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Formulation and evaluation of Antifungal Drug Turbinafine Hydrochloride for the treatment of Atheletes Foot

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Abstract : The stratum corneum pharmacokinetics of terbinafine following single dose administration of a novel cutaneous solution containing Turbinafine Hydrochloride and film forming agent, was investigated in three studies . Terbinafine 1% cream Lamisil was included as benchmark in two of this studies .

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I. INTRODUCTION.

Over the last decades, the treatment of infection has been accomplished by administrating drugs to the human body via various routes namely oral, parenteral, topical, inhalation, etc. Every medical condition demands appropriate and accurate treatment, the thought of resolving the patient's disease with the least harm done to the patient's health is said to be the basic goal of any therapy. Moreover, a good treatment technique necessitates thorough knowledge of pharmacodynamics and pharmacokinetics of the intended drug.

1.1 TINEA PEDIS (ATHLETE'S FOOT)

It is one of the most common superficial fungal infection of the skin in all region of the world. It is more common in communities such as army barracks, boarding schools and among those frequenting swimming pools, when the feet are occluded with nonporous shoes. The incidence of this infection is higher in warm humid climates which are known to promote the growth of fungi, but has been found to occur less frequently in areas of the world where shoes are not commonly worn. Tinea pedis produced by dermatophytic filaments, although were tight-fitting shoes promotes infection and its spread. (Vikas Kumar et al., 2011).

1.2 CLINICAL PRESENTATION

- There are four distinct clinical types of tinea pedis – interdigital, hyperkeratotic, ulcerative and Vesicular.

1. INTERDIGITAL TINEA PEDIS:

- It occurs in two forms, most common form of this infection usually arise in the interspace between 4th and 5th toes, occasionally spreading to the underside of the foot.
- First type of interdigital tinea pedis, known as dermatophytosis simplex, is largely asymptomatic and present as dry, scaly, minimally peeling interspaces with occasional pruritus. The second form dermatophytosis complex is symptomatic and usually present with wet, macerated interdigital spaces along with fissuring of the interspace, hyperkeratosis, leukokeratosis and erosions.

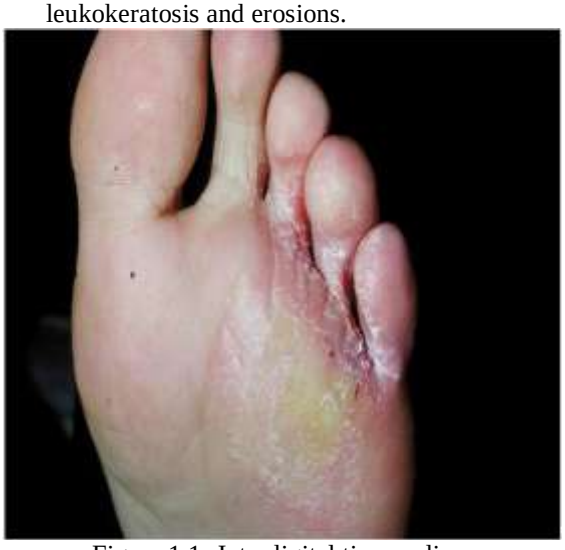

Figure 1.1- Interdigital tineapedis.

2. HYPERKERATOTIC OR MOCCASIN TYPE TINEA PEDIS:

- This consist of scaling and hyperkeratosis involving the plantar and lateral aspect of the foot,resembling a slipper. This type of infection is thought to be due to Trichophyton rubrum, usually in patient with an atopic background or a hereditary predisposition to infection. (Vikas Kumar et al., 2011).

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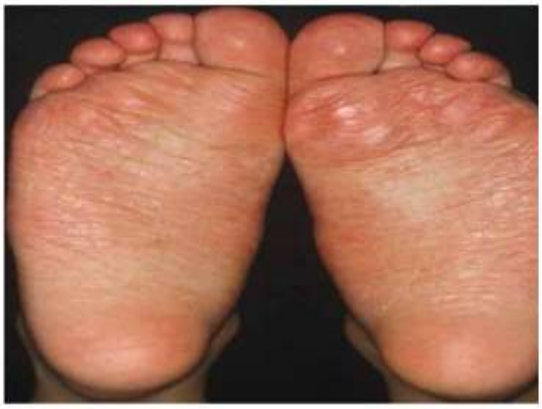
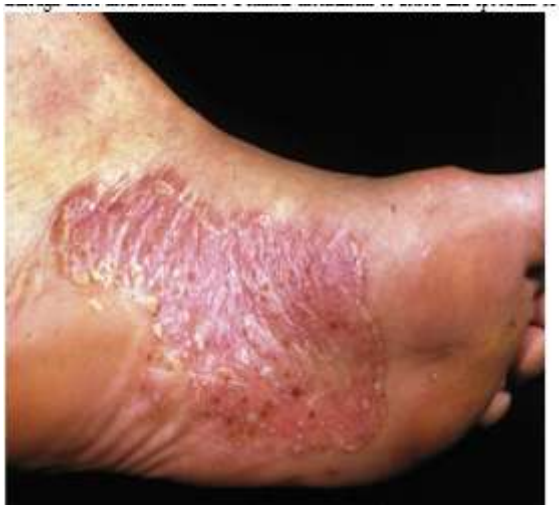


Figure 1.2- Moccasin type of tineapedis

3. ULCERATIVE TINEA PEDIS:

There is an acute ulcerative process usually affecting the soles and associated with maceration,denudation of the skin and oozing. (Vikas Kumar et al., 2011).

It is also known as vesicobullous tinea pedis. Tinea mentagrophytes is the most common causal organism. Initially, there is inflammation at the in-step of the entire sole. The mildest form of vesicbullous tinea pedis starts with the development of small, isolated vesicles filled with clear fluid



AN OVERVIEW OF THE MEDICATION MOST OFTEN USED TO TREAT TINEA PEDIS: (Nkatoko Freddy Makola et al., 2018). 1. The azole antifungal agents: The azoles are a class of five-membered, heterocyclic compounds containing a nitrogen atom and at least one other non-carbon atom (i.e. nitrogen, sulfur or oxygen) as part of the ring structure. Azoles that are available for clinical use are classified as either imidazoles or triazoles, according to the number of nitrogen atoms they contain in their chemical structure. • Imidazoles (ketoconazole, miconazole, econazole and clotrimazole) • Triazoles (fluconazole, itraconazole and voriconazole). Although these medications share a similar mechanism of action and spectrum of activity, their pharmacokinetics and therapeutic uses vary significantly. 6 Imidazoles, ingeneral, are fungistatic.

II. TERBINAFINE:

Terbinafine hydrochloride belongs to BCS class II drug. It is an allylamine derivative reported to have a broad spectrum of antifungal activity against dermatophytes, certain dimorphic fungi,yeasts, and molds. It is used to treat a fungus infection on your skin, including tinea pedis(“athlete’s foot”), tinea corporis (“ringworm”), and tinea cruris (“jock itch”), and also fingernails and toenails.

The oral therapy with terbinafine hydrochloride has been associated with severe side effects, toxicity, drug interaction, and a high rate of recurrence. There is a strong need for an effective, safe, and patient compliance topical formulation capable of delivering and maintaining

Therapeutic concentrations of terbinafine hydrochloride in the nail bed.

Marketed formulations that are currently available for Terbinafine hydrochloride are creams and tablets. (Terbicip and Lamisil) respectively. (Ghannoum, M. A et al., 2009, Jan S et al., 2014).

III. NEED OF WORK

- Topical drug delivery system is defined as the application of pharmaceutical dosage formTo the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of The general disease,
- Tinea pedis, commonly known as athlete’s foot, which is a dermatophytic infection of the Feet, can involve the interdigital web spaces or the the sides of the feet and may be a Chronic or recurring condition. The most common etiological agents are anthropophiles, Such as Trichophyton rubrum.
- Terbinafine is an effective antifungal agent used orally as well as topically in the Treatment of various fungal infections. Marketed topical formulations of terbinafine Include cream, gel, solution, spray, tablets and ointment which show disadvantage of Poor permeation and hence lower efficacy in treating the fungal infections.
- Paint formulation are more suitable as a topical drug delivery system because, it can be Administered with good tolerance, reducing the

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need for the frequent administration and it Gives more retentive time.

 Terbinafine has been widely used as an antifungal agent hence, the present study is an Attempt carried out to formulate and evaluate terbinafine paint formulation for the Treatment of athlete's foot

IV. AIM AND OBJECTIVES

AIM

To formulate and evaluate the topical delivery system of terbinafine hydrochloride for the treatment of athlete's foot (tinea pedis).

OBJECTIVES

Determination of minimum inhibitory concentration of topical formulation against selected fungal strains like Trichophyton rubrum.

2) Preparation and optimization of topical formulation containing terbinafine hydrochloride.
3) Evaluation of optimized topical formulation, followed by stability studies.

V. PLAN OF WORK

 The dissertation work was planned as follows:
1. Literature survey
2. Characterization of drug
  Melting point
  Solubility, Calibration curve in PBS of pH 7.4
  FTIR
3. Procurement of microorganism Its characterization
4. Preformulation study
5. Determination of antifungal activity of drug
6. Preparation of topical formulation, optimization of formula
7. Evaluation of topical formulation
  Drying time
  Non-volatile content
  Smoothness to flow
  Spreadability
  pH determination
  Viscosity determination
  Antifungal activity
  Drug release
  Assay
8. Stability study

5.1 DRUG PROFILE

Terbinafine hydrochloride
Proprietary name: Fungotek, Sebifin, Lamisil
IUPAC Name: (E)-N,6,6-trimethyl-N-(naphthalene-1-ylmethyl)hept-2-en-4-yn-1-amine,hydrochloride.

Molecular formula: C21H26ClN
Molecular weight: 327.9g/mol
CAS No. : 78628-80-5
Log P: 5.53
Solubility: It is freely soluble in methanol and dichloromethane, soluble in ethanol, and slightly soluble in water.
Description: Terbinafine hydrochloride is a white fine crystalline powder.
Structure

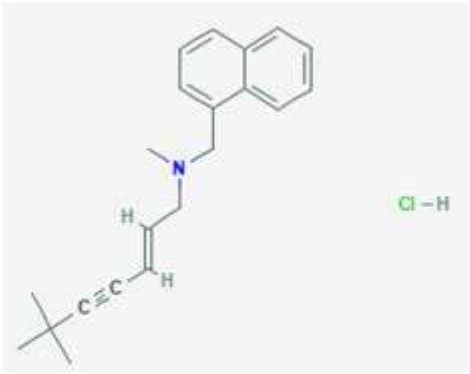

Figure no. 5.1: Structure of Terbinafine hydrochloride

Mechanism of action:

Allylamines act by inhibiting the squalene epoxidase enzyme thereby blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. Accumulation of toxic amounts of squalene results in increased membrane permeability and death of fungal cells. Terbinafine is
the drug of choice for treating onychomycosis.

Applicable pharmacokinetics:

More than 70% of the drug is absorbed and it is highly bound to plasma proteins. However, due to the first-pass effect only 40% of the ingested drug is available to the systemic circulation. It is metabolised in the liver by several CYP 450 isoenzymes and mainly excreted in the urine. It accumulates in breast milk and should not be given to nursing mothers.

EVALUATION OF TOPICAL PAINT FORMULATION
Nonvolatile content
B) Drying time
C) Viscosity
D) Smoothness to flow

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E) Determination of antifungal activity

The evaluation of terbinafine paint formulation
Non volatile content
Drying time
Viscosity
Smoothness to flow
Antifungal activity of terbinafine paint formulation

Literature Review
Tinea pedis pathophysiology and treatment James L.Leyden.MD Philadelphia, Pennsylvania.
In the present work tinea pedis commonly known as athlete's foot ,is the most common form of dermatophytosis .This disorder Can generally be classified into three categories :1 interdigitated infection 2.scaling hyperkeratic moccasin type infection of the plantar surface ,and 3 .highly inflammatory vesiculobullouseruotions.

Interdigital infection
Interdigital toe web infection have usually been catogarized as fungal diseases.they usually start as a dermatophyte infection with scaling, and when the bacteria proliferate maceration occurs.toe web infection can be viewed as an ecological interplay between dermatophyte (trichophytonrubrum and trychophytonmentagrophyts) various bacterial species and although rare , candida species .
Dermatophyte are the primary instigating factor ,the use of a fungicidal agent ,such as an allylamine ,is preferable the stratum corneum ,and select growth of bacteria that damage tissue .
Any other reservoir of fungi eg .toenails must be addressed.

Planter Moccasin type infection
The planter Moccasin type infection results in diffuse hyperkeratotic scaling of the palnter surface and is often associated with nail involvement .
Terbinafine antifungal agents penetrate more quickly to exert a greater antifungal activity than other agents .
Terbinafine ,an allylamine ,and ketoconazol ,an inidazole ,appear to penetrate the most efficiently.

Vesiculobullous Tinea Pedis
Highly inflammatory eruptions particularly on the arch and the side of the foot ,occure with T.mentagrophytesinfection . The intense inflammatory reaction represent immune T-cell immune host response.Compresses and topical or systematic corticosteroids in conjugation with antifungal agents are used with acute attacks.
The allyalamines ,which are fungicidal appear to be the best choice.

Tinea pedis : The etiology and global epidemiology of a common fungal infection
Macitllkit and Murat Durdu

In the present work tinea pedis is a dermatophytic infection of the feet , can involve the interdigital web spaces or the sides of the feet and may be a chronic or recurring condition .
The most common etioloical agents are antropophiles ,including Trichophyton rubrum sensustricto,which is the most common ,followed by Trichophyton interdigitale and Epidermophyton floccosum .This review was amused to provides a solid overview of the current stratus and changing pattern of tinea pedis .

This mycotic infection is contagious , frequently misdiagnosed and often inadequatly treated .
Considering the uprising prevalence of tinea pedis ,in this review article predisposing factors , etiologic agents involved in pathogenesis , clinical presentation of the disease , proper diagnosis tests and the treatment options commercially available are reviewed.

ANALYTICAL METHODS
Preparation of Phosphate buffer solution (PBS)
a) Preparation of 0.2M sodium hydroxide solution
8gm of sodium hydroxide was dissolved in sufficient quantity of distilled water in a1000ml volumetric flask and volume was made up to 1000ml with distilled water.
27.218gm of potassium dihydrogen ortho phosphate was dissolved in sufficient quantityOf distilled water in a 1000ml volumetric flask and volume was made up to 1000ml with Distilled water.

b) Preparation of phosphate buffer solution of pH 7.4
50ml of 0.2M potassium dihydrogen ortho phosphate solution was taken in a 200ml Volumetric flask and 39.1ml of 0.2M sodium hydroxide solution was added and made up To 200ml with distilled water.

2. Determination of λ max and standard plot for TH in phosphate buffer of pH7.4
About 10 mg of drug TH was accurately weighed and dissolved in about 5ml of Methanol. The volume was then made up to 10 ml with methanol

in volumetric flask to obtain 1000 µg/ml solution. From above solution, 1ml of aliquot was taken and furtherdiluted to 100ml in volumetric flask with phosphate buffer pH 7.4 to obtain 10 µg/mlstock solution. The above solution was scanned in the range of 400-200 nm on UVspectrophotometer to determine the λmax. (Make and model-Shimadzu, UV-1700). From the stock solution, working standard solutions of drug having concentrations in the rangeof 2, 4, 6, 8 and 10 µg/ml were prepared by appropriate dilutions with phosphate bufferpH 7.4. These solutions were analyzed at 283nm on UV spectrophotometer. Theexperiment was performed in triplicate. The standard plot was obtained by plotting Absorbance versus concentration.

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