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Review on medicated nail lacquer for onychomycosis, the carrier system is transungual delivery system for antifungal drug

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Abstract
The objective if written review paper on antifungal nail lacquer which is used in treatment of onychomycosis nail fungal disorder was focus on the disease causes and treatment by nail lacquer, onychomycosis is common fungal nail infection causes by the pathogens. In this article several methods are described for the drug delivery through nail by incorporating the permeability enhancer. Nail lacquer is mostly applicable for those drugs which have poor bioavailability in oral formulation this technique is used to maximize the topical bioavailability of drug across the nail. In this luliconazole nail lacquer is described for onychomycosis. The high permeation rate helps to reduce the treatment period for the disease.

Keywords: Nail lacquer, luliconazole, castor oil, methanol, toluene

Introduction
Topical treatment of skin and nail diseases is desirable in terms of patient acceptability and reduction of side effects associated with systemic drug delivery. This is particularly the case for nail diseases as they are frequently difficult to cure and also require long periods of treatment [1]. The nail plate is a highly keratinized tissue, which is characterized by low permeability to diffusing substance. The nail diseases are widely spread in the population, particularly among elderly and immune- compromised patients. Current research on nail permeation focuses on altering the, nail plate barrier by means of chemical treatments and penetration enhancers. Physical and mechanical methods are also under examination. The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized [2]. It is also very variable among individuals. The plates can be small, large, wide, narrow, hard, smooth, ridged and thin, etc.

Fungal Infection
Fungal infections are common throughout much of the natural world. In humans, fungal infections occur when an invading fungus takes over an area of the body and is too much for the immune system to handle. Fungi can live in the air, soil, water, and plants. Like many microbes, there are helpful fungi and harmful fungi.

Examples of infections that topical antifungals may include
- Onychomycosis
- Onychatrophia
- Onychogryposis
- Leuconychia
- Koilonychia

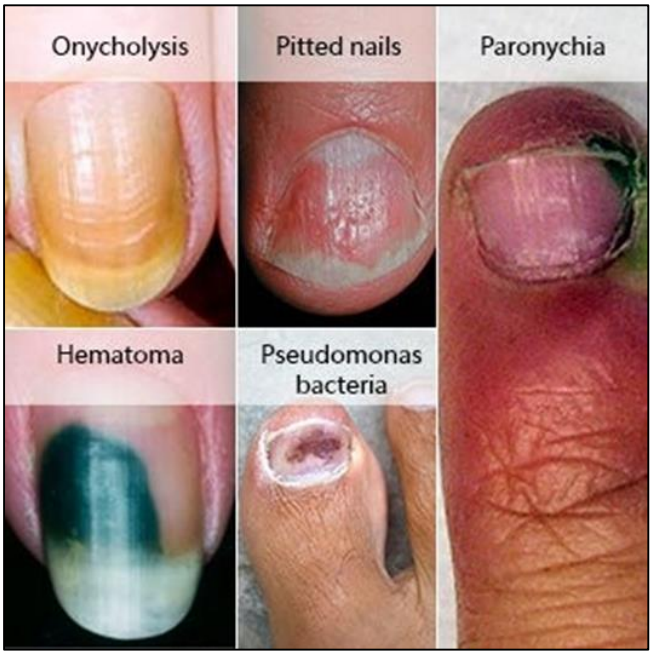

Fig 1

Disorders of nail unit range from relatively innocuous conditions such as the pigmentation in heavy smokers, to painful and debilitating states where the nail unit can be dystrophies, hypertrophied, inflamed, infected etc. Such conditions affect patients physically as well as socially and psychologically and can seriously affect the quality of life [3].
Many nail diseases are notoriously difficult to cure, need a long duration of treatment is common. Oral therapy has the inherent disadvantages of systemic adverse effects and drug interactions while topical therapy is limited by the low permeability of the nail plate.
Thus, a suitable carrier may be needed to enhance drug penetration through the nail barrier. Dermatologists and podiatrists have long used mechanical methods of enhancing nail penetration, including nail abrasion and nail avulsion, but these methods have varying results in addition to being invasive and potentially painful [4].
Therefore, current research focuses on less invasive chemical and physical modes of nail penetration enhancement.
Treatment of the fungal infections of nails such as onychomycosis, nail psoriasis involved oral therapy with antifungals, but it caused systemic side effects such as liver toxicity and bioavailability problems due to first pass metabolism and drug interactions.
Therefore, the topical delivery through nails also known as transungual drug delivery system came into picture. But transungual delivery had its own challenges.
Nail plate is made up of cross-linked keratin and linkages which impart extensive bonding responsible for hardness of the nail plate. To overcome these problems mechanical and chemical approaches were studied. Chemical ones included use of penetration enhancers which weaken the integrity of nail, enhancing flux through nails [5].
In spite of using this approach topical permeability was limited by its barrier properties. This necessitated lookout for novel the approaches which enhanced treatment efficacy and reduced treatment time.
The physiochemical properties of the nail, are evidenced in various experiments to indicate that nail behaves more like a hydrophilic gel membrane as opposed to lipophilic membrane, such as the stratum conium. In the human nail plate, the most visible part of the nail apparatus which is responsible for penetration of the drug across it. The architecture and the composition of the nail plate severely limits penetration of drugs, only a fraction of topical drug penetrates across it.
Topical therapy is a lucrative option however, due to its non-invasiveness, drug targeting to the site of action, elimination of systemic adverse events and drug interactions, increased patient compliance and possibly reduced cost of treatment. The importance of nail permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis, which affects approximately 19% of the population.
Recent advances in topical transungual delivery had come up with antifungal nail lacquers. Current research on nail permeation focuses on altering the nail plate barrier by means of chemical treatments and penetration.
Development of the newer penetration enhancers, studies on water-based nail lacquers, nail varnish with antimycotic agent, are being studied extensively. Patch based delivery are made up of an occlusive backing layer and a pressure sensitive adhesive matrix layer with the active agent, is also being investigated as an alternative treatment for onychomycosis [6].

The advantages of topical antifungals

1. Lack of systemic side effects and complications due to limited systemic absorption.
2. Very low incidence of drug interactions.
3. Ease of use.
4. Comparatively low cost of therapy.
5. Additional benefit of anti-inflammatory activity of several topical antifungals including allyl amines.

The disadvantages of topical antifungals

1. Difficult to use in extensive dermatophytic infections.
2. Application of inadequate amount results in poor response.
3. Inability to apply in difficult-to-reach areas (e.g., natal cleft) may leave residual foci of infection.
4. Low effectiveness in onychomycosis due to inadequate penetration.
5. Rarely contact dermatitis.

Hence the absorption of drugs into the nail unit, to the nail plate, is highly desirable to treat nail disorders. The nail plate behaves like a concentrated hydro gel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of nonelectrolytes through polymer gels.
For optimal transungual permeation and uptake of drug, drug molecules must be small in size and should remain non-ionic form.
Current review on nail permeation focuses on the anatomy of a human nail, diseases related to nail plate, altering the nail plate barrier by means of chemical treatments, penetration enhancers as well as physical and mechanical methods used to enhance the topical bioavailability of the drugs across the nail and latest trends in drug delivery across the nail [7].

Classifications of antifungals

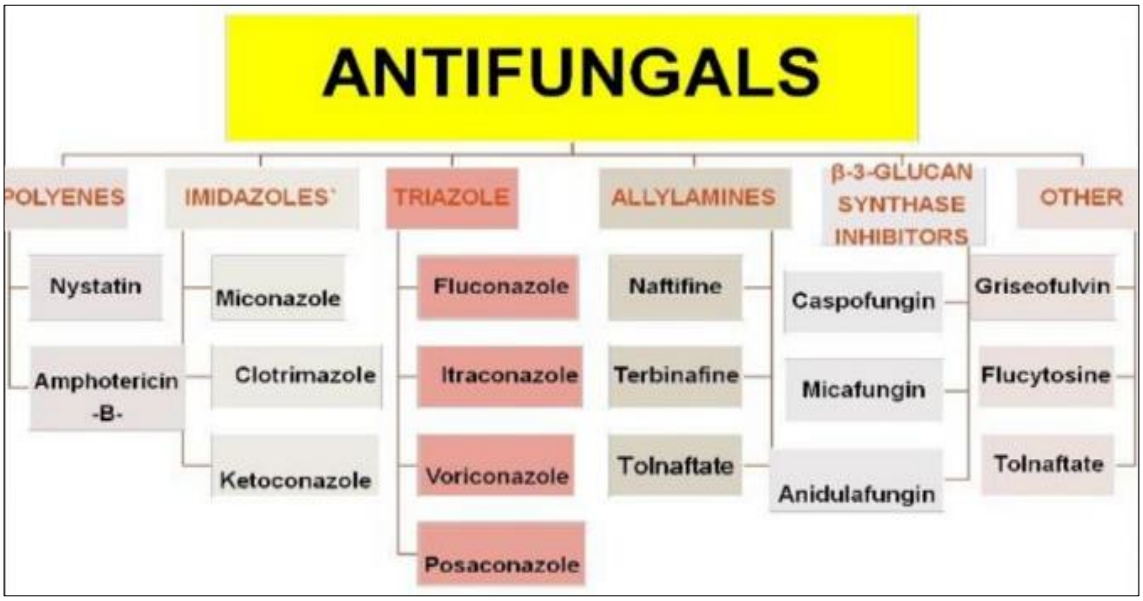

Fig 2

Mechanism of Drug Delivery through Nail

When applied to the nail plate, the solvent evaporates leaving a polymer film (containing drug) onto the nail plate. The drug is then slowly released from the film, penetrates into the nail plate and the nail bed.

Effective penetration remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneoum (SC). It increases in toe nail thickness along the nail.

Mean nail plate thickness increased progressively along the entire length of the nail ranging between 590µm and 1080µm.

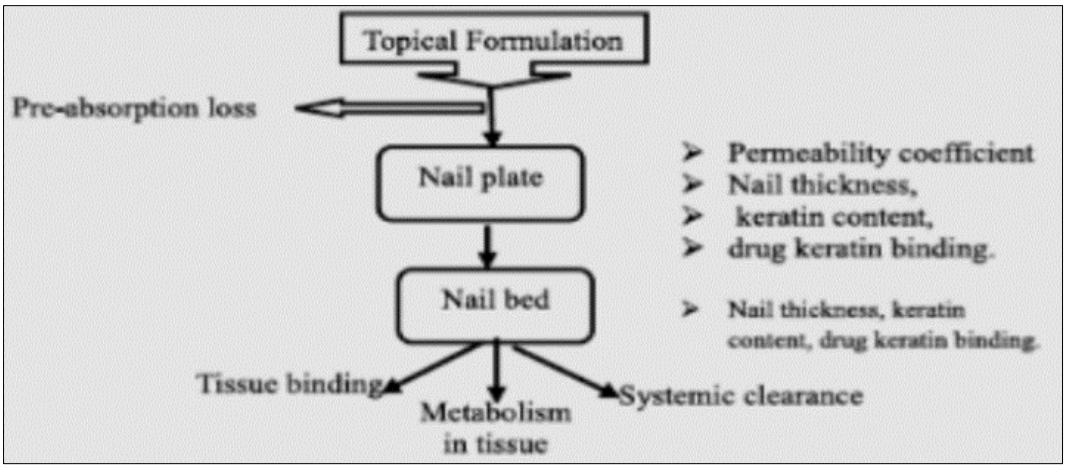

Fig 3

Treatment available for onychomycosis

1. Removal of infected nail.
2. Oral therapy.
3. Ungual therapy.

Anatomy of the nail

The nail consists of the nail plate, the nail matrix and the nail bed below it, and the grooves surrounding it.

Matrix: (matrix unguis, keratogenous membrane, nail matrix, onychostroma). It is the tissue (or germinal matrix) upon which the nail rests, the part of the nail bed that extends beneath the nail root and contains nerves, lymph and blood vessels. The matrix is responsible for the production of the cells that become the nail plate.

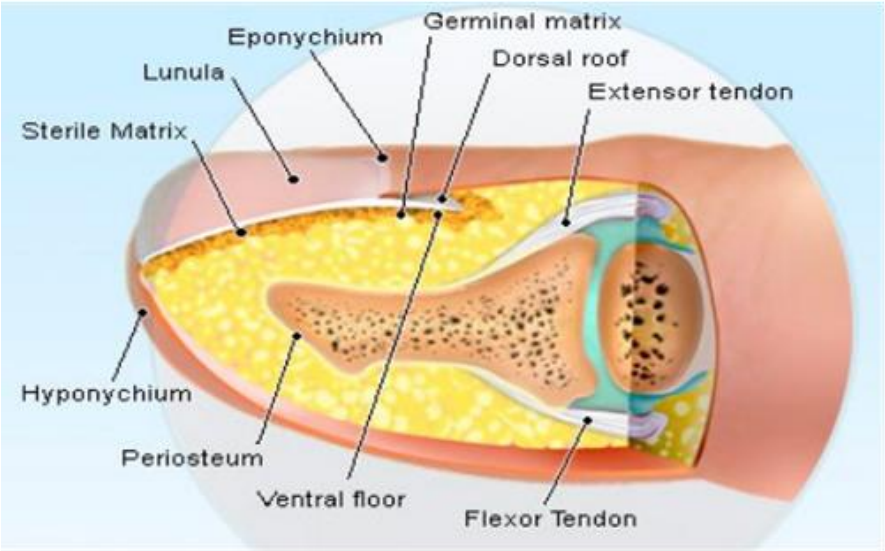

Fig 4

- Lunula: ("the moon"). It is the visible part of the matrix, the whitish crescent-shaped base of the visible nail [8]. The lunula is largest in the thumb and often absent in the little finger.
- Nail bed: Itis the skin beneath the nail plate. Like all skin, it is composed of two types of tissues.
- The Deeper Dermis - the living tissue fixed to the bone which contains capillaries and glands.
- The Superficial Epidermis - the layer just beneath the nail plate which moves forward with the plate.
- Nail Sinus (sinus unguis): It is the deep furrow into which the nail root is inserted.
- Nail Root (radix unguis): It is the part of nail situated in the nail sinus i.e. the base of the nail embedded underneath the skin. It originates from the actively growing tissue below, the matrix.
- Hyponychium ("quick"): It 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.
- Onychodermal Band: It 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, greyish colour (in fair-skinned people).
- Nail Wall (vallum unguis): It is the cutaneous fold overlapping the sides and proximal end of the nail [9].
- Lateral Margin (Margo lateralis): It is lying beneath the nail wall on the sides of the nail and the nail grooveor fold (sulcus matricis unguis) are the cutaneous slits into which the lateral margins are embedded.

Function of Nail

1. A healthy nail protects the distal phalanx, the fingertip, and the surrounding soft tissues from injuries [10].
2. It also serves to enhance precise delicate movements of the distal digits through counter-pressure exerted on the pulp of the finger.
3. The nail acts as a counterforce when the end of the finger touches an object, thereby enhancing the sensitivity of the fingertip even though there are no nerve endings in the nail itself.

Mechanical Methods to Enhance Nail Penetration

Mechanical methods including nail abrasion and nail avulsion have been used by dermatologists and podiatrists for many years-with varying results. Additionally, they are invasive and potentially painful.

Thus, current research focuses on less invasive chemical and physical modes of nail penetration enhancement. Nail abrasion simply stated, nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely.

Sandpaper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discomfort.

An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece. Additionally, dentist's drills have been used to make small holes in the nail plate, enhancing topical medication penetration.

Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed. In doing so, it may enhance the action of antifungal nail lacquer. The procedure may be repeated for optimal efficacy.

Nail avulsion Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion.

Urea or a combination of urea and salicylic acid has been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis. Nail abrasion, using sandpaper nail files, prior to antifungal nail lacquer treatment may decrease the critical fungal mass and aid penetration [11].

Chemical methods to enhance nail penetration

Studies examining the efficacy of chemical compounds with transungual penetration properties are currently underway. As would be expected, skin penetration enhancers do not usually have the same effect on nails. Thus far, only a few chemicals which enhance drug penetration into the nail plate have been described [12]. Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. This would destabilize the keratin, compromise the integrity

of the nail barrier and allow penetration of drug molecules. Identified the disulphide, peptide, hydrogen and polar bonds in keratin that could potentially be targeted by chemical enhancers.

Nail Softening Agents Or Keratolytic Enhancers - Guerrero *et al*. described the effect of keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole) Urea and salicylic acid hydrate and soften nail plates.

Urea and salicylic acid also damage the surface of nail plates, resulting in a fractured surface. Effects were penetrated specific, but the use of a reducing agent followed by an oxidizing agent (urea, H2O2) dramatically improved human nail penetration while reversing the application order of the PEs was only mildly effective.

Both nail PEs are likely to function via disruption of keratin disulphide bonds and the associated formation of pores that provide more 'open' drug transport channels.

Compounds Containing Sulfhydryl Groups

Compounds which contain sulfhydryl (SH) groups such as acetylcysteine, cysteine, mercaptoethanol can reduce, thus cleave the disulphide bonds in nail proteins, as shown in the reaction sequence below:

2 Nail-SH+R-S-S-R _Nail-S-S-Nail+R-SH

R represents a sulfydryl-containing compound.

However, post-treatment barrier integrity studies demonstrated that changes induced in the nail keratin matrix by these effective chemical modifiers were irreversible. It is believed that these enhancers act by breaking disulphide bonds, which are responsible for nail integrity thus producing structural changes in the nail plate [13].

Keratinolytic Enzymes

Due to an abundance of keratin filaments, keratinic tissues like the SC are effectively hydrolyzed by keratinase. Mohorcic *et al*. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing transungual drug permeation. Keratinase act on both the intercellular matrix that holds the cells of the nail plate together and the dorsal nail corneocytes by corroding their surface.

Physical Methods to Enhance Nail Penetration

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents. We discuss several physical enhancement methods, both established and experimental.

Iontophoresis

Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis.

electrorepulsion/ electrophoresis, interaction between the electric field and the charge of the ionic per meantu; electroosmosis, convective solvent flow in preexisting and newly created charged pathways and permeabilization/electroporation, electric fieldinduced pore induction. While transport enhancement of neutral permeants relies on electroosmosis, transport enhancement of ionic permeants relies on electrophoresis and electroosmosis. The effects of electric current on nails are reversible *In vitro*; nail plates will return to normal after iontophoresis treatment [14].

Etching

"Etching" results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities. These microporosities increase wettability and surface area, and decrease contact angle; they provide an ideal surface for bonding material. Presence of micro porosities improves "interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent".

Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Roughness of the nail surface results in increased surface area, providing "greater opportunity for polymer chains to inter-diffuse and bond with the nail plate, improving bio adhesion and retention of a drug delivery system." Surface modifications influence polymer–substrate interactions-increasing adhesive force and toughness.

Carbon dioxide

Laser CO2 laser may result in positive, but unpredictable, results. One method involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm2 (power density) [15]. Thus, underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO2 laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes.

Hydration and Occlusion

Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Additionally, hydrated nails are more elastic and permeable. Decreases in transonychial water loss, ceramide concentration, and water binding capacity may result from onychomycosis. Occlusion may resolve these changes via reconstitution of water and lipid homeostatisis in dystrophic nails.

Nail lacquer

Nail polish (also known as nail varnish or nail enamel) is a lacquer that can be applied to the human fingernail or toenails to decorate and protect the nail plates. The formula has been revised repeatedly to enhance its decorative effects and to suppress cracking or peeling. Nail polish consists of a mix of an organic polymer and several other components that give it its unique color and texture.

Ingredients of nail lacquer

- Nail polish consists of a film-forming polymer dissolved in a volatile organic solvent. Nitrocellulose that is dissolved in butyl acetate or ethyl acetate is common.
- Plasticizers to yield non-brittle films. Dibutylphthalate and camphor are typical plasticizers.
- Dyes and pigments. Representative compounds include chromium oxide greens, chromium hydroxide, ferric ferrocyanide, stannic oxide, titanium dioxide, iron oxide, carmine, and manganese violet.
- Opalescent pigments. The glittery/shimmer look in the color can be conferred by mica, bismuth oxychloride, natural pearls, and aluminum powder.
- Adhesive polymers ensure that the nitrocellulose adheres to the nail's surface. One modifier used is tosylamide-

formaldehyde resin [16]. Thickening agents are added to maintain the sparkling particles in suspension while in the bottle. A typical thickener is stearalkonium hectorite. Thickening agent's exhibit thixotropy, their solutions are viscous when still but free flowing when agitated. This duality is convenient for easily applying the freshly shaken mixture to give a film that quickly rigidifies. Ultraviolet stabilizers resist color changes when the dry film is exposed to sunlight. A typical stabilizer is benzophenone-1.

Evaluation of Nail Lacquer

Nonvolatile content

10 ml of sample was taken in a petri dish and initial weights were recorded. The dish was placed in the oven at 1050C for 1hr, the petri dish was removed, cooled and weighed. The difference in weights was recorded.

Drying time

A film of sample was applied on a petri dish with the help of a brush. The time to form a dry-to- touch film was noted with the help of stop watch.

Smoothness

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

Gloss

Sample of nail lacquer was applied over the nail and gloss was visually seen, compared with marketed cosmetic nail lacquer.

Viscosity

Viscosity was determined using Brookfield Viscometer, model LVF at room. Temperature using spindle No.3 at 20 rpm.

Adhesion

There is no quantitative evaluation tools available to assess the medicinal nail lacquer at this time. Hence equipment designed in the Pharmaceutics Lab has been used to determine the adhesive property of nail lacquer. The instrument is a modification of chemical balance used in the normal laboratory as shown in Figure No.10. One pan of the balance was replaced with two stainless steel plates. In between the plates a film of 4 cm2 was prepared and adhered. The equilibrium of the balance was adjusted by adding a weight to the right pan of balance. The force required to pull away the plates is recorded and compared with a commercial cosmetic nail lacquer sample [17].

Force of Adhesion = Mass x Acceleration due to gravity Adhesive

$$\text{Strength} = \frac{\text{Force of Adhesion (N)}}{\text{Surface area (m2)}}$$

Drug content estimation

Nail lacquer equivalent to 200mg was dissolved in 50 ml phosphate buffer solution of pH 7.4. Then the solution was ultra sonicated for 15 mints. The resulting solution was filtered, made up to 100 ml with phosphate buffer solution of pH 7.4. From the above solution take 10ml and made up to 100ml with PBS of pH 7.4. Then the diluted solution was estimated spectrophotometrically at wavelength of 223 nm and determined the drug content.

Diffusion studies across artificial membrane

Diffusion studies were performed by Franz diffusion cell using artificial membrane (cellophane) of 0.8µm. The membrane was soaked for 24hrs in solvent system and the receptor compartment was filled with solvent. Nail lacquer equivalent to 200mg was applied evenly on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37°C and the speed of stirring was kept constant for 20hrs. The 5ml aliquot of drug sample was taken at time intervals of 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 16hr and 20hrs and was replaced by the fresh solvent. Samples were analyzed by double-beam UV spectrophotometer as per method mentioned in drug content estimation. Each experiment was repeated thrice.

***In vitro* ungual permeation studies**

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24hrs. Membranes of about 1mm thickness were cut from the distal part of hooves. *In vitro* permeation studies were carried out by using Franz diffusion cell, the hoof membrane was placed carefully on the cell. Then the nail lacquer equivalent to 200mg was applied evenly on the surface of the nail membrane [18]. The receptor compartment was filled with solvent phosphate buffer solution of pH 7.4, and the whole assembly was maintained at 37°C with constant stirring for 48hrs. The 5ml aliquot of drug sample was taken after a time intervals of 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48hrs and was replaced by the fresh solvent. The drug analysis was done by using double-beam UV spectrophotometer at 223nm.

Stability study

Stability studies of nail lacquers were carried out as per ICH guidelines. Samples were stored at temperature of 25±2 0C/60 ± 5% RH for 6months and 40 ± 2oC/75 ± 5% RH for 1 month. Then the samples were analyzed for non -volatile content, drying time, gloss, smoothness of flow, drug content and diffusion across artificial membrane.

Conclusion

In the coming year, topical drug delivery will be used more to impart better patient compliance. Since nail lacquer is helpful in enhancing spreadability adhesion and permeability. In present investigation topical medicated luliconazole nail lacquer is useful for proper and accurate delivery of drug through nails. Nail lacquers have been suggested to possess efficient permeability across the nail plate. Delivery of these drugs via nail lacquers is found to be safe and effective in the therapy for onychomycosis.

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