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Formulation and Evaluation of Nail Lacquer of Clotrimazole for Treatment of Onychomycosis

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ABSTRACT

Nails are the hard and durable epidermal. The nail plate is responsible for the penetration of the drug across it. There is the number of formulations with antifungal agents viz. gels, creams, and oral antifungal for the treatment of transungual infections. Among these entire nail lacquers is a new concept in treating nail infections. These nail lacquers are effective as monotherapy in the treatment of superficial, distal, and subungual diseases. The medicated lacquer preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of antifungal drugs. It is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of the nail itself in conditions like onychomycosis and nail psoriasis. In this research paper we used Clotrimazole drug for formulation of nail lacquer by using simple method of preparation. We prepare five batches named as C1, C2, C3, C4 and C5 by using different quantity of some ingredients. The factors, which affect the drug uptake and permeation of drugs through the nail plate, are solute molecular size, hydrophilicity/hydrophobicity, charge, and the nature of the vehicle. The film formed after application of nail lacquer on the nail surface acts as a drug depot that permits optimized and sustained diffusion across the nail leading to enhanced efficacy. After evaluation of all batches by different parameters we found that batch C5 shows results in appropriate range. As oral therapy is limited by its systemic toxicity, topical therapy especially the medicated nail lacquers can be used as the most effective tool for the transungual drug delivery system especially in the treatment of onychomycosis difficulty of penetration is overcome by many strategies. So the nail lacquers seem to be the vehicle of the future when topical products for the nail are desired.

INTRODUCTION

The nail is a horny structure. The nail plate is responsible for the penetration of drugs across it. As it is hard enough the penetration becomes tricky, and an only a small quantity of topical drug penetrates across it. Thus the effective therapeutic concentration is not achieved. The nail plate may appear irregular as a result of decreased glow. It's the participation of nail bed, less blood supply, physical or chemical features of the nail bed. As a result, different diseases occurs[1]. These diseases can be treated by achieving the desired therapeutic concentration of drug by nail drug delivery system. The human nail plate consists of three layers; the dorsal and intermediate layer derived from the matrix and the ventral layer from the nail bed. The intermediate layer is three - quarter of the whole nail thickness and consists of the soft keratin. The upper layer, dorsal, is only few cell layer thick but consist of hard keratin, with relatively high sulfur content, mainly in the form of amino acids cysteine, which constitutes 94 % by weight of nail. The upper layer of the nail mainly diffuses through the nail plate. The ventral layer consists of soft hyponychial in which many pathological changes occur. Thus, in the treatment of these nail diseases; an effective drug concentration in the ventral nail plate would be of huge importance.

Transungual Drug Delivery System:

"Trans" means "through" and "Unguis" means "Nail", it is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of the nail itself in conditions like onychomycosis and nail psoriasis.

Anatomy of Nail:

A. Parts of the nail:

The matrix (sometimes called the matrix unguis, nail matrix, keratogenous membrane, or onychostroma) is the tissue that the nail protects, the part of the nail bed that rests beneath the nail and contains nerves, lymph and blood vessels[2]. The matrix is responsible for producing cells that become the nail plate. The width and thickness of the nail plate are determined by the size, length, and thickness of the matrix. Whereas the shape of the fingertip itself shows if the nail plate is flat, arched, or hooked. The matrix will continue to produce as long as it receives nutrition and remains in a healthy condition. As new nail plate cells are made, they push older nail plate cells onward and in this way, older cells turn into compressed, flat, and

translucent. This makes the capillaries in the nail bed below visible, resulting in a pink color[3]. The lunula (or simply "the moon") is the visible part of the matrix, the whitish crescent-shaped base of the visible nail. The lunula can be seen as the largest in the thumb and often is not present in the little finger.

The nail bed is the skin beneath the nail plate like all skin. It is made of two types of tissues: the deeper dermis, the living tissue fixed to the bone which includes capillaries and glands, and the superficial epidermis, the layer just beneath the nail plate which moves forward with the plate. The epidermis is attached to the dermis by tiny longitudinal "grooves known as matrix crests. During old age, the plate slim and these grooves are more visible[4]. The nail sinus is where the nail root is inserted. The nail root is the part of the nail situated in the nail sinus, i.e. the base of the nail under beneath the skin. It originates from the actively rising tissue below, the matrix. The nail plate is the actual nail, made of translucent keratin protein. Several layers of dead, compacted cells cause the nail to be strong but flexible.

Its transversal shape is determined by the form of the underlying bone. In ordinary usage, the word nail often refers to this part only. The free margin or distal edge is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail. The hyponychium is the epithelium located beneath the nail plate at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed. The onychodermal band is the seal between the nail plate and the hyponychium. It is found just under the free edge in that portion of the nail where the nail bed ends and can be recognized by its glassy, grayish color (in fair-skinned people). It is not detectable in some individuals while it is highly prominent on others. The eponychium is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. Frequently and erroneously called the "proximal fold" or"cuticle", the eponychium is the end of the proximal fold that folds back upon itself to shed the epidermal layer of skin onto the newly formed nail plate. This layer of nonliving, almost invisible skin is the cuticle that "rides out" on the surface of the nail plate.

B. Diseases of Nail:

The nail plate may appear abnormal as a result of a congenital defect, disease of the skin with the involvement of the nail bed, systematic disease, reduction of blood supply, local trauma, tumors of the nail fold or nail bed, infection of the nail fold and infection of the nail plate.

a. **Leuconychia:** White spots or lines appears on one or more nails and grow out spontaneously.

b. **Onychomycosis:** Yellow-brown patches close to the lateral border of the nail. Beneath the masses of soft horny debris accumulate and the nail plate gradually becomes thickened, broken, and irregularly distorted. One or many nails may be affected and there may be associated infection of the skin. Most of the infections are caused by Trichophyton rubrum, T. interdigital. Onychomycosis[5, 6] accounts for one-third of integumentary fungal infections and one half of all nail disease. Tinea unguium is more than a cosmetic problem, Even though persons with this infection are often embarrassed about their nail disfigurement. As it can sometimes limit mobility, onychomycosis may indirectly reduce peripheral circulation, thus worsening conditions such as venous stasis and diabetic foot ulcers. Fungal infections of the nails can also spread to other areas of the body and perhaps to other persons[7, 8].

c. **Tinea Unguis**: Also known as ringworm of the nails. It is characterized by nail thickening, deformity, and eventually results in nail plate loss.

d. **Onychatrophia:** It is wasting away from the nail plate which causes it to lose its luster, become smaller, and sometimes shed entirely. Injury or disease may account for this irregularity.

e. **Onychogryposis:** Claw-type nails are characterized by a thickened nail plate and are often the result of trauma. This type of nail plate will curve inward, pinching the nail bed, and sometimes requires surgical intervention to relieve the pain.

f. **Onychorrhexis:** Brittle Nails often split vertically, the peel has vertical ridges. This irregularity can be the result of heredity, the use of strong solvents in the workplace or the home, including household cleaning solutions. Though oil or paraffin treatments will rehydrate the nail plate, one may wish to discuss with a physician to rule out disease.

g. **Onychauxis:** It is evidenced by the over thickening of the nail plate and maybe the result of internal disorders.

h. **Leuconychia:** White lines or spots in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma. This condition may be genetic and treatment is required as the spots will grow out with the nail plate.

i. **Beaus lines:** Nails that are distinguished by horizontal lines of darkened cells and linear depressions. The disorder may be caused by trauma, illness, malnutrition, or any major metabolic condition, chemotherapy, or another damaging event. This is the result of any interruption in the protein formation of the nail plate.

j. **Koilonychia:** Typically caused by iron deficiency anemia. These nails show raised ridges and are thin and concave.

k. **Melanonychia:** Vertical pigmented bands, often described as nail 'moles', which usually form in the nail matrix. It could indicate a malignant melanoma or lesion. Dark streaks may be a normal occurrence in dark-skinned individuals and are fairly common.

l. **Psoriasis:** Nails are distinguished by raw, scaly skin and is sometimes confused with eczema. When it attacks the nail plate, it will leave it pitted, dry and it will often crumble. The plate may separate from the nail bed and may also appear red, orange, or brown with red spots in the lunula. Do not attempt salon treatments on clients with nail psoriasis.

MATERIALS AND METHODS

Materials

Clotrimazole, 2-HP β -CD, Salicylic acid were obtained from Research-Lab Fine Chem. Industries, Mumbai. Nitrocellulose, Propylene glycol, and Ethanol were procured from Yarrow chemicals, Mumbai. In the whole attempt, AR grade chemicals were consumed.

Methods

Formulation of Nail Lacquer by Using Clotrimazole: [9]

The Clotrimazole and nitrocellulose were dissolved in Ethyl alcohol in the required quantity. By using a magnetic stirrer stir the solution until a solution occurs clear at a constant speed. To the above clear solution required quantity of 2-HP β- CD, Salicylic acid, and propylene glycol were mixed systematically. Make up the volume with ethanol up to 100ml with continuous stirring. The prepared nail lacquer was transferred to a narrow-mouthed, plastic screw-capped glass bottle. The different formulations of nail lacquer were done as per values given in Table 1**.**

Table No. 1: Formulation table for preparation of nail lacquer

Ingredients (%)	C1	C2	C3	C4	C5
Clotrimazole	2	2	2	2	2
Nitrocellulose	6	6	6	6	6
Salicylic acid	2.5	5	7.5	10	12.5
2-HP β -CD	2	4	6	8	10
Propylene glycol	10	10	10	10	10
Ethanol q.s.	100	100	100	100	100

Evaluation of Nail Lacquer:[10, 11, 12]

A) Nonvolatile content:

1. 10 ml of sample was taken in a petri dish and initial weights were recorded.
2. The dish was placed in the oven at 105ºC for 1hr.
3. The petri dish was removed, cooled, and weighed.
4. The difference in weights was recorded.
5. Average of triplicate readings were noted.

B) Drying time:

1. A film of the sample was applied to a petri dish with the help of a brush.
2. The time to form a dry-to- touch film was noted with the help of a stopwatch.

C) Smoothness to flow:

1. The sample was poured from a height of 1.5 inches into a glass plate and spread on a glass plate.
2. Made to rise vertically and visually observed for smoothness of film.

D) Gloss:

1. A sample of nail lacquer was applied over the nail.

2. Gloss was visually seen, compared with marketed cosmetic nail lacquer.

E) Viscosity:

1. Viscosity was determined using Brookfield Viscometer at room temperature using spindle no. 3 at 20 rpm.

F) Adhesion:

1. There are no quantitative evaluation tools available to assess the medicinal nail lacquer at this time.

2. Hence equipment designed in the Pharmaceutics Lab has been used to determine the adhesive property of nail lacquer.

3. The instrument is a modification of chemical balance used in the normal laboratory.

4. One pan of the balance was replaced with two stainless steel plates.

5. In between the plates, a film of 4 cm^2 was prepared and adhered to.

6. The equilibrium of the balance was adjusted by adding weight to the right pan of a balance.

7. The force required to pull away the plates is recorded and compared with a commercial cosmetic nail lacquer sample.

Force of Adhesion = Mass × Acceleration due to gravity

= Kilogram. Meter/$Second^2$

= Newtons. Meter/$Seconds^2$

Adhesive Strength = Force of Adhesion (N) / Surface area (m^2).

G) Drug content estimation:

1. Nail lacquer equivalent to 200mg was dissolved in 50 ml phosphate buffer solution of pH 7.4. Then the solution was ultrasonicated for 15 mints.

2. The resulting solution was filtered, made up to 100 ml with a phosphate buffer solution of pH 7.4. From the above solution take 10ml and made up to 100ml with PBS of pH 7.4.

3. Then the diluted solution was estimated spectrophotometrically at a wavelength of 263 nm and determined the drug content.

H) Stability study:

1. Stability studies of nail lacquers were carried out as per ICH guidelines.

2. Samples were stored at a temperature of 25±2^{0}C/60 ± 5% RH for 6 months and 40 ± 2^{o}C/75 ± 5% RH for 1 month.

3. Then the samples were analyzed for non - volatile content, drying time, gloss, smoothness of flow, viscosity, and drug content.

RESULTS AND DISCUSSION

A) Nonvolatile content:

The desired amount of nonvolatile matter (36 - 43%) was seen with complete evaporation of volatile matter leaving a thin film. The results of the Nonvolatile contents of all batches are presented in Table 2.

Table No. 2: Nonvolatile content of nail lacquer formulations

Batches	Nonvolatile content
C1	36±0.41
C2	41±0.38
C3	37±0.42
C4	43±0.40
C5	39±0.56

B) Drying time (Sec):

Drying time was found within 46 - 68 sec. All formulations showed rapid drying rate less than 60 seconds except batch C4 which shows 68 sec. These results are summarized in Table 3.

Table No. 3: Drying time of nail lacquer formulations

Batches	Drying time (Sec)
C1	46
C2	52
C3	55
C4	68
C5	57

C) Smoothness to flow and Gloss:

Both these parameters were found to be satisfactory as can be observed. The nail lacquer poured onto the glass plate was found to spread and result in a uniform smooth film. The gloss of the applied lacquer was comparable with marketed cosmetic sample proving cosmetic acceptance.

D) Viscosity:

The viscosity of the sample ranged from 90-170 centipoise. It was observed that between the range 130-150 centipoise the product was clear and glossy. Moreover, this viscosity range provided good adherence and flow property. Viscosity outside this range produces clouding and decreases gloss which will not be cosmetically acceptable. The results of viscosity are presented in Table 4.

Table No. 4: Viscosity of nail lacquer formulations

Batches	Viscosity
C1	97
C2	104
C3	129
C4	133
C5	143

E) Adhesive strength:

The adhesive strength of the optimized batch was found to be comparable with the marketed sample and hence can be expected to possess adequate adhesive strength on applied nail surface (Table 5).

Table No. 5: Adhesive strength of nail lacquer formulation

Batch	Force of adhesion (N)	Adhesive strength (N/m^2)
C5	0.4	10.5
Market Sample	0.5	13.5

F) Percentage of drug content determination:

Percentage drug content for all the lacquers was found to be satisfactory and between 84-96% which is reported in Table 6. The highest % of drug content was found to be 95.68% of batch C5 and the lowest % of drug content was 84.28% of batch C1. Drug content more than 90% in the formulation shows the high amount of drug present in the formulation, making sure that the methods of formulation and the ingredients selected are not doing impact on the stability of the drug. High drug content also gives the guarantee that a good therapeutic outcome can be expected.

Table No. 6: Percentage drug content of nail lacquer formulations

Batches	Drug content (%)
C1	84.28
C2	87
C3	93.81
C4	91.59
C5	95.68

G) Stability study:

In this study batch, C5 was subjected to accelerated stability studies for 1 month. Accelerated stability studies were performed following ICH guidelines with necessary modifications. The evaluation of formulations after stability charging showed there was no major change with respect Non -volatile content, Drying time, viscosity, and % drug content and regarding

results obtained before stability charging. Thus it was concluded that the formulations were found to possess stability compliance requirements as per ICH guidelines. The results were reported in Table 7.

Table No. 7: Stability study of nail lacquer formulations

Parameters	Initial	After
Nonvolatile content	39±0.56	38±0.82
Drying time (Sec)	57	59
Viscosity	143	146
Drug content	95.68	94.71

CONCLUSION

The principle of the present research was to formulate and evaluate the Clotrimazole nail lacquer as an ungual drug delivery system for the treatment of onychomycosis. Drug delivery to the nail represents a major challenge, with the lack of understanding of both the difficult properties of the nail and formulations to achieve improved ungula delivery restricting the effectiveness of topical treatments for nail disorders. From the above learning, it can be concluded that medicated nail lacquers proved to be a better tool as a drug delivery system for the ungual drug delivery of an antifungal in the treatment of onychomycosis. Despite treating the nail infections, the medicated nail lacquers can be also used for beautification of nails with ease of application. This improves patient compliance and acceptability.

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