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FORMULATION AND EVALUATION OF TOPICAL GEL CONTAINING ECONAZOLE NITRATE

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ABSTRACT

The purpose of this work was to develop a novel topical formulation of econazole nitrate based on gel that can be easily scaled up in one pot for the potential treatment of fungal and yeast infections. Econazole nitrate is a topical antifungal, is used to treat tinea versicolor, tinea pedis, and tinea cruris. Compared to applying cream or ointment, topical gels offer numerous advantages, one of which is that the drug is released more quickly to the intended site of action. A viscous mixture of propylene glycol, Triethanolamine, methyl paraben, and econazole nitrate were mixed together before being formulated into the optimized gel bases. The gel's color, appearance, and homogeneity were assessed visually. For every formulation, the drug content, pH, viscosity, spreadability, and gel strength were characterized. The manufactured formulations were transparent, half white, pale yellow, and exhibited excellent homogeneity. The pH and viscosity are in within the limit. The drug diffusion of F1 93.81, F2 97.56, F3 92.36, F4 90.95, F5 93.18, and F6 90.14 .From among all the developed formulation, F2 shows better drug diffusion that is 97.56.

KEYWORDS: Econazole Nitrate, permeation enhancer, Viscosity, Spreadability, Invitro drug release.

INTRODUCTION

Over the past few decades, illness treatment has primarily involved administering drugs through various routes, including oral, sublingual, rectal, parenteral, topical, and inhalation methods. Topical delivery refers to applying a drug-containing formulation directly to the skin to treat skin conditions such as acne or the skin manifestations of systemic diseases like psoriasis, with the goal of confining the drug's effects to the skin surface or within the skin. While semi-solid formulations such as creams, ointments, and gels dominate the field of topical delivery, other forms are also utilized, including foams, sprays, medicated powders, solutions, and medicated adhesive systems. These diverse formulations offer various advantages, such as improved drug penetration, targeted action, and enhanced patient compliance. For instance, foams and sprays can provide easier application over large areas or hard-to-reach spots, while medicated powders and solutions may be preferred for their drying and immediate relief properties.[1]

Advances in pharmaceutical technologies have driven formulation scientists to explore alternative routes beyond oral and parenteral methods for efficiently and effectively delivering drugs to their target sites. Effective drug administration involves achieving optimal therapeutic delivery at the site of action within a specified time frame. The topical delivery system is a method where formulations are applied to surface areas such as the skin, eyes, nose, and vagina to treat local conditions.[2-4] Applying drugs to these topical surfaces bypasses issues like hepatic first-pass metabolism, variations in gastric pH, and fluctuations in plasma levels, which are commonly encountered with oral administration.[5]

Other advantages of the topical drug delivery system include.

- Increased patient compliance and acceptance.
- A painless and noninvasive application method.
- Enhanced drug bioavailability.
- Improved physiological and pharmacological responses.
- Reduced systemic toxicity and minimized exposure of the drug to non-target tissues or sites.[6]

MATERIALS AND METHODS

Materials

The material such as Econazole Nitrate, Sodium alginate, hydroxy propyl cellulose, triethanolamine, methyl paraben, methanol. Of pharma grade, or the best possible laboratory was used as supplied by the manufacturers.

All materials(AR Grade) and instruments utilized in the work were sourced from various sources**.**

Methods

Preparation of Econazole nitrate gel[7]

Gels were prepared by cold mechanical method described by Kumar et al.

Step 1- Required quantity of polymer (Natural polymer and Synthetic polymer) was weighed and it was sprinkled slowly on surface of purified water for 2 hrs. After which it was continuously stirred by mechanical stirrer, till the polymer soaked in the water.

Step 2- With continuous stirring, triethanolamine was added to neutralize the gel and it maintains the pH of the gel. Now the appropriate quantity of DMSO (Dimethyl sulfoxide) was added to the gel, which behaves as the penetration enhancer, followed by the required quantity of methyl paraben as a preservative.

Step 3- Finally the drug Econazole Nitrate was added to the gel with continuous stirring till drug get dispersed in gel completely.

Table No 1: Formulation of Econazole Nitrate gel.

Ingredients (%w/w)	F_1	F_2	F_3	F_4	F_5	F_6
Econazole nitrate (mg)	150	150	150	150	150	150
Sodium alginate (gm)	2	-	0.5	1	0.5	1.5
HPMC (gm)	-	2	0.5	1	1.5	0.5
Triethanolamine	0.23	0.23	0.23	0.23	0.23	0.23
Methyl paraben (mg)	15	15	15	15	15	15
Methanol (ml)	2.2	2.2	2.2	2.2	2.2	2.2
Water in gms	qs	qs	qs	qs	qs	qs

EVALUATION OF ECANOZOLE NITRATE GELS

Preformulation studies

1. Melting point determination

A few quantities of ecanozole nitrate are taken and placed in a thin-walled capillary tube about 8-10 cm long and 1mm inside diameter and closed at one end, and then it is tied to a thermometer, suspended into Thiele tube containing oil bath. The apparatus can be heated slowly, the temperature range over which the sample is observed to melt is taken as the melting point.

2. Determination of λ max

Ecanozole nitrate 10 µg/ml concentration was prepared in methanol. The solution was scanned from 200 to 400 nm by UV spectro photometer and a spectrum was observed for absorption maxima.

3. Standard calibration curve of Ecanozole nitrate

100 mg of accurately weighed ecanozole nitrate was dissolved in equal volume of 100 ml methanol as stock solution.10 ml of the above stock solution was diluted to 100 ml methanol. From the above solution 6, 12, 18, 24 and 30 µg/ml was prepared and analyzed by UV spectrophotometer at λ max. The graph of absorbance concentration in µg/ml was plotted and r^2 value of this graph was calculated to check the linearity of the absorbance against concentration.

Post formulation studies

1. Physical evaluation[8]

All the formulations of econazole nitrate were evaluated for organoleptic characteristics, occlusive ness and washability.

2. Measurement of pH

The pH of the formulated gels was determined using digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter.

3. Spreadability

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations.

4. Viscosity studies[9-10]

The measurement of viscosity of formulations was done with a Brookfield Viscometer. The gels were rotated at 10 and gels at 20 rpm using spindle no. 64. At each speed, the corresponding dial reading was noted.

5. Drug content studies

Econazole nitrate gel (500 mg) was taken and dissolved in 50 ml of phosphate buffer pH 7.4. The volumetric flasks were kept for 2 h and shaken well in a shaker to mix it properly.

The solution was passed through the Whatman filter paper and filtrates were analyzed for drug content spectrophotometrically at 285 nm against corresponding gel concentration as blanks.

6. In vitro drug release studies

Before experiment, the cellophane membrane was washed in the running water and diffusion studies of prepared gels were carried out in hollow tube diffusion cell using prehydrated cellophane membrane and phosphate buffer pH 7.4 (100 ml) as receptor compartment. 500 mg of each of formulation was spread uniformly on the membrane (Yamaguchi *et al* 1996). The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.5°C. The solution on the receptor side were stirred by externally driven teflon coated magnetic bars. At

predetermined time intervals, 5 ml of solution from the receptor compartment was pipetted out and immediately replaced with fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically at 285 nm against appropriate blank. Calculation of percentage drug release was done using the formula.

$$\% \text{ drug release} = \frac{(\text{Conc. of drug (in mg)} \times \text{Volume of receptor compartment}) \times 100}{\text{Label claim (amount of drug in donor compartment)}}$$

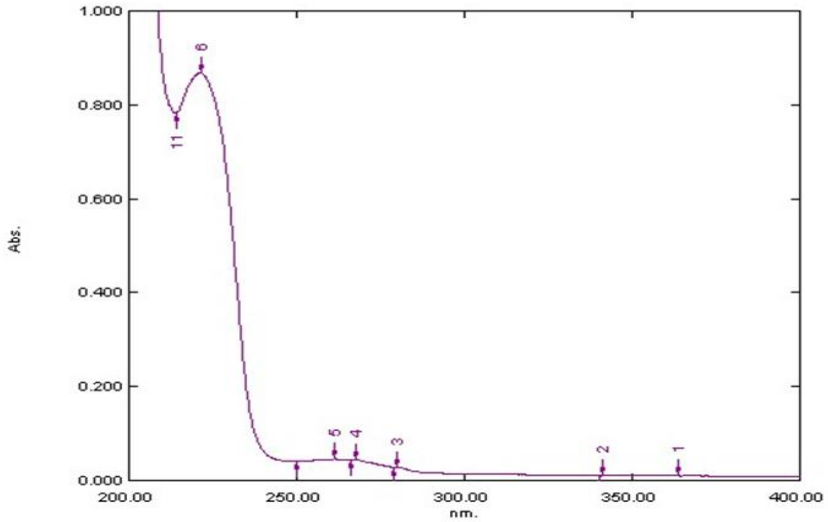
RESULT AND DISCUSSION

Preformulation studies

1. Melting point determination

Reported	Method	Observed
161-163℃	Thiel's tube method	162℃

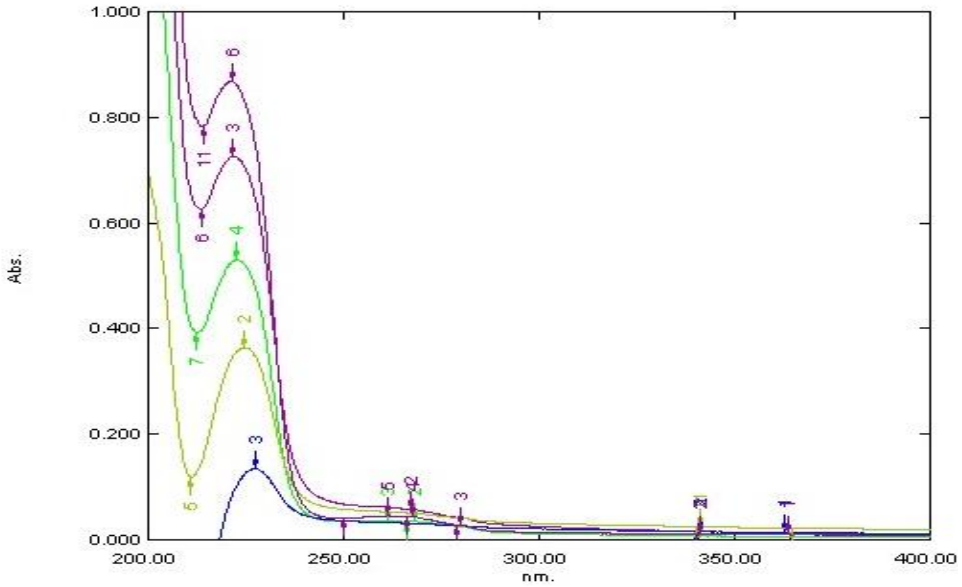
Econazole Nitrate topical gel shows a 162℃ by the Thiel's tube method.



UV Spectrum of Econazole Nitrate.

Table No 4: Data for standard calibration curve of Econazole Nitrate.

Sl. no	Concentration in µg/ml	Absorbance at 260nm			Standard deviation (SD)
		Trail-I	Trail-II	Trail-III	
1.	5	0.182	0.179	0.183	0.181
2.	10	0.381	0.387	0.38	0.383
3.	15	0.571	0.575	0.57	0.572
4.	20	0.762	0.763	0.76	0.762
5.	25	0.963	0.921	0.96	0.961



Plot of standard calibration curve of Econazole Nitrate

Post formulations studies

1. Physical evaluation

The prepared gel formulation was inspected visually for their colour and appearance. The developed formulations F1, F2, F3, F4, F5, F6 were transparent, pale yellow, half white. All the formulations were much clear.

Table No 2: properties of Econazole Nitrate gel.

Topical formulation	Colour	Phase separation	Spreadability ($gm.cm^2$)	pH	Drug content (%)	Viscosity in centipoise
F1	Pale yellow	No phase separation	11.16	6.5	99.1	8950
F2	Transparent		11.72	6.2	98.5	9223
F3	Transparent		10.88	6.6	98.3	8874
F4	Half white		11.07	6.9	99.1	8954
F5	Transparent		10.65	7.1	97.9	9122
F6	Pale yellow		11.97	6.4	98.1	8824

2. Measurement of pH

The pH of gels was determined using digital pH meter. The F1 to F6 shows 6.2 to 7.1 pH. The pH results are given in table no.2

3. Viscosity study

The F1 to F6 batches shows 8950 to 8824 cps of viscosity. As the polymer concentration increases, the viscosity also increase. The viscosity results are given in table no.2

4. Spreadability

The value of spreadability indicates the degree of shear required to apply the gel. The spreadability results are shown in table no.2

5. Drug content

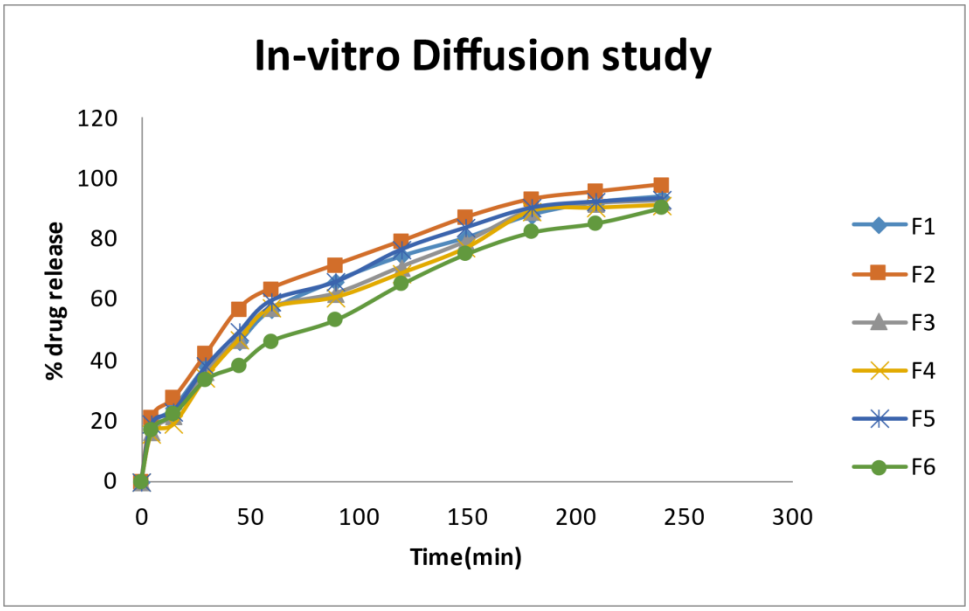
The drug content of all batches of all formulations were in the range of 97.9 to 99.1%. The F1 and F4 batch shows maximum 99.1% and F5 batch shows minimum 97.9% drug content. The drug content determination showed that the drug was uniformly distributed throughout the gel. The drug content results are given in table no.2.

6. In vitro diffusion studies

Econazole Nitrate topical gel containing the formulations F1 to F6 in which formulation F1 containing sodium alginate shows drug release of 93.81% F2 containing HPMC shows drug release of 97.56% up to 4 hrs. Formulation F3, F4, F5 and F6 containing both sodium alginate and HPMC shows drug release is about 92.36, 90.95, 93.18 and 90.14% up to 4 hrs. Formulation F2 shows the highest drug release with prolonged period of time.

Table No 3: In vitro diffusion study of econazole nitrate.

Time	F1	F2	F3	F4	F5	F6
5	18.04	21.06	16.26	15.83	19.00	16.81
15	24.02	27.30	21.87	18.75	23.13	21.97
30	37.76	42.02	36.03	34.38	37.85	33.47
45	45.84	56.75	46.96	46.56	49.06	38.10
60	56.36	63.44	57.26	57.06	59.51	46.19
90	66.10	71.29	61.89	60.6	65.75	53.23
120	74.10	78.96	70.58	68.47	76.36	64.90
150	80.24	86.86	78.98	76.87	83.65	74.95
180	87.78	92.75	89.26	88.92	90.13	82.06
210	91.90	95.24	91.50	90.01	92.15	85.12
240	93.81	97.56	92.36	90.95	93.18	90.14



CONCLUSION

Various formulation (F1, F2, F3, F4, F5, F6) were developed by using Sodium alginate and HPMC Developed formulations of Econazole Nitrate gel were evaluated for the physio chemical parameters such as drug content, pH, viscosity, spreadability, in vitro drug diffusion. Viscosity studies of various formulations revealed that formulation F2 was better to compare to others. The drug diffusion of F1 93.81, F2 97.56, F3 92.36, F4 90.95, F5 93.18, and F6 90.14. From among all the developed formulation, F2 shows better drug diffusion that is 97.56. pH of the F2 formulation is sufficient enough to treat the skin infections. The viscosity of HPMC gels was very high as compared to Sodium alginate gels but both gels showed a decrease in drug release with an increase in polymer concentration. Thus, gels can be successfully prepared using Sodium alginate and HPMC as gelling agents suitable for topical application Hence formulation F2 should be further developed for scale-up to industrial production.

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