FORMULATIONS AND EVALUATION OF TRANSUNGUAL DRUG DELIVARY SYSTEM OF MICONAZOLE NITRATE OF AN ANTI-FUNGAL ACTIVITY

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ABSTRACT

A fungal infection of the nail, onychomycosis is also referred to as dermatophytid onychomycosis or tinea unicum. The pathogens that cause onychomycosis are nondermatophyticmolds, dermatophytes, and Candida. This effort has created a medicated antifungal nail lacquer using miconazole nitrate. The study's goal was to cut down on the frequency of administration by providing a sustained release of miconazole nitrate over a 48-hour period. This was anticipated to increase both patient compliance and clinical efficacy. Through straightforward mixing, the nail lacquer formulation was created, and its non-volatile content, gloss, smoothness of flow, drug diffusion tests, drug content estimation, and anti-microbial research were all examined.

The nail lacquer made with 2% Miconazole nitrate, 6% Nitrocellulose, 1% Ethyl cellulose, 15% Acetone, 10% Iso Propyl Alcohol, 10% Di Butyl Palathee, and 5% Ethyl Acetate showed the best non-volatile content, drug release, drug content estimation, and zone of inhibition out of all the formulations. A complete release of 98.12% was noted, and the medication release could be prolonged for up to 48 hours. Drug and excipient compatibility was demonstrated by FTIR tests. Following ICH recommendations, an accelerated stability investigation of the chosen optimized formulation, F4, was conducted for one month at 40±20C. The results showed no discernible change from the baseline features. These systems are thought to be simple and safe to develop and use. Thus, it is possible that antifungal nail lacquer is one of the innovative dosage forms that have the potential to completely transform the pharmaceutical and medical industries.

KEYWORDS: Lacquer, Nail Plate, Onychomycosis, Miconazole nitrate, dibutyl phthalate, Nitrocellulose.

INTRODUCTION

Benefits such as non-invasiveness, medication targeting to the site of action, decreased systemic side effects and drug interactions, and improved patient compliance make transungual delivery of active pharmaceutical components appealing.Transungual therapy of the nail plate is limited by the low penetration of the drug and the systemic side effects of oral Miconazole Nitrate therapy. Several keratolytic drugs have been found to be necessary for improving nail permeability in the treatment of onychomycosis. [1]

Transungual medication administration primarily aims to modify the structure of the nail plate. Enhancing nail permeability can be done in three ways. To improve nail permeability, physical methods include photodynamic therapy, electroporation, iontophoresis, acid etching, hydration and occlusion, and phonophoresis. hydrogen peroxides, urea, sulfites, mercaptans, keratolytic agents, and keratinolytic enzymes are examples of chemicals that increase chemical penetration. Enhancing nail permeability involves mechanical methods such as nail abrasion and avulsion for medication penetration. In [2] Medicated nail lacquers are the most effective way to obtain maximum antifungal effectiveness.[3]
Tinea ungums, another name for onychomycosis, is a persistent fungal illness that affects the nail plate and nail bed. [3, 4] Onychomycosis can be caused by a variety of fungi, including Fusarium and dermatophytes. Males are more likely than females to experience it, while older adults are more impacted. [5,6]
A synthetic allylamine antifungal medication is miconazole nitrate. It is used to treat athlete's foot, jock itch, ringworm, fungal nail infections, and pityriasis versicolor. Additionally, it works well against skin yeast infections brought on by Malassezia furfur and Candida species. It is a very lipophilic substance that builds up in fatty tissues, skin, and nails. Only 40% of oral terbinafine is accessible because of first-pass metabolism, despite its >70% absorption rate. The maximal concentration of the medication is reached in two hours, and its maximum plasma drug concentration is 1µg/mL with an AUC of 4.56µg h/mL. The majority of drugs are removed in urine (80%), with the remainder being excreted in feces. The commercially available preparations, such as creams and ointments, include 1% Miconazole Nitrate, although they are ineffective in treating nail infections.

MATERIALS AND METHODS

Materials

Miconazole Nitrate was procured from (yarrow chemicals, Mumbai), Ethyl cellulose procured from (Kemphasol chemicals, Mumbai), Nitro cellulose procured from (Kemphasol chemicals, Mumbai), Acetone procured from (Chirag organic chemical, Mumbai), Iso propyl alcohol procedurefrom(SD lab

Chemicals, Mumbai), Dibutyl phthalate procured (S D Lab. Chemicals, Mumbai), Ethyl acetate procured (Rex international chemicals, Mumbai), curcumin longa procedure from (natural sources), Guava procured from (natural sources).

The extraction procedure of curcumin:

Step 1:

10gmofpowder+100mlpetroleum

ether stir for 5ml

Kept on magnetic stirrer for 15minutes.

Filtered and collect the residue and allow to dry.

Step 2:

Dry residue +100ml chloroform stir for 5minutes.Kept on magnetic stirrer for 15minutesFiltered and collect the residue and allow to dry

Step 3:

Take the residue and add 100ml of methanol stir for 5minutes.Kept on magnetic stirrer for 15minutesfiltered and collect the residue.

The extraction procedure of guava:

1) Collect the leaves of guava plant were shade dried for 10-15days in room temperature After completion of drying, we have to crush the leaves and separate the leaves from the branches
2) After separation make into the powder by usage of blenders**.** later weight that powder Weight 45grams of powder were subjected for extraction 225ml of methanol as a extract by shaking the mixture for about one day with manually at room temperature
3) Subsequently, samples were filtered on Whitman filter paper. Then the filter was collected. Finally, extract was collected in sterile labeledcontainers. Then extract was dried for 2-3 days at room temperature. Collect and storied in tight container.

Preparation of Nail lacquer:

The mixture takes Nitrocellulose or Ethyl cellulose (10gms) and measure the 75% Acetone (100ml) which is ratio of 10:5 and mix both until the full film form will dissolve and appears the clear solution.

To above clear solution measure require quantity of Dibutyl phthalate(5ml) after that add required quantity of ethyl acetate (5ml) mix well in only one direction.

While mixing add the 5% of Miconazole nitrate (500mg) and mix thoroughly until it appears like clear solution which like viscose at last made up to the volume up to 100ml with solvents and later finally add curcumin longa or guava which is act like colouring agents. The prepared nail lacquer was transferred to a narrow mouthed, plastic screw capped glass bottle.

Table 1: Formulation of Miconazole Nitrate nail lacquer.

Ingredients (%)	F1	F2	F3	F4
Miconazole nitrate	500mg	500mg	500mg	500mg
Nitrocellulose	…..	….	10g	10g
Ethylcellulose	10g	10g	….	….
Acetone	100ml	100ml	….	….
Isopropyl alcohol	….	….	100ml	100ml
Dibutyl phthalate	5ml	5ml	5ml	5ml
Ethyl acetate	5ml	5ml	5ml	5ml

PREFORMULATIONS STUDIES:

A) Solubility studies:

In triplicate, 10 milliliters of distilled water, ethanol, and acetone were used to create saturated solubility of miconazole nitrate in a 25 milliliter volumetric flask. Care was taken to ensure that the medication remained in the medium in excess.For 48 hours, the flasks were shaken using a mechanical shaker. Samples were taken on the 24th and 48th hours. After being drawn (1 ml after filtering), the sample was diluted with the proper medium and examined at 223 nm using a UV spectrophotometer.

B) Melting point determination:

The melting point of the medicine was ascertained by placing a little amount of the medication in a capillary tube that was sealed at one end. The tube was then placed in Thief's melting point apparatus, and the average of the three readings was recorded.

C) Determination of λmax:

In order to make 100 milliliters, 100 milligrams of pure miconazole nitrate were placed in a volumetric flask and dissolved in a little amount of phosphate buffer with a pH of 7.4.Of the aforementioned solutions, 1 ml was added to 100 ml. In a double beam UV-visible spectrophotometer, the aforementioned solutions were tested for maximum absorbance

between 400 and 200 nm against phosphate buffer PH 7.4 using blank duplicate readings, and the average was computed.

D) Nonvolatile content:

A petri plate dish containing 10 milliliters of the sample was used, and beginning weights were noted. After one hour of baking at 105 degrees Celsius, the petri dish was taken out, allowed to cool, and then weighed. It was noted that the weights were different. Three copies of the readings were averaged.

EVALUATION PARAMETERS:

A) Drying time:

A petri dish was covered with a sample film using a brush. With the use of a stopwatch, the amount of time needed to develop a dry-to-touch film was measured.

B) Smoothness to flow:

To check for film smoothness, the sample was poured into a glass plate from a height of 1.5 inches, spread out on the plate, and allowed to rise vertically.

C) Gloss:

Applying a sample of nail lacquer on the nail allowed for a visual comparison of the gloss with commercially available cosmetic nail lacquer.

D) Viscosity:

The Brookfield Viscometer, model LVF, was used to measure viscosity at room temperature with spindle number three spinning at 20 rpm.

E) Anti-fungal activity:

Miconazole nitrate-containing nail lacquer's antifungal properties were tested using the cup plate method. Candida albicans was the fungus culture utilized for this activity.

Procedure:

1.Sterilized agar medium was poured in Petri plates in appropriate level. Then this plate was freeze to solidify.Later take the bread which forms the fungus agent take the fungus growth and make a hole on agar solidify medium on the holes place the breads peace's containing fungal agents a keep into the incubator at 37 degrees C for 2-3 days and label the plates.

2.Later check the place the fungus will growth will appear on the areas of fungal growth pour the 4 formulations of nail lacquer in each plate same again keep in incubator for 2-3 days.After again prepare the agar medium later ware the bread peace's in medium and mix thoroughly and pour in Petri plates equal amount in each plate and let it solidify for 10min.Finally make a hole on solidify agar medium with test tube and pour our 4 formulations of nail lacquer in each petri plates and keep in incubator at 37 degrees C for 2-3 days.

F) In-vitro diffusion studies:

The lab-fabricated classical standard cylindrical tube was used to study the in vitro diffusion of medications from various dermatological preparations. A glass tube with an internal diameter of 15 mm and a height of 100 mm was used as a sample modification of the cell.
The diffusion cell membrane, which served as a donor compartment, was applied with 1 gram of formulation and fastened firmly to one end of the tube while leaving the other end exposed to the environment. For two hours, the system was kept at 37±0.5°C. The cell was inverted and submerged slightly in 250 ml of breaker that contained 100 ml of phosphate buffer pH 7.4 as a receptor phase. Over the course of two hours, the sample was taken out every ten minutes.Using a magnetic bead hot plate magnetic stirrer, the medium was agitated.

RESULTS AND DISCUSSIONS

A) Solubility studies:

Ethanol-0.78, Water-0.03, and Acetone-0.36 are the outcomes of solubility tests conducted on pure miconazole nitrate. According to the findings, Miconazole nitrate's solubility profile showed that it was soluble in ethanol and acetone but insoluble in water.

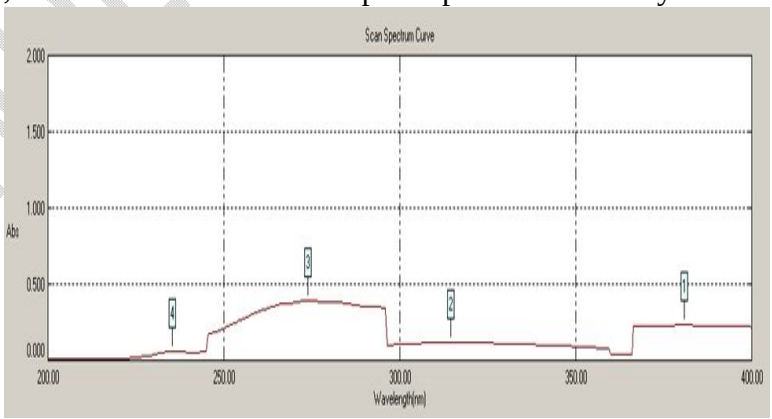
B) Melting point determination:

The melting point was found to be 161 °C ± 0.577 and as per the IP 2007 melting point of Miconazole nitrate was within the range of 160-185 °C

Trial 1-184□, **Trial 2**-185□, **Trail 3**-180□

Scanning of drug:

A UV visible spectrophotometer was used to scan a pure Miconazole nitrate sample between 200 and 400 nm using phosphate buffer solution (PBS) with a pH of 7.4. Miconazole nitrate's highest peak was found at 223 nm (see below figure), hence this wavelength was chosen for the λmax of Miconazole nitrate, which was used for other spectrophotometric analyses throughout the study.



UV spectrum of Miconazole nitrate in phosphate buffer solution of pH 7.4

Below table is wave length and absorption

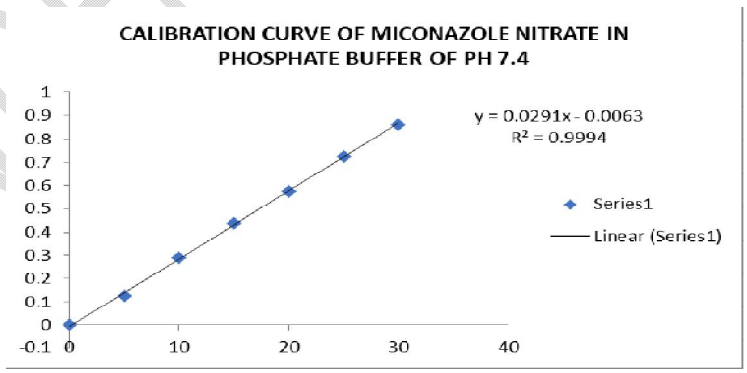
Wave length	Absorption
381.00	0.228
314.50	0.112
274.00	0.391
235.50	0.058

C) Determination of λmax:

Miconazole nitrate standard solutions at varying concentrations were made with PBS pH 7.4, and the absorption of each solution was measured at 223 nm. Plotting drug concentration against absorbance is shown in the table below.

Standard curve data for Miconazole nitrate in phosphate buffer of pH 7.4

Concentrations Mg/ml	Absorbance at 232nm
0	0
5	0.124
10	0.289
15	0.438
20	0.576
25	0.726
30	0.863



D) Non-volatile content

The non-volatile content of all formulations has been reported.

F1-33±0.38, F2-41±0.81, F3-39±0.40, F4-37±0.81.

E) Drying time:

The drying time (sec) of all formulations has been reported.F1-55, F 2-58, F3-127, F4-60.

F) Smoothness to flow and Gloss:

Both of these parameters were deemed satisfactory, as seen in the figure below. A homogeneous, smooth layer was produced when the nail lacquer was put into the glass plate. The applied lacquer's sheen was comparable to a cosmetic sample that was sold, demonstrating its cosmetic acceptability.

G) Viscosity:

A clear and shiny product was detected between 140 and 160 centipoises, while the sample's viscosity ranged from 100 to 220 centipoises. This range of viscosity also offered good flow and adhesion properties. Anything beyond this range of viscosity results in clouding and a reduction in shine, which is unacceptable from a cosmetic standpoint?F1-100, F2-111, F3-122, F4-133

Anti-fungal activity:

Antifungal activity showed result for formulated itraconazole nail lacquer against fungal strain of Candida albicans.

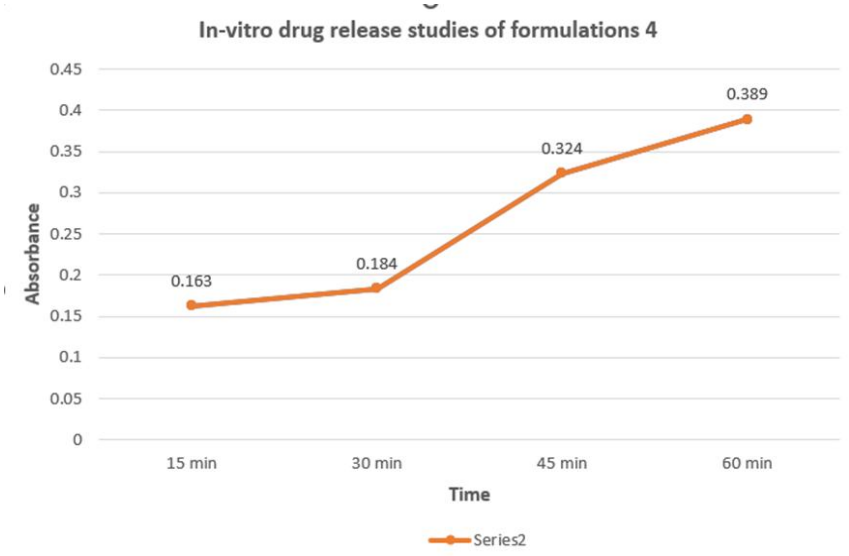
Formulation 4

In-vitro diffusion studies:

- In-vitro drug diffusion studies of formulation 4 was shown in below table

SI.NO	TIME	ABSORBANCE
1	15 min	0.163
2	30 min	0.184
3	45 min	0.324
4	60 min	0.389

From the above values of formulation 4 the graph will be plot it shown in below graph



CONCLUSION:

- The current study set out to develop and assess a transungual medication delivery system for the treatment of onychomycosis: Miconazole nitrate nail lacquer.
- A formulation containing permeation enhancers di butyl phthalate was created using miconazole nitrate as the model medication.Drying duration, non-volatile drug content, drug diffusion, and antifungal research were the purposes of these lacquers.
- FTIR studies confirmed drug-excipient compatibility, film formulations, drying time, smooth flow, and volatile content. Formulations were sensitive to Candida albicans, indicating compatibility.
- The formulations were stable at 40 degrees centigrade for a few days, indicating a good in vitro in vivo correlation from the transungual permeation study.
- The findings of the in vitro investigations reveal that formulation F4 exhibited a full drug release that persisted for 48 hours. 10% nitrocellulose was used as a film-forming agent and dibutyl phthalate was used as a resin in the F4 formulation. This suggests that the combination of the permeation enhancer leads to both a full and prolonged release of the medication and an enhanced rate of permeation.
- The F4 formulation's non-volatile content was determined to be 37±0.81. When all of the volatile substance evaporated, the appropriate amount of non-volatile matter was seen.
- F4 formulation showed rapid drying rate.
- F4 formulations were found to have a viscosity of 133, making them shiny and transparent.

- ❖ The adhesive strength of F4 formulations compared with marketed sample and its posses' adequate adhesive strength on applied nail surface.

The formulation of nail lacquer that contains miconazole nitrate is a patient-friendly and efficient dosage form for treating fungal nail infections, it may be inferred. For the transungual medication administration of an antifungal in the treatment of onychomycosis, medicated nail lacquers proven to be a more effective instrument as a drug delivery mechanism, according to the research mentioned above. Medicated nail lacquers are not only useful for treating nail infections, but they may also be used to easily beautify nails. This increases patient compliance and acceptability.

Future prospectives

Further clinical and pharmacokinetic research is necessary to examine the viability of this system for usage in people, even though this work has demonstrated that medicated nail lacquers can serve as a helpful tool for the ungual drug administration of an antifungal in the treatment of onychomycosis.

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