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Original Article

DEVELOPMENT OF EFINACONAZOLE NAIL GEL FOR THE TREATMENT OF ONCHOMYCOSIS

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ABSTRACT

Objective: The present research has been undertaken with the aim to develop a topical nail gel formulation of Efinaconazole. Efinaconazole is considered highly desirable to treat common nail disorders such as Onychomycosis due to localized effects and improved adherence. Efinaconazole topical gel preparations are not yet available in the market thus, this formulation is made for better patient compliance. Efinaconazole nail gel is formulated with unique ingredients added to an alcohol-based formulation to provide low surface tension and good wetting properties.

Methods: The nail gels were formulated by using different gelling agents. Various formulations [F_1-F_{10}] were developed using a suitable polymer [Carbopol-934, Xanthan gum, CMC]. The formulations were evaluated for pH, viscosity, spreadability, % Drug content, extrudability, stability testing, *in vitro* drug diffusion studies, and *in vitro* antifungal activity.

Results: The results showed that Efinaconazole nail gel had good antifungal activity. Viscosity studies and pH studies revealed that formulation F2 was better when compared to other formulations. Results indicate that the 0.75% concentration of carbopol-934 is the ideal among other formulations.

Conclusion: It was concluded that formulation F2, containing a 0.75% concentration of Carbopol-934 was the best formulation of all.

Keywords: Efinaconazole, Carbopol-934, Xanthan gum, CMC

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INTRODUCTION

Onychomycosis is a fungal infection of the nail unit caused by dermatophytes, yeasts, and non-dermatophyte molds. It is a common disease with a prevalence of 10%-12% in the US [1, 2]. The treatment objective is to eradicate the fungus and produce a normal nail. There are four approved classes of antifungal drugs for the treatment of Onychomycosis, allylamine, azoles, morpholines, and hydroxypyridinones [3].

Efinaconazole is the First azole FDA-approved in the USA to be used topically in the treatment of Onychomycosis [4].

Dermatophytes are the causative organism of toenail or fingernail fungal infection, which is a superficial fungus infection. A fungal microorganism infects the nail bed, causing the illness. Onychomycosis and Tinea unguium are two forms of a fungal nail infection. Finger nails and toenails thicken, darken, disfigure, and split as a result of a fungal nail infection called as mycotic nails [5, 6].

Efinaconazole, a triazole, is used for the treatment of Onychomycosis and is effective against a broad spectrum of fungal species. There may be extended therapeutic use of this drug beyond Onychomycosis in the future [7, 8].

MATERIALS AND METHODS [9, 10]

Materials

Efinaconazole, Carbopol-934, Xanthan gum, Carboxy methyl cellulose, Ethanol, methylparaben, Triethanolamine, water.

Method

Carbopol-934, Xanthan gum, or CMC as polymer, purified water, and methylparaben as a preservative were taken in a beaker and allowed to stir on a magnetic stirrer. To the above mixture, required amount of organic phase [drug and ethanol mixture] was added. Triethanolamine as a pH adjuster was added dropwise with continuous stirring until a homogeneous nail gel was formed.

Table 1: Optimized formulation of efinaconazole nail gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Efinaconazole	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g
Carbopol-934	0.05g	0.075g	0.1g	0.15g	-	-	-	-	-	-
Xanthan gum	-	-	-	-	0.05g	0.1g	0.15g	-	-	-
CMC	-	-	-	-	--	-	-	0.1g	0.15g	0.2g
Ethanol	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml
Methylparaben	0.01g	0.01g	0.01g	0.01g	0.01g	0.01g	0.01g	0.01g	0.01g	0.01g
Water	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Triethanolamine	To Adjust pH									

Evaluation of efinaconazole nail gels [11-15]

The formulated nail gel was evaluated for pharmaceutical properties like homogeneity, drug content, pH determination, spreadability and viscosity.

Homogeneity

The formulations were tested for their homogeneity by visual appearance after the nail gel was applied as a thin layer on the slide.

Drug content

The drug content of gels was determined by taking the weighed amount of gel into a 10 ml volumetric flask and the volume was made with methanol. The Samples were analyzed spectrophotometrically at 262 nm by using the below formula.

$$\text{Drug Content} = \frac{\text{Absorbance}}{\text{Slope}} \text{x Dilution factor x} \frac{1}{1000}$$

Determination of pH

The pH of all gel formulations was recorded using the pH meter. The gel formulations were suitably diluted for determining the pH.

Spreadability

The spreadability of gels was measured by the parallel plate method. 1g of the prepared gel was placed between two glass plates 10 x 10 cm. A weight of 100g was placed on the top. Then the diameter of the Samples between the plates was measured.

$$S = M. L/T$$

Where S= Spreadability, M= Weight tied to the upper slide

L=Length of a glass slide, T=Time taken to separate the slides

Viscosity

Viscosity determinations of the prepared gels were carried out by Brookfield viscometer using spindle no 64. It was measured at an angular velocity of 100rpm and at 37 °C temperature. The averages of two readings were used to calculate the viscosity and all the evaluations were conducted in triplicate.

Antifungal efficacy studies

The antifungal efficacy study against candida albicans was determined by agar diffusion method employing Cup Plate technique. Known concentrations of prepared Efinaconazole nail gel and placebo gels were poured into cups bored into a petri dish previously inoculated with test organism. After allowing diffusion of the gels for 2h, the agar plates were incubated at 37 °C for 48 h. The zone of inhibition of optimized nail gel was measured and compared with that of the zone of inhibition of placebo nail gel. The entire procedure was carried out in aseptic condition throughout the study and the study was conducted in triplicate.

***In vitro* study**

Franz diffusion cell was used for the drug release studies. Presoaked dialysis membrane was clamped between the donor and the receptor chamber of the diffusion cell. Weighed amount of nail gel was placed onto the surface of the dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH-5.5) solution to solubilize the drug and the diffusion cell was placed on a magnetic stirrer. The sample (1.0 ml aliquots) was collected at suitable time intervals. Samples were analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the dialysis membrane was determined as a function of time.

Stability studies

The optimized nail gel was immediately evaluated for its homogeneity, pH, organoleptic and rheological properties. Then the gel was stored at three different temperatures, i.e., low temperature (4±2 °C), room temperature (27±2 °C), and hot temperature (40±2 °C), for 12 w. The organoleptic properties and p^H of the gels were checked for every two weeks.

RESULTS AND DISCUSSION

Table 2: Drug content of efinaconazole nail gel formulations

Formulation code	Drug content (%)
F1	92.86±0.12
F2	97.38±0.18
F3	95.21±0.21
F4	95.11±0.81
F5	94.42±0.62
F6	96.80±0.41
F7	97.56±0.86
F8	94.85±0.62
F9	98.31±6.12
F10	97.45±4.11

Drug content analysis was done for all the ten formulations and the values were expressed as mean±SD. The drug content of all the formulations was found to be uniform.

Table 3: Data showing physicochemical attributes of Efinaconazole Nail gel formulations

Formulation code	Viscosity (cps)	P^H	Spreadability (cm)
F1	1012±10	7.00±0.2	2.5±0.36
F2	1023±10	6.45±0.1	2.1±0.44
F3	1065±20	6.26±0.2	2.0±0.56
F4	1202±10	5.83±0.3	1.5±0.24
F5	1002±20	7.90±0.2	3.0±0.33
F6	1212±10	7.81±0.1	2.8±0.43
F7	1311±10	7.50±0.4	2.6±0.55
F8	1015±10	7.83±0.2	3.4±0.36
F9	1232±20	7.70±0.1	3.2±0.24
F10	1246±20	7.60±0.5	3.0±0.44

Viscosity, p^H and spreadability were performed for all the ten formulations and it was observed that the spreadability decreased with an increase in polymer concentration. This is because the higher the polymer concentration, the thicker and more viscous the gel will be. A thicker and more viscous gel will be more difficult to spread. Viscosity has been seen to be increased as polymer concentration increases. This is because the polymer molecules become more entangled with each other as the concentration increases. This entanglement creates more friction between molecules, which makes it more difficult for them to flow. The pH of formulations was found to be in the range of 5.8 to 7.8.

Table 4: *In vitro* drug release study

Time (H)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	14.12±0.34	18.43±0.52	9.42±0.33	7.02±0.22	10.62±0.21	7.11±0.26	6.44±0.22	7.62±0.25	7.82±0.11	6.31±0.21
2	31.54±0.22	32.64±0.32	28.42±0.26	20.12±0.23	29.11±0.42	22.31±0.22	19.34±0.36	26.34±0.32	25.33±0.43	18.21±0.23
3	48.62±0.55	51.36±0.63	48.45±0.24	36.33±0.21	46.43±0.18	38.26±0.19	32.11±0.37	39.36±0.24	40.22±0.21	31.32±0.25
4	69.33±0.31	72.44±0.38	65.58±0.33	48.41±0.12	68.22±0.26	50.28±0.21	47.42±0.22	53.23±0.21	54.22±0.32	49.43±0.14
5	82.40±0.32	85.53±0.46	79.24±0.32	65.22±0.24	80.20±0.44	65.27±0.42	60.35±0.21	68.37±0.22	69.24±0.16	61.32±0.24
6	96.77±0.41	98.31±0.44	90.45±0.21	82.33±0.12	94.11±0.24	85.34±0.43	75.36±0.24	85.21±0.28	80.27±0.25	74.21±0.31

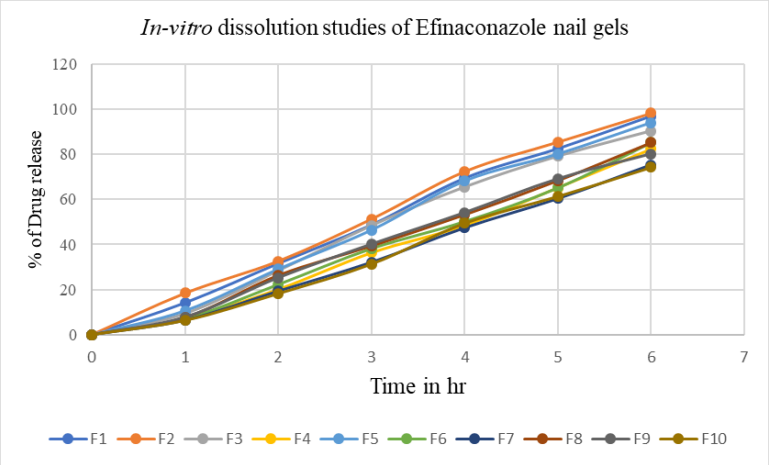

Fig. 1: *In vitro* drug release study

The drug release study was done for all the ten formulations using Franz's diffusion cell. The study was conducted for 6 h with an optimal interval of sampling. Results were shown in table 4 and fig. 1. *In vitro* release is 74 to 98% at the end of 6th h. Among all the ten formulations, F2 formulation exhibited 98.31±0.44% of drug release at the end of the study.

The formulated gels were tested for antifungal activity. The results are shown in fig. 2, 3 and table 4

Table 4: Evaluation of antifungal activity by agar well diffusion method

Samples	Zone of inhibition in mm	Fungal culture
Placebo	-	Candida albicans
Gel-(Carbopol-934)	10.6	

Fig. 2: Placebo nail gel formulation

Anti-fungal efficacy of the optimized nail gel formulation and placebo nail gel was performed by agar diffusion method and from the above table zone of inhibition of the placebo formulation was zero when compared to the optimised formulation F2 which showed 10.6 mm. However, a larger zone of inhibition indicates that the fungal isolate is more susceptible to antifungal agent.

Fig. 3: Antifungal activity of optimized formulation (F2) nail gel

Table 5: Stability studies of gel formulations

Formulation code	Appearance	Spreadability (cm)	Viscosity (cps)	pH
F2	Homogenous	2.14±0.42	1014±10	6.5±0.1

Stability studies for the optimized F2 formulation was performed. It has homogenous appearance and 2.14 cm spreadability and 1014 viscosity cps and have a p^{H} 6.5. All the properties are having ideal characteristics for good stability.

CONCLUSION

The purpose of the present investigation was to formulate and evaluate the efinaconazole nail gel for the treatment of onychomycosis. Various nail gel formulations (F1 to F10) were developed using a suitable polymer (Carbopol-934, Xanthan gum, CMC). Developed formulations of Efinaconazole were evaluated for the physiochemical parameters such as drug content, pH, viscosity, spreadability, extrudability, *in vitro* drug diffusion studies, and *in vitro* antifungal activity. Viscosity studies, PH studies, and *in vitro* drug diffusion studies of various formulations revealed that formulation F2 was ideal when compared to others. Stability studies of gel formulations carried out were satisfactory. Efinaconazole nail gel demonstrated antifungal efficiency against candida albicans. It can be concluded that the side effects of oral therapy of antifungal agents for onychomycosis can be avoided by using topical

efinaconazole nail gel formulation, which serves as a better tool for ungual drug delivery.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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