Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation and Evaluation of Lacquer of fluconazole for Transungual Drug Delivery System

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Cite this paper as: Vishal Verma, Manoj Bisht, Manoj Bhardwaj, (2025) Formulation and Evaluation of Lacquer of fluconazole for Transungual Drug Delivery System. *Journal of Neonatal Surgery*, 14 (32s), 7233-7241.

ABSTRACT

Transungal drug delivery system refers to the delivery of drugs through the nail plate (the hard, visible part of the nail) for therapeutic purposes. The study was based on the Formulation and Evaluation of Lacquer of fluconazole for Transungual Drug Delivery System. The fluconazole was purchased from the Dhamtec Pharma and Consultants, Navi Mumbai, India. The nail lacquer using fluconazole was formulated by simple mixing method. Characterization of nail lacquer was done through various parameters i.e., non-volatile content, drying time, smoothness, gloss, water resistance, viscosity, color, in-vitro transungual permeation studies and stability studies. Evaluation of antifungal activity of nail lacquers using disc diffusion method. In results, the color was found as transparent and homogenous in F1-F4 Nail Lacquers of fluconazole. It exhibited a maximum in-vitro transungual permeation in F3 as 95.7±0.6 %. The stability test was carried out for 1 month and there was no significant change observed in colour, non-volatile content, drying time, smoothness and water resistance. All the formulations of fluconazole lacquer exhibited significant anti-fungal activity. Zone inhibition was estimated as 11.2 mm, 13.8 mm, 19.4mm, 16.1 mm and 32.4 mm in F1, F2, F3, F4 and Fluconazole group. In conclusion, fluconazole lacquer (F1-F4) demonstrated a potential characterization parameter when estimated for color, non-volatile content, drying time, smoothness, water resistance and in-vitro transungual permeation studies. However, F3 exhibited a much significant data. The anti-fungal potential was also estimated highest in F3. Thus, it can be said that F3 is the optimized formulations.

Keywords: *Transungual Drug Delivery System, nail lacquer, fluconazole, -vitro transungual permeation studies.*

1. INTRODUCTION

The term "transungal drug delivery system" describes the therapeutic administration of medications via the nail plate, which is the hard, visible portion of the nail. This technique provides a special way to administer medication, which is especially helpful for treating conditions that affect the nail bed and adjacent tissues. A new and creative method for delivering drugs via the nail plate and into the underlying tissues is transungual drug delivery [1]. However, because of its non-invasiveness, ability to target the drug to the site of action where it is needed, ability to eliminate or remove systemic side effects and drug interactions, greater patient compliance, and potential for lower treatment costs, topical therapy is a profitable choice [2]. In the treatment of onychomycosis, which affects roughly 19% of the population, the significance of nail permeability to topical treatments has been recognized [3].

A bis-triazole antifungal medication, fluconazole has unique pharmacokinetic characteristics (metabolic stability, comparatively high water solubility) that support its therapeutic action. Only a small number of mycoses have been the subject of clinical experience, and as may be expected at this early stage of development, the best dosage and length of treatment for some significant mycoses are still unknown [4].

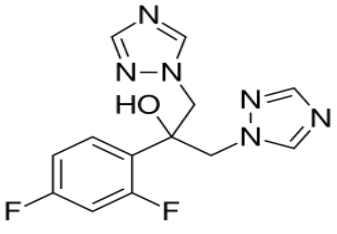

Fig 1. Structure of fluconazole

Mol. Formula: $C_{13}H_{12}F_2N_6O$

Mol. Mass: 306.277

The cytochrome P-450 enzyme 14-demethylase, which catalyzes the conversion of lanosterol to ergosterol, interacts with fluconazole. Since ergosterol is an essential component of the fungal cell membrane, fluconazole increases cellular permeability by blocking its synthesis [5].

2. MATERIALS AND METHODS

Experimental requirements

The fluconazole was purchased from the Dhamtec Pharma and Consultants, Navi Mumbai, India. Ethanol, distilled water and other excipients were procured from the college laboratory.

Preparation of nail lacquers of fluconazole

The nail lacquer was formulated by simple mixing method. Fluconazole was used 5% w/v was used in 50ml formulation. the concentration of Fluconazole in all formulation was kept constant. Required quantity of Eudragit RL-100 was added then weighed amount of ethyl cellulose was added, then to this mixture fluconazole, triacetin, and ethyl acetate was added and mixed until no lumps, the volume is made up to 50ml with ethanol [6].

Table 1. List of composition for preparation of nail lacquers of fluconazole [50ml]

Composition	F1	F2	F3	F4
Fluconazole (w/v)	5%	5%	5%	5%
Eudragit RL 100 (g)	0.5	1.0	1.5	2.0
Ethyl cellulose (g)	2	3	4	5
Triacetin (ml)	2.0	2.5	3.0	2.0
Ethyl acetate (ml)	16	14	12	10
Ethanol (ml)	q. s.	q. s.	q. s.	q. s.

Characterizations of Nail Lacquers formulations

Non-volatile content

A glass petri dish with a diameter of roughly 8 cm was used to collect the material. Using tared wire, the samples were distributed uniformly. After an hour at 105ºC in the oven, the petri dish was taken out, allowed to cool, and then weighed. After drying, the sample's weight difference was calculated [7][8][9].

Drying time

A film of sample was applied on a glass petri dish with the help of brush. The time to form a dry-to-touch film was noted using a stopwatch [10].

Smoothness

The smoothness was determined by pouring the sample of nail lacquer approximately 1.5 inches on a glass plate and made to raise vertically [11].

Gloss

Gloss of the film was visually seen, within the specifications [11].

Water resistance

This is a measure of the film's resistance to water permeability. Three glass plates should be covered with a thin layer, allowed to dry, and then weighed. After that, the plates must be submerged for 24 hours at 37ºC in a water bath filled with distilled water. After removing and drying the panels by sandwiching the plate between absorbent sheets, the panels should be

weighed again. The weight increase is computed. Water resistance decreases as weight increases [12].

Viscosity

The Brookfield viscometer13 was used to measure the viscosity of nail lacquer. In order to reduce solvent evaporation, samples are collected in a closed jar. Shake well at 25 °C, set a timer, and then put the spindle into the sample until it reaches the scored line while the motor is spinning at 60 RPM. After ten minutes, read the instrument again, then change the speed control to six RPM and read the instrument once more after ten more minutes. The dial reading should be multiplied by 60 rpm X 20 and 6 rpm X 200 to convert it to centipoises. Cream nail viscosity-thixotropy should be between 375 and 500 cps at 60 rpm and 25 °C [13].

Colour

Colour comparing with master color standards by applying on thumbnails, holding them side by side, moving the thumb with the standard first on the right and then on left. Artificial acrylic nails have been utilized as well for matching comparative shades [14].

In-vitro transungual permeation studies

A modified Franz diffusion cell was used for the in-vitro diffusion testing. The diffusion cell was a 10 cm tall glass cylinder with a 3.7-centimeter-outside diameter and a 3.1-centimeter-inside diameter. To create a diffusion cell, a sheep mucosa was attached to the cylinder at one end. The active diffusion area was 0.25 cm. The receiver compartment was stirred at 600 rpm with a 3 mm magnetic stir bar. Intermittent samples of 2 ml were drawn from the receiver compartment at 2 h intervals for 36 h and the amount of fluconazole transported was measured. The receptor compartment was in touch with the entire cell surface, and it was kept at 37 degrees Celsius while being magnetically agitated. To keep the sink condition constant, 10 ml of samples from the receptor compartment were removed and replaced with the same volume.

Stability Studies

According to ICH guidelines at 40 ± 2 oC/75 ± 5% RH sample was stored in stability chamber for one month. The sample was evaluated for non-volatile content, drying time, smoothness and water resistance [15].

Evaluation of antifungal activity of nail lacquers

Disc diffusion method16 was used to screen for antifungal activity. The P. notatum microbiological culture (72-hour culture) was added to the Sabouraud's dextrose agar plates. Test tubes were used to prepare cultures of Sabouraud Dextrose Broth. To create grass cultures, the surface of Sabouraud's Dextrose Agar plates was swabbed with a sterile cotton swab. Wells were aseptically excavated using a sterile cork borer five minutes after the agar surface had dried. Four different nail lacquer formulations were applied to the wells. For comparison, a standard fluconazole CD was utilized. For 24 to 48 hours, the plates were incubated at 28 oC. A scale to the closest millimeter was used to quantify the widths of the zones of inhibition [16].

3. RESULTS AND DISCUSSION

Characterizations of Nail Lacquers formulations

Color

The color was found as transparent and homogenous in F1-F4 Nail Lacquers of fluconazole.

Table 2. Color of fluconazole lacquer

Formulation	Color
F1	Transparent; homogenous
F2	Transparent; homogenous
F3	Transparent; homogenous
F4	Transparent; homogenous

Non-volatile content

The highest non-volatile content was estimated in F3 as 37.1±0.27 %.

Table 3. Non-volatile content of fluconazole lacquer

Formulation	Non-volatile content (%)
F1	24.2±0.31
F2	26.4±0.21
F3	37.1±0.27
F4	31.6±0.18

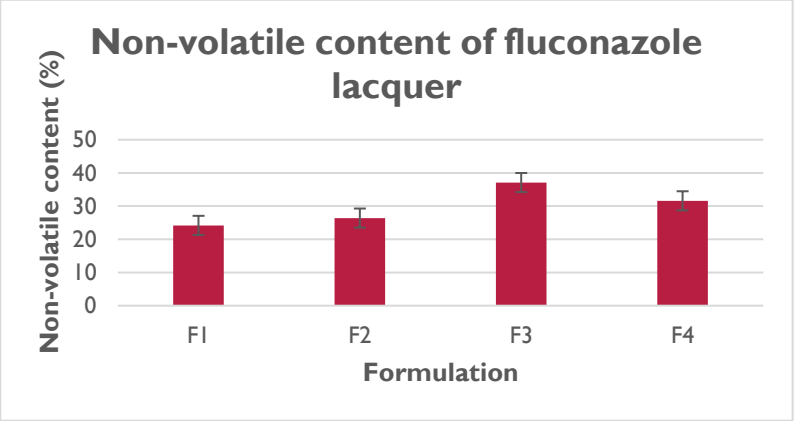

Fig 2. Non-volatile content of fluconazole lacquer

Drying time

In fluconazole lacquer, the drying time was estimated in the range of 63.5±0.19 sec to 72.2±0.34 sec.

Table 4. Drying time of fluconazole lacquer

Formulation	Drying time (Sec)
F1	69.1±0.12
F2	72.2±0.34
F3	63.5±0.19
F4	66.2±0.39

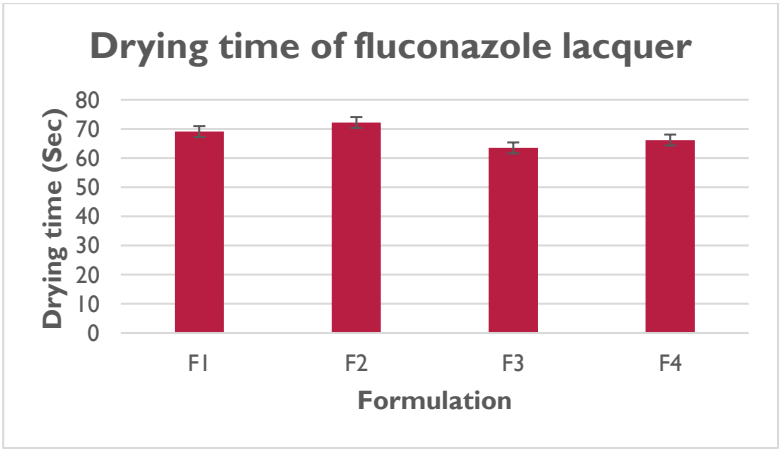

Fig 3. Drying time of fluconazole lacquer

Smoothness

4. TABLE 5. SMOOTHNESS OF FLUCONAZOLE LACQUER

Formulation	Smoothness
F1	Significantly smooth
F2	Significantly smooth
F3	Very smooth
F4	Significantly smooth

Water resistance

Water resistance was estimated highest as 82 mg in F3 formulation of fluconazole lacquer.

Table 6. Water resistance of fluconazole lacquer

Formulation	Water resistance (mg)
F1	57
F2	62
F3	82
F4	74

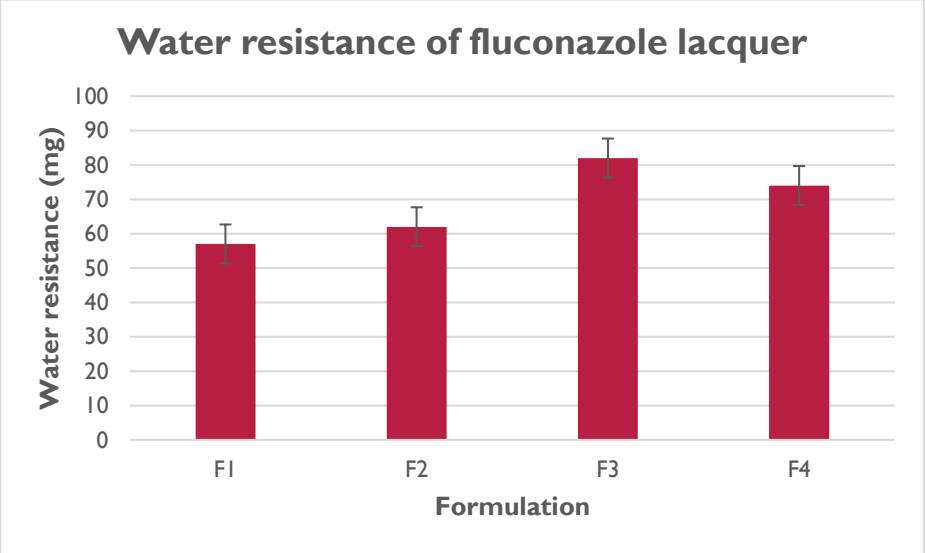

Fig 4. Water resistance of fluconazole lacquer

Viscosity

It exhibited a significant viscosity to adhere on the nails. It ranges from 263.3±0.10 cps to 315.4±0.25 cps.

Table 7. Viscosity (cps) of fluconazole lacquer

Formulation	Viscosity (cps)
F1	263.3±0.10
F2	286.2±0.18

F3	315.4±0.25
F4	304.1±0.13

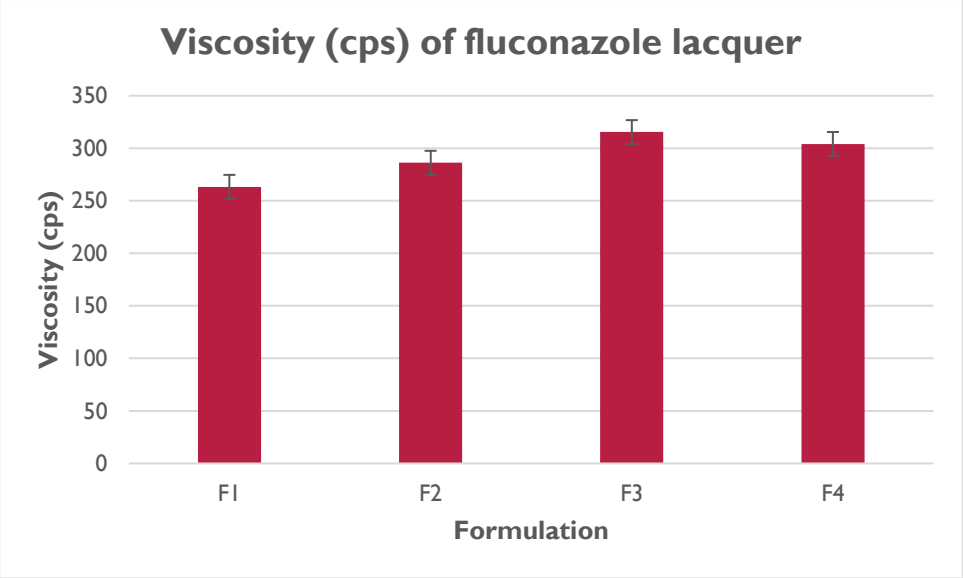

Fig 5. Viscosity (cps) of fluconazole lacquer

Gloss

All the formulations were found significant glossy in nature.

Table 8. Gloss nature of fluconazole lacquer

Formulation	Gloss
F1	Significant glossy
F2	Significant glossy
F3	Very glossy
F4	Significant glossy

In-vitro transungual permeation studies

It exhibited a maximum in-vitro transungual permeation in F3 as 95.7±0.6 %.

Table 9. In-vitro transungual permeation studies of fluconazole lacquer

Time (hr)	% Drug release± S. D. F1	F2	F3	F4
1	14.4±0.4	17.2±0.2	12.3±0.6	16.4±0.1
2	26.2±0.4	29.3±0.1	37.3±0.5	32.5±0.1
4	41.5±0.2	36.4±0.2	41.5±0.6	39.2±0.4

6	55.4±0.4	54.3±0.2	59.2±0.6	51.4±0.3
8	67.7±0.4	63.2±0.4	69.2±0.6	62.4±0.1
10	79.2±0.4	76.2±0.9	82.4±0.8	74.3±0.7
12	91.6±0.2	87.4±0.5	95.7±0.6	85.4±0.2

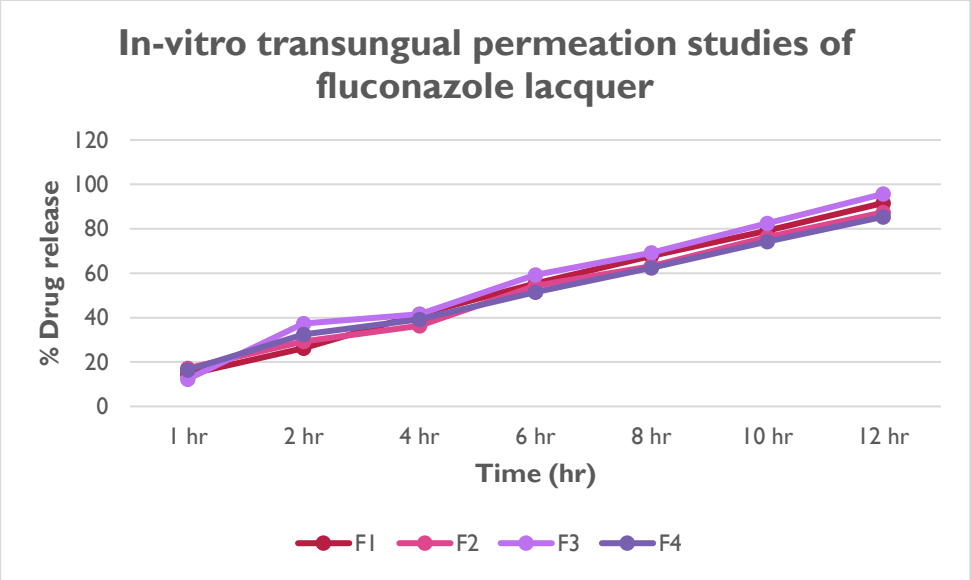

Fig 6. In-vitro transungual permeation studies of fluconazole lacquer

Stability Studies

The stability test was carried out for 1 month and there was no significant change observed in colour, non-volatile content, drying time, smoothness and water resistance.

Evaluation of anti-fungal activity of nail lacquers

All the formulations of fluconazole lacquer exhibited significant anti-fungal activity. Zone inhibition was estimated as 11.2 mm, 13.8 mm, 19.4mm, 16.1 mm and 32.4 mm in F1, F2, F3, F4 and Fluconazole group.

Table 10. Anti-fungal activity of fluconazole lacquer

Formulation	**Zone of inhibition (mm) against *P. notatum***
F1	11.2
F2	13.8
F3	19.4
F4	16.1
Fluconazole	32.4

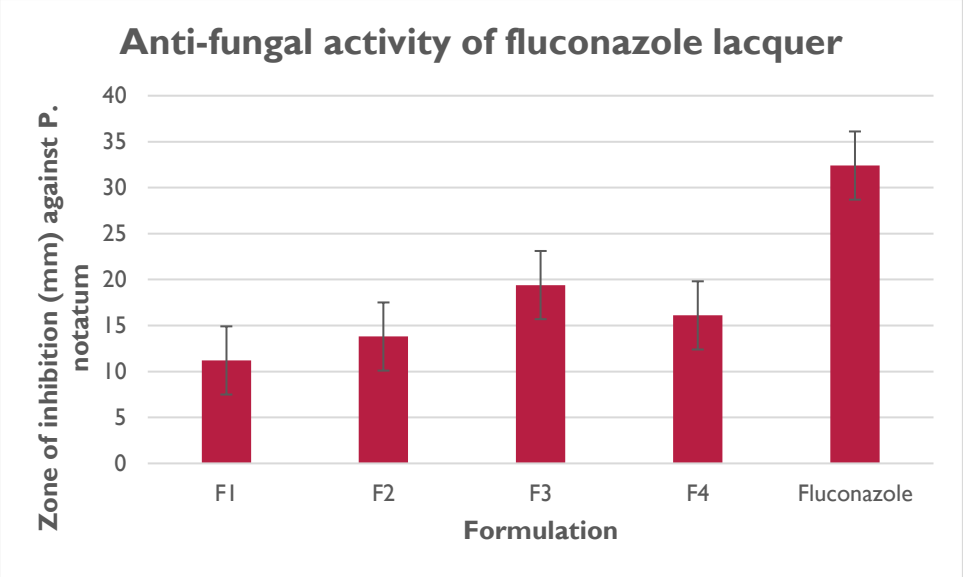

Fig 7. Anti-fungal activity of fluconazole lacquer

Onychomycosis and nail psoriasis, which comprise the majority of nail disorders and affect 2–13 and 1-3 percent of the general population, respectively, are particularly well-suited for topical medication administration. Topical treatment would eliminate the side effects and drug interactions associated with systemic antifungal medications as well as the discomfort associated with injecting antipsoriatic medications into the afflicted nail folds. However, because of the nail plate's extremely poor permeability, topical therapy is very difficult to achieve. The goal of the current work is to create a medicated nail patch employing the hydrophilic polymers HPMCK4M and EC. The preferred medication for treating onychomycosis is clotrimazole because of its effective antifungal action against T. mentagrophytes, the causal organism. A total of five Clotrimazole-medicated nail patches were made and assessed for a number of factors, including... Diffusion study in vitro: Table 3 displays the in vitro drug release results from various formulations. When compared to other formulations, such as F1, F2, F4, and F5, the developed formulation F3 exhibits a better release profile. Good physicochemical characteristics, such as thickness, weight variation, drug content, flatness, folding durability, moisture content, and moisture uptake, were also demonstrated by all formulations. According to the invitro release data, the types and concentrations of polymers used in the patch formulation have an impact on drug release. Increasing the polymer concentration also increases the release of the medication. Thioglycolic acid, a penetration enhancer, was tested for its impact on drug permeability in vitro [17].

Investigating medicated antifungal nail lacquer for onychomycosis was the aim of the study. A dense network of keratin fibers makes up nails, which function as a hydrogel membrane and a barrier for many medications. However, it has been discovered that a variety of bacteria impact the nail plate, leading to nail disorders. The nail condition is far more typically associated with dermatophytes. Onychomycosis, psoriasis, leuconychia, and other nail illnesses can be treated with various formulations, including creams, lotions, patches, and solutions. However, because of some limitations, such as inability to function well after application, potential for wiping or washing off, and decreased medication retention at the site, the formulations are relatively difficult to manage. The general idea behind medicated nail lacquers is that they will create a film on the application surface, from which the medication is released over time at a regulated rate. Therefore, we can conclude that nail lacquers are the greatest, most affordable, and should have higher patient compliance than other formulations or more recent methods used to improve drug transport across the nail plate.

5. CONCLUSION

The goal of the current study was to use several polymers to create and assess an ungula drug delivery system that contains fluconazole. It was discovered that this medication delivery method had strong antifungal properties. It was discovered that this nail lacquer had no negative effects. Physical evaluation of the created nail lacquers revealed good results within standard specifications. According to stability investigations, the created formulations' evaluation parameters remained constant. Comparing all nail lacquer formulations to the common antifungal drug fluconazole, the antifungal activity revealed notable zones of inhibition.

In conclusion, fluconazole lacquer (F1-F4) demonstrated a potential characterization parameter when estimated for color, non-volatile content, drying time, smoothness, water resistance and in-vitro transungual permeation studies. However, F3 exhibited a much significant data. The anti-fungal potential was also estimated highest in F3. Thus, it can be said that F3 is the optimized formulations.

CONFLICT OF INTEREST

None.

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