formulated batches

Batches	Colour	Odour	Appearance
F1	White	Characteristic	Smooth
F2	White	Characteristic	Smooth
F3	White	Characteristic	Smooth
F4	White	Characteristic	Smooth
F5	White	Characteristic	Smooth
F6	White	Characteristic	Viscous
F7	White	Characteristic	Smooth
F8	White	Characteristic	Viscous
F9	White	Characteristic	Viscous

DISCUSSION:

Percentage of Carbopol 940 and Span 80 in formulation having impact on diffusion of drug. As % Carbopol 940 increases diffusion get decreased and as % Span 80 increases in formulation diffusion get increase. Span 80 was having high impact on diffusion as compare to Carbopol 940 as its P value was very low as compare to Carbopol 940.

Table 8. Summary of effect of independent variable on dependent variables

Sr. No.	Independent Variables	Viscosity	Diffusion
1	% Carbopol 940 in formulation	Directly proportional (As Carbopol 940 increases, viscosity also increases)	Inversely proportional (As Carbopol 940 increases, diffusion decreases)
2	% Span 80 in formulation	Directly proportional (As Span80 increases, viscosity also increases)	Inversely proportional (As Span80 increases, diffusion decreases)

Antifungal testing of optimized batch:

Antifungal study was performed as per the standard procedure mentioned under experimental work. For the optimized batch zone of inhibition was found as 27 mm. For the standard antifungal agent (Nystatin) zone of inhibition was found as 28 mm. On the basis of antifungal results, it was proved that optimized batch of emulgel was having sufficient antifungal activity. The results were expressed in Figure 11.

Figure 11: Antifungal plate

Table 9: Antifungal study (zone of inhibition)

Sr.no.	Sample	Zone of inhibition (mm)
1.	Optimized batch (F4)	27 mm
2.	Standard agent for antifungal activity (Nystatin)	28 mm

Nystatin and Zone of Inhibition

Nystatin is an antifungal medication that produces a measurable zone of inhibition when tested against susceptible microorganisms using agar diffusion methods. The diameter of this zone, usually expressed in millimeters, reflects the extent of antifungal activity. A larger zone indicates greater susceptibility of the microorganism to nystatin.

Factors Affecting the Zone of Inhibition

Microorganism species

Different fungal species have variable susceptibility to nystatin, leading to differences in zone size.

Nystatin concentration

Higher concentrations generally produce larger zones of inhibition due to increased antifungal effect.

Incubation conditions

Temperature, duration, and atmospheric conditions can influence both microbial growth and drug diffusion.

Agar medium

The composition and thickness of the medium affect the diffusion of nystatin and, consequently, the size of the inhibition zone.

CONCLUSION:

Econazole nitrate emulgel represents a significant advancement in the treatment of superficial fungal infections, integrating the efficacy of antifungal agents with a user- friendly formulation. This thesis has demonstrated that econazole nitrate, as an imidazole antifungal, effectively targets fungal cell membranes by inhibiting ergosterol synthesis, which is crucial for maintaining fungal cell integrity. The emulgel formulation,

characterized by its emulsion in a gel base, enhances the drug's penetration and bioavailability while offering a non-greasy and aesthetically pleasing application form. In summary, econazole nitrate emulgel is a valuable addition to the antifungal armamentarium, offering a practical and effective solution for managing fungal skin infections. Its formulation advances both therapeutic efficacy and patient compliance, marking a significant contribution to dermatological treatments. Continued research and clinical experience will further solidify its role and potentially uncover additional benefits and applications in the field of dermatology.

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