

# Formulation and Evaluation of Topical Anti Fungal Gel Containing Econazole Nitrate

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Date of Submission: 10-06-2021

Date of Acceptance: 25-06-2021

## ABSTRACT

**Objective:** The present research has been undertaken with the aim to develop a topical gel formulation of Econazole Nitrate. Econazole Nitrate is an imidazole derivative and used for the treatment of local and systemic fungal infection. The oral use of Econazole Nitrate

is not much recommended. Commercially Econazole Nitrate topical gel preparation are not available in the market, thus this formulation is made for better patient compliance and to reduce the dose of the drug and to avoid the side effects like liver damage and kidney damage.

**Methods:** The gel was formulated by changing the polymer ratio. Various formulations (F1 to F12) were developed by using suitable polymer (carbopol 934p, Sodium alginate, DMSO, HPMC, Triethanolamine). The formulation was evaluated for % drug content, Clarity, pH, spreadability, Extrudability and viscosity in vitro drug release study, stability testing.

**Results:** Viscosity studies of various formulations revealed that formulation F5 was better to compare to others. From among all the developed formulations, F7 shows better drug diffusion, did good Rheological properties. pH of the F9 formulation is sufficient enough to treat the skin infections.

Results indicated that the concentration of carbopol-934 and HPMCK4M significantly affects drug release and rheological properties of the gels.

**Conclusion:** It was concluded that formulation F2 AND

F7 was the best formulation among this formulation.

**Keywords:** Econazole Nitrate, Carbopol 934p, HPMC, DMSO

## I. INTRODUCTION

Fungal infection of the skin is nowadays one of the common

dermatological problems. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form to liquid dosage formulation. Among the topical formulation, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals [1]. Topical treatment of dermatological diseases as well as skin care, a wide variety of vehicles ranging from solid to semisolid and liquid preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and pharmaceutical preparation [2]. For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drug to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, cream, gel, ointments, liquids, aerosols and injectable, as drug carriers. Delivery of drug to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first-pass effect, only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages, the gel formulations have been proposed as a topical application. Gels are defined as "semisolid systems in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking is introduced".

Econazole Nitrate is a synthetic antifungal agent of the imidazole class; it works by slowing the growth of fungus that cause infection. It is used to treat fungal infection. Triazole drug targets the fungal-specific synthesis of membrane lipids. Alkylation of imidazole (2) with bromo ketone (1) prepared from o,p-dichloroacetophenone affords the displacement product (3). Reduction of ketone with sodium bromohydrate gives the corresponding alcohol (4). Alkylation of the alkoxide from alcohol with p-chlorobenzyl chloride leads to Econazole (5).

## II. MATERIALS AND METHODS [5,6]

### Material

Econazole Nitrate, HPMC, carbopol 934, triethanolamine, Methyl paraben, DMSO, Sodium alginate, water.

### Method

It is performed by cold mechanical method. Polymer (like Carbopol 934 or HPMC) and purified water were taken in a beaker and allowed to soak for 2h. To this required amount of drug (2gm) was dispersed in water and then Carbopol 934 or HPMC was then neutralized with sufficient quantity of Triethanolamine. Then approx. quantity of DMSO was added which behaves as penetration enhancer. Methyl paraben as preservatives were added slowly with continuous gentle stirring until the homogenous gel was formed.

**Table 1: Optimized formulae of Econazole Nitrate gel**

Constituents	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Econazole nitrate (gm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Alginate (gm)	1	-	-	0.5	0.25	0.75	-	-	-	0.5	0.25	0.75
HPMC K4M (gm)	-	1	-	0.5	0.75	0.25	0.5	0.25	0.75	-	-	-
Carbopol 934 (gm)	-	-	1	-	-	-	0.5	0.75	0.25	0.5	0.75	0.25
Triethanolamine (ml)	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023	.023
DMSO (ml)	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Methyl Paraben (mg)	15	15	15	15	15	15	15	15	15	15	15	15
Water upto 100ml												

### Evaluation of Econazole Nitrate gels

#### Drug content

Weighed 10 gm of each gel formulation were transferred in 250 ml of the volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol and again 1 ml of the above solution was further diluted to 10 ml with alcohol.

The absorbance of the solution was measured spectrophotometrically at 260 nm. Drug content was calculated by the following formula

#### Determination of Ph

Weighed 50 gm of each gel formulation were transferred in 10 ml of the beaker and measured it by using the digital pH meter. pH of the topical gel formulations should be between 3-9 to treat the skin infections.

**Spreadability**

The spreadability of the gel formulation was determined, by measuring the diameter of 1 gm gel between horizontal plates (20×20cm<sup>2</sup>) after 1 minute. The standardized weight tied on the upper plate was 125 gm.

**Extrudability**

The gel formulations were filled into a collapsible metal tube or aluminium collapsible tube. The tube was pressed to exert the material and the extrudability of the formulation was checked.

**Viscosity estimation**

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-bars spindle in combination with a helipath stand.

- a) **Selection of spindle:** Spindle T95 was used for the measurement of viscosity of all the gels.
- b) **Sample container size:** The viscosity was measured using 50 gm of gel filled in a 100 ml beaker.
- c) **Spindle immersion:** The T-bars spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch the bottom of the jar.
- d) **Measurement of viscosity:** The T-bars spindle (T95) was used for determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. which affect the viscosity were maintained during the process. The helipath T-bars spindle was

moved up and down giving viscosities at a number of points along the path.

The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

**In vitro diffusion study**

In-vitro diffusion study was carried out for 4 hours using diffusion cell. The cumulative % amount of the drug release from the gel at the end of 240 mins was found to be 99.29 % in formulation F7 containing 0.5% w/w of Carbopol and HPMC K4M each. The cumulative % amount of the drug release from the gel at the end of 240 mins was found to be 75.01 % in formulation F12 containing 0.75% w/w of Sodium alginate and Carbopol 0.25% w/w. Individual gel formulations F1, F2 and F3 prepared by using 1% w/w of Carbopol, HPMC K4M and Sodium alginate. Showing the release of 93.71%, 97.58 and 92.55. Amongst which F2 showed the best and highest release of 97.58% was selected. In combination formulation F4, F7 and F10 (0.5% w/w of Carbopol, HPMC k4M and Sodium alginate) which showed the release of 90.95%, 99.29% and 78.53% out of which F7 was considered the best formulation for showing the release of 99.29%. Combination formulation F5, F8 and F11 (0.25% w/w of Carbopol, HPMC K4M and sodium alginate) which showed the release of 93.16%, 96.38 and 88.43%. out of which F8 showed the best release of 96.38%. Combination formulation F6, F9 and F12 (0.75% w/w of Carbopol, HPMCK4M and sodium alginate) which showed the release of 90.14%, 89.74% and 75.01%. out of which F6 showed the best release of 90.14%.

**III. RESULTS AND DISCUSSION**

FORMULATION CODE	% DRUG CONENT
F1	98.5%
F2	98.4%
F3	98.1%
F4	98.3%
F5	98.6%
F6	98.7%
F7	98.4%
F8	98.1%
F9	98.4%
F10	98.5%
F11	98.2%
F12	98.0%

**Table 2: Percent drug content of gel formulations**

FORMULATION CODE	pH
F1	6.8
F2	6.5
F3	6.7
F4	6.9
F5	6.2
F6	6.1
F7	6.6
F8	6.9
F9	6.3
F10	6.6
F11	6.9
F12	6.2

**Table3:pHofgelformulations**

FORMULATION CODE	VISCOSITY
F1	8952
F2	8120
F3	8631
F4	8222
F5	9321
F6	8887
F7	8140
F8	8824
F9	9113
F10	8871
F11	8952
F12	8761

**Table4:Viscosityofgelformulations**

FORMULATION CODE	SPREADABILITY
F1	18.60±0.0113
F2	24.9±0.0150
F3	18.03±0.0153
F4	25.80±0.0249
F5	28.20±0.052
F6	22.03±0.0301
F7	27.52±0.0262
F8	25.45±0.0150
F9	18.04±0.0112
F10	23.08±0.0053
F11	22.31±0.022
F12	18.70±0.0200

**Table5:Spreadabilityofgelformulations**

**Table6:Extrudabilityofgelformulations**

FORMULATION CODE	EXTRUDABILITY
F1	++
F2	+++
F3	++
F4	++
F5	++
F6	++
F7	+++
F8	++
F9	+
F10	++
F11	++
F12	++

**Table7:Clarityofgelformulations**

FORMULATION CODE	CLARITY
F1	++
F2	+++
F3	++
F4	+
F5	++
F6	+
F7	++
F8	++
F9	+
F10	++
F11	++
F12	+

Excellent (+++), Good(++), Average(+), Poor(-)

#### IV. CONCLUSION

Various formulation (F1 to F12) were developed by using a suitable polymer (carbopol 934 and HPMC). Preformulation studies on EN comply with the reported literature limits. The adopted method yielded uniform and reproducible release gel prepared using EN. The Average drug content, spreadability, viscosity, extrudability, washability and in-vitro release were uniform and reproducible. The release was directly proportional to concentration of polymers used. The adopted methods yielded uniform and reproducible gel formulations with all the polymers used. Gel formulations prepared with carbopol 934 and HPMC K4M showed good homogeneity, no skin irritation, good stability, and antifungal activity. However, the carbopol 934 and HPMC k4m based gel proved to be the formula of choice, since it showed the highest percentage of drug release and good rheological properties. In-vitro release rate studies showed that the drug release were maximum from formulations F2 (containing 1% w/w of HPMC polymer) that is 97.58% and F7 (containing combination of 0.5% w/w Carbopol + 0.5 % w/w HPMC K4M polymers) that is 99.29%. It can be concluded from the present investigation that proper selection of polymers and drug is a prerequisite for designing and developing a topical drug delivery system. The IR and UV studies suggest that polymer selected i.e Carbopol 934, HPMC, sodium alginate were found to be compatible with the drug EN. The varying concentrations of the three polymers were found to affect the gel parameters like drug release, spreadability and its viscosity. Overall formulation F2 (containing 1% of HPMC polymer) and F7 (containing combination of 0.5% Carbopol + 0.5 %

HPMC K4M polymers) based on diffusion release, viscosity and antifungal activity were found to be an excellent gels. The Selected best formulations F2 and F7 were found to follow zero order release followed by non fickian diffusion control mechanism (Higuchi's model). The combination of EN Carbopol 934, HPMC with DMSO provides results and no side effects such as skin irritation. All formulation containing triethanolamine, which act as a not only preservative but it also, acts as slight penetration enhancer didn't show any kind of interaction. Anti-fungal effects of gels had been observed just in 72 hours after inoculation. The % zone of inhibition of selected formulation F2 and F7 tested in Candida albicans was found to be good when compared to econazole nitrate alone. All the formulations were found to be stable over the storage period.

#### V. SUMMARY

In the present study an attempts were made to formulate and evaluate topical gels of Econazole Nitrate. In our preliminary study the standardization of Econazole Nitrate was carried out for purity and identity. Estimation of Econazole Nitrate was done in phosphate buffer pH 7.4 spectrophotometrically at 220nm. The formulation studies include identification, melting point, pH, solubility and In-vitro release studies were carried out. The gels of all formulation have acceptable physical parameters. The gels prepared by cold mechanical method showed drug content in the range of 98 ±0.0147 %, 98.9 ±0.0146%, in-vitro diffusion release of 88.43% to 99.29 %, viscosity was found in between 8874 cps to 9856 cps, Spreadability was found to be between 18.08 ±0.0152 to 27.72 ±0.0264, pH ranging between 6 to

6.9. All the gels were evaluated for their appearance, pH, drug content, rheological properties, in-vitro release, stability studies and anti-fungal activity. Visually Carbopol gels were sparkling & transparent, HPMC gels were translucent, sodium alginate gels were translucent. The pH range of Carbopol gels, HPMC gels and sodium alginate gels were found to be suitable for topical application. The drug content of formulated gels found in the range of 98.1% and 98.96% respectively. The viscosity measurement was done for selected gels using Brookfield viscometer at room temperature. Which was found between 8874 cps to 9856 cps. Anti-fungal activity of selected best gels was compared with Econazole nitrate using *Candida albicans* using cup plate method. The percentage of zone of inhibition observed for carbopol and HPMC in 0.5% w/w each and carbopol 1% w/w alone showed good results

#### SCOPE OF STUDY

Further studies can be carried out by using different proportions and different combination of natural, synthetic and semisynthetic polymers with econazole nitrate by other methods method.

The work can be extended to in-vivo studies by using Rabbit as animal model.

#### AUTHORS CONTRIBUTIONS

All the authors have contributed equally

#### CONFLICT OF INTERESTS

Declared none

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