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# A DETAILED REVIEW ON PREPARATION, CHARACTERIZATION AND EVALUATION STUDY OF FLUCONAZOLE VANISHING CREAM

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## ABSTRACT

The purpose of this article is to overcome the systemic adverse effect of fluconazole that is hepatotoxicity and nephrotoxicity by topical application of fluconazole. Emulsion which are viscous, liquid or semisolid emulsion is called cream. Fluconazole is an azole antifungal and used in the treatment of local and systemic fungal infections like tinea corporis, onychomycosis and dermatophytosis. The topical formulation is used to introduce the drug into the skin or mucous membrane of the skin and also for the different skin disorders. For efficient delivery of drug to skin tissue, a fluconazole vanishing cream was not developed till date. But we can found various formulations like fluconazole capsule, tablets etc. Skin creams are generally W/O and O/W. In the skin creams various vitamins like vit. A, E and D3 and fatty acid used. The main objective of the study is to treat fungal infections. Fungal infection is very common and can affect persons of all ages. So, Fluconazole vanishing cream formulation was developed in this study and is promising for better patient compliance as no any traces when applied.

**KEYWORDS:** Fluconazole, Emollients, Dermatophytosis, Candida krusei.

## INTRODUCTION

A vanishing cream is a cream with low fat moisturizer that disappears into the skin. It softens skin, leaving nothing behind. It is perhaps the commonest prescribed topical medicament. As it is less oily, messy and sticky, most patients find it more user-friendly.[1] Fungal infection

son scalf are common and some of them causes serious illness. The scalf infections such as Tinea vesicular, (pityriasis, versicolar), Seborrhea dermatitis, pityriasis capititis have been mentioned as a scaling disorders, will affect scalf and hair abruptly. The genus malassezia responsible for variety of superficial cutaneous as well as systemic fungal infections and pityriasis versicolor is the most commonly presenting diseases.[2]

**Vanishing Cream.** One or more active ingredients dissolved or uniformly dispersed in a suitable excipients contains vanishing cream, paste or ointment and suitable bases such as, antioxidants, viscosity increasing agents, antimicrobial agents, stabilizing agents and emulsifier etc.[1,2] The type of cream that leaves no any visible trace or seem to be disappear while rubbing or while spraying on skin is known as vanishing cream. Where other system of drug administration fails there topical drug delivery system is used or it is mainly used in pain and urinary disturbance. The various formulation aspects, various tests, various tests, various challenges of topical drug delivery describes.

Two basic type of product topical drug delivery includes.

- **External Topical:** Generally that dispersed and spread on to the cutaneous tissue to cover the affected area.
- **Internal Topical:** Generally that applied on the mucus membrane orally and through vagina for local activity.[4]

**Advantages of Vanishing cream**

- They give prolonged contact in their site of application than other doses form formulations.
- When applied to skin it gives no irritation and easily water washable.
- Efficacy with lower daily dosage of drug by continuous drug input can be achieved.
- More safely drug deliver to a specific site.
- Physiological and pharmacological response is increased.
- It has large area of application in comparison with buckle or nasal cavity.
- The main objective of study is to treat fungal infection like Candida krusei Candida albicans, Candida tropcialis, Cryptococcus neoformans, Candida glabrata.
- Prolonged contact in their site of application can give than other doses forms.

**Disadvantages of vanishing cream**

- Allergy such as skin may occur at site of application due to drug /excipients.
- Larger particles cannot be absorbed absorbed from topical doses forms.
- When applied to skin, inflammation may occur.
- Small plasma concentration drug cannot be used.

**Types of cream**

1. Oil in water (o/w) cream, example. Vanishing cream
2. Water in oil (w/o) cream, example. Cold cream

**Advantages of topical use of Fluconazole**

1) When applied to skin it gives no irritation and easily water washable.

2) Drug level is minimum in inter and intra patient variation by fluctuation.

3) More safely drug deliver to a specific site.

4) Physiological and pharmacological response is increased.

5) A relatively large area of application in comparison with buckle or nasal cavity.

6) The main objective of study is to treat fungal infection like Candida krusei Candida albicans, Candida tropcialis, Cryptococcus neoformans, Candida glabrata.

7) To avoid the first pass hepatic metabolism.

8) The drug Bio-availability is increased.

9) Better patient compliance can be achived.(6)

**Disadvantages of vanishing cream**

- Due to drug /excipients allergy such as skin may occur at site of application.
- From the topical doses forms larger particles cannot be absorbed.
- Inflammation may occur when applied to skin.

**Ideal Properties of Semisolid Dosage Forms**

Physical Properties

- Smooth texture
- Elegant in appearance
- Non dehydrating
- Non greasy and non-staining
- Non hygroscopic

Physiological Properties

- Non irritating
- Do not alter membrane / skin functioning
- Miscible with skin secretion
- Have low sensitization index

**Application Properties**

- Easily applicable with efficient drug release
- High aqueous washability

**MODE OF ACTION OF SEMISOLID**

**• Local and topical**

In intimate contact with skin with the site of action for a period of time e.g. sunscreen.

**• Localized systemic action**

Penetrate through skin.

Release drugs from base and penetrate across different layers of skin.

Reach local circulation underneath skin o e.g. acne

**Classification of Topical Drug Delivery Systems**

**Classification of Semi-solid doses form are given below**

- Ointment
- Cream
- Jelly
- Gel
- Suppository
- Ointment

**1.5 Physiology of the skin**

Skin is the largest organ of the body. The outermost part of the body is known as skin. Skin has several layers such as outer layer is epidermis, which layer below the epidermis is dermis, which contain several network of blood vessels, sweet gland, hair follicles and sebaceous gland. The subcutaneous fatty tissues lies beneath the dermis.

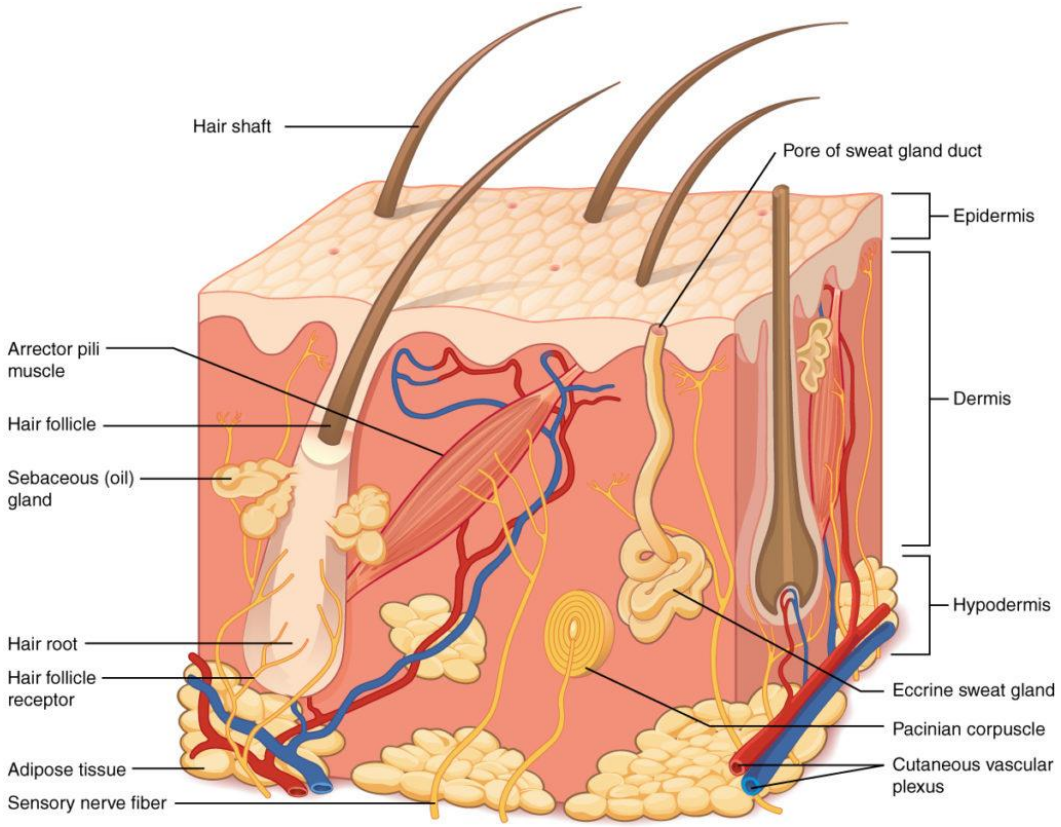


**Figure 1.2: Anatomy of Human Skin.**

**Functions of skin**

- Skin protects from external and internal environment**.**
- It contain body fluid and and tissues.
- It protects from external stimuli like pollution, chemicals, light, radiation, heat, cold,
- It helps in the synthesis of biochemical.
- It helps in metabolism and disposal of biochemical wastes.
- It helps to maintain body temperature and controlling of blood pressure.
- It also works as cushions against mechanical shock.
- It helps to prevents from loss of moisture.
- It reduces harmful effects of UV radiation.
- Skin also acts as a sensory organ (touch, feel, detects temperature).
- It helps to regulate body temperature.
- Skin also works as an immune organ which detects infections etc.

## BIOCHEMISTRY OF SKIN

### Epidermis

The outer layer of skin which acts water-proof barrier of the body is known as epidermis. Squamous epithelial tissue having four kinds of cells is composed of the epidermis layer of skin. Marker cells, Langerhans, Melanocytes and last one is keratinocytes. Our body or internal organ through the external environmental condition such as microbes and other external elements is protected by epidermal layer. To produce keratin protein which helps to keep safe the skin and tissue from heat, microbes and other external chemicals keratinocytes of epidermal layer are responsible. Source of energy for the lower portion of epidermis and lactic acid is end product of the metabolism that accumulates in the skin is glucose. For the pigmentation of skin and brown- black and yellow-red pigment melanin is liable. Melanin supply skin color is produced by melanocytes of epidermal layer. Stratum basal, stratum granulose, stratum spin sum, stratum lucidum and stratum corneum fifth layer present in the epidermal cells as. The entire cellular make-up changes during differentiation from basal cells to stratum conium by degradation of the existing cellular components. Host enzyme of lysosomes an release for intracellular lies is lytic enzymes and the epidermis is reservoir.[8-11]

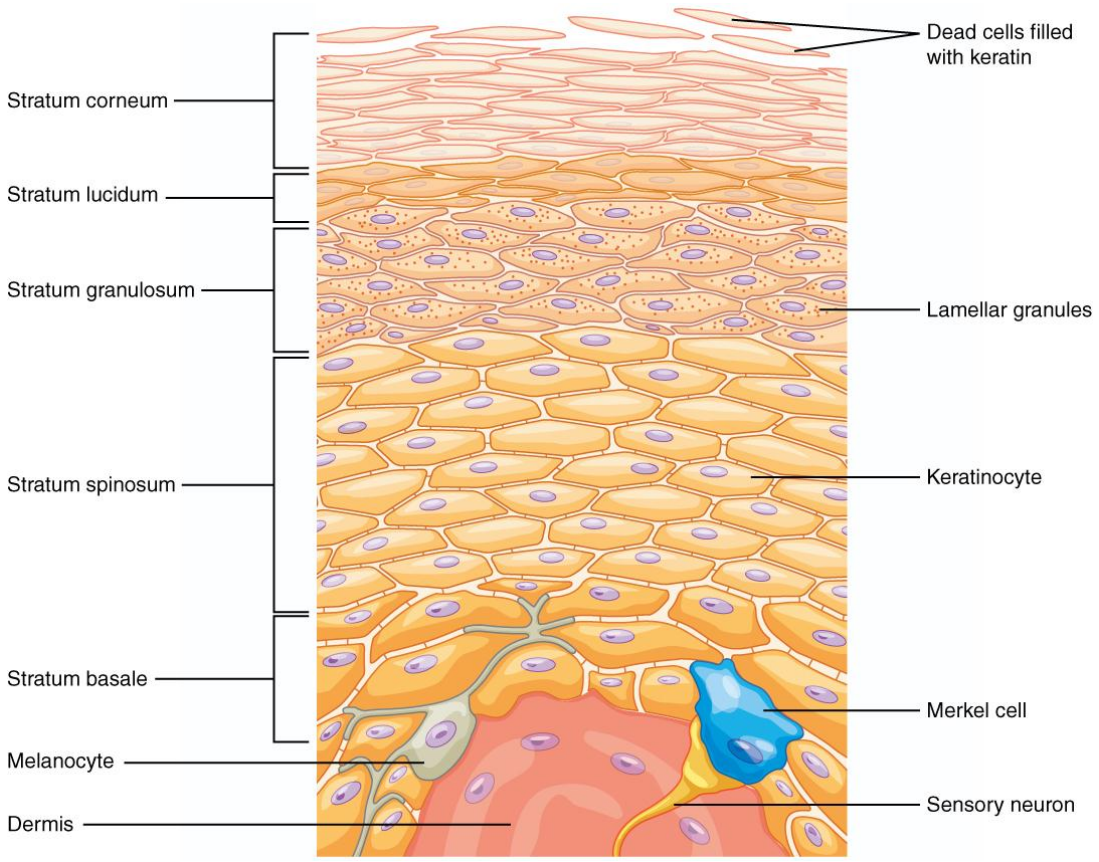


**Figure 1.3: Epidermis layer of skin.**

**DERMIS**

Beneath the epidermis layer and subcutaneous layer the inner layer of skin which is found is known as dermis and despite its larger area of skin, Cellular and a cellular structure is comprising by dermis and composed of hair follicles, blood vessels, nerve, amorphous and fibrous connective tissue, dermal cells and receptors. Due to dermal papillae the surface area of dermis is large. For Several cell types including multi-functional cells of the immune system like macrophages and mast cells the dermis is home.[12,13]

**Hypodermis**

Hypodermis layer composed of the cells called adipose tissue, fibroblast, fat cells, microphages and blood vessels. Hypodermis layer is made up of areolar and adipose tissue.[14]

**Absorption through skin**

Absorption route are identified by two basic pathways.

- **Pathway 1 (Trans-epidermal absorption)**

For cross the skin pathway1 act by diffusing principle and responsible. At the stratum conium when a permeating drug exists at the stratum conium, it enters the wet cell mass of the epidermis and no direct blood supply by the epidermis. A single field of diffusion in models is considered as a viable epidermis.[17-20]

- **Pathway 2 (shunt pathway) absorption**

A “diffusional resistor.” membranes act as Resistance(R) which is proportional to the thickness (h) and inversely proportional to the diffusive mobility of matter to the diffusion coefficient (D), where there is more than one (F) to the fractional area of a route and to the carrying capacity of a phase.[22,22]

R=H/FDK

R =Resistance of diffusion resistor

H = Thickness

F = Fractional area

K = Relative capacity

D = diffusivity

**Basic principle of permeation**

Drugs molecules may penetrate the skin along the hair follicles or sweat ducts in the starting diffusion stage and then be absorbed through the sebaceous glands and follicular epithelium. Diffusion through stratum corneum due to dominant pathway is initiated through Steady state. Under steady condition the membrane-limited flux (J) is described by expression.

$$J = \frac{DAKO/W\ r\ C}{\text{----------}}$$

Where:

J = Amount of drug passing through the membrane system per unit area, per unit area per unit time.

A= Area of the membrane

D= Diffusion coefficient

Ko/w= Membranes / vehicle partition coefficient

C= Concentration gradient

h= Thickness of the membrane.

**Following are the factor affecting topical permeation**

Physicochemical properties of drug substances

Drug solubility

Partition coefficient

PH- condition

Particle size

Concentration

Molecular weight

Polymorphism

**Penetration enhancer**

**Chemical penetration enhancer**

These are classified into following types:

**Solvents**

For penetration enhancer solvents play an important role. Increased penetration of these compounds possibly by pump the polar pathway and/or by fluidizing lipids. Propylene glycol, isopropyl alcohol, glycerin, transcutol-p, water, alcohols, methanol and ethanol.

**Surface active agent**

Agents that increase the polar pathway transport, especially of hydrophilic drugs are surface active agents. To change or alter the penetration function of polar head group and the hydrocarbon chain length is the function of surface acting agents.[29]

**Anionic surfactant**

Surfactants having negative charge on their hydrophilic head that responds to provide excellent detergency properties due to ability to bind positive charge particles are known as anionic surfactant. Interact strongly with skin theses surfactant can penetrate. Some examples of anionic surfactants include are alkyl ether sulfates, sodium dodecyl sulfate, benzyl sulfonates, Decodecylmethyl sulphoxide, Sodium lauryl sulphate etc.[30]

**Cationic surfactant**

These having negative charge on their water loving head unlike to anionic surfactants but is not widely used as skin penetration enhancer so these are known as cationic surfactant. Examples: Dodecyl trimethyl ammonium chloride.

**Non-ionic surfactant**

Examples include: castor oil ethoxylate amines, Pluronic F68 etc.

**Binary system**

Examples are 1, 4-butane diol- linoleic acid and Prolylene glycol -oleic acid.

**Miscellaneous chemicals**

Miscellaneous includes N, N-dimethyl-m-toluidine, urea, calcium thioglycolate etc.

**Physicochemical properties of topical**

**Nature of vehicle**

In this, water hating vehicle (lipophilic) decrease permeation of drug molecule and Water soluble vehicle (Lipophilic) increase permeation of drug molecule.

**Composition of drug delivery system**

In this delivery system, low molecular weight that leads to decrease in permeation is Polyethylene glycols.

**Release characteristics**

In the drug release system, the drug molecules are dissolved or suspended in the delivery system release of drugs depends. From delivery systems to the skin pH of the vehicle the interfacial partition coefficient of drug.

**Penetration enhancer**

These can be achieved by two ways either by chemical enhancer or by physical method.

**Chemical penetration enhancer**

These are classified into following types:

**Solvents**

For penetration enhancer solvents play an important role. Increased penetration of these compounds possibly by pump the polar pathway and/or by fluidizing lipids. Propylene glycol, isopropyl alcohol, glycerin, transcutol-p, water, alcohols, methanol and ethanol; dimethyl sulfoxide, alkyl methyl sulfoxide, alkyl homologs of methyl sulfide, and dimethylformamide and dimethyl acetamide; pyrrolidones- 2 -pyrrolidone, (Ozone), miseellancous solvents-glycerol, silicone fluids, propylene glycol, isopropyl palmitate.sss, These are the some of the examples.

**Surface active agent**

Agents that increase the polar pathway transport, especially of hydrophilic drugs are surface active agents. To change or alter the penetration function of polar head group and the hydrocarbon chain length is the function of surface acting agents.[25]

**Anionic surfactant**

Surfactants having negative charge on their hydrophilic head that responds to provide excellent detergency properties due to ability to bind positive charge particles are known as anionic surfactant. Interact strongly with skin theses surfactant can penetrate. Some examples of anionic surfactants include are alkyl ether sulfates, sodium dodecyl sulfate, benzyl sulfonates, Decodecylmethyl sulphoxide, Sodium lauryl sulphate, etc.[26]

**Cationic surfactant**

These having negative charge on their water loving head unlike to anionic surfactants but is not widely used as skin penetration enhancer so these are known as cationic surfactant. Examples: Dodecyl trimethyl ammonium chloride.

**Non-ionic surfactant**

Least potential for irritation are the properties of non-ionic surfactant.

Examples include: castor oil ethoxylate, Ethoxylated amines, and Pluronic F68 etc.

**Binary system**

Binary system, heterogeneous multilaminated pathway as well as the continuous pathways these systems apparently include. Examples are 1,4-butane dial- linoleic acid and Propylene glycol -oleic acid.

**Miscellaneous chemicals**

Miscellaneous includes N, N-dimethyl-m-toluidine, urea, calcium thioglycolate etc.

**Physical method of topical drug delivery**

Through intact skin by the passage of direct or periodic weak electric current, using an appropriate electrode polarity through an electrolyte solution containing the ionic molecules to be delivered in this process the ionic drug molecule can be transported.

**Phonophoresis**

Phonophoresis is the movement of drugs through living intact skin and into soft tissues under the ultrasound application is called phonophoresis.

**Sonophoresis**

In this process, the drug delivery process that involves the usage of the ultrasound waves is called sonophoresis. In permeation of low frequency ultrasound the ultrasound application has resulted was shown to increase the permeability of human skin by several orders of magnitude too many drugs are included high molecular weight.

**Physicochemical properties of topical**

**Nature of vehicle**

In this, water hating vehicle (lyophobic) decrease permeation of drug molecule and Water soluble vehicle (Lipophilic) increase permeation of drug molecule.

**Composition of drug delivery system**

In this delivery system, low molecular weight that leads to decrease in permeation is Polyethylene glycols.

## EVALUATION PARAMETER

### Identification of Drug

- IR Spectroscopy
- Solubility Studies of drug molecules
- Melting Point determination
- Partition-Coefficient
- Compatibility Studies of drug
- Physical Identification of Drug

### Physical identification of drug

By the physical properties of drug like odor, color, taste, their texture, organoleptic properties the drug molecules was identified.

### Melting Point Determination

In this apparatus small amount of drug molecules fluconazole was taken in clean and empty capillary tube and after that the capillary tube is sealed at one side. After that the capillary tube was kept on visual melting point apparatus or on heater at which the sample was start to melt and the temperature of melting of drug was noted.

### Infra-red spectrum studies

The absorption of infrared light by molecule for the determination of function group present in the sample or molecule caries in these studies. In this identification, the comparison between two sample to each other was identified.

### Partition Coefficient

In this, Partition coefficient is used to identify the hydrophilic/Lipophilic nature of drug molecules which can affect extend of drug absorption as well as the rate of absorption of drug. By the lipophilicity, the partition coefficient of drug is measured and it also have the tendency to cross biological membrane. The log p value of lipophilic drug is much greater than 1 and the hydrophilic drugs has partition coefficient value always less than 1.

Pw/o = (C aqueous/ organic)

Po/w = (C organic/C aqueous)

For partition coefficient using n-Octanol/ buffer and n-Octanol/ water general procedure should followed and at the 250nm the absorbance was taken.

**Drug -excipient compatibility studies**

In this, the drug- excipient is mixed with together in 1:1 ratio and placed it in the borosilicate colored glass vials and in the humidity chamber by maintaining at 400C these vials are placed at 75% Relative Humidity (RH) for 21 days. After these all the sample was observed after 7, 14 and 21 days for identification of any lump formation as well as color change formation. Therefore the FTIR studies are carried out by these all mixtures.

**PH of the formulation**

The pH of formulation was measured by using Ph. meter or Ph. paper.[27], [28], [29]

**Viscosity measurement:** Viscosities of formulations were measured by using Brookfield DV-I viscometer.[30]

**Drug content**

The drug content was determined by UV Spectrophotometry.

**Basic principle of permeation**

Drugs molecules may penetrate the skin along the hair follicles or sweat ducts in the starting diffusion stage and then be absorbed through the sebaceous glands and follicular epithelium. Diffusion through stratum corneum due to dominant pathway is initiated through Steady state. Under steady condition the membrane-limited flux (J) is described by expression

$$J = \frac{DAKO/W\ r\ C}{\text{----------}}$$

Where:

J = Amount of drug passing through the membrane system per unit area, per unit area per unit time.

A= Area of the membrane

D= Diffusion coefficient

Ko/w= Membranes / vehicle partition coefficient

C= Concentration gradient

h= Thickness of the membrane.

**Kinetics of permeation**

For the development of topical formulation, knowledge of skin permeation plays the vital to the successful development.

The following steps involves during the permeation of a drug,

- By stratum corneum Sorption,
- Through viable epidermis penetration of drug,
- By the capillary network in the dermal papillary layer uptake of the drug.

Due to physicochemical properties drug molecule permeation can be possible only.

The skin (dQ/dt) the rate of permeation across is given by:

$dQdt=Ps(Cd-Cr)$

Where,

The concentrations of skin penetrate in the donor compartment and in the receptor compartment are Cd and Cr (e.g., body) respectively.

Ps is permeability coefficient.

By the relationship this permeability coefficient is given:

$Ps=KsDss/Hs.$[23,24]

**Physicochemical properties of drug substances**

Drug solubility

Partition coefficient

PH- condition

Particle size

Concentration

Molecular weight

Polymorphism

**Candida krusei**

Frequent use of fluconazole can select for the emergence of *Candida krusei* as a commonly isolated opportunistic pathogen in some medical centers. Frequent use of fluconazole cause Candida Krusei.(7)

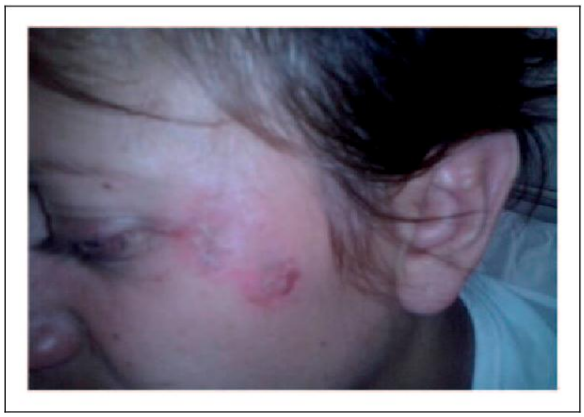

**Fig 1. Candida krusei.**

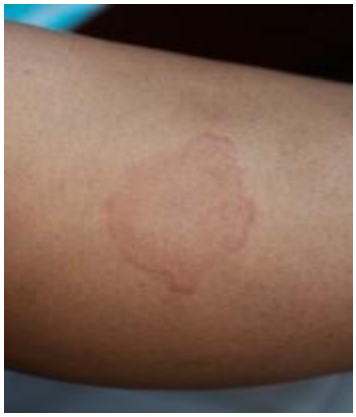

**Fig 2. Candida glabrata.**

**Mechanism of Fluconazole Resistance in Candida krusei**

The first one is an alteration in the target enzyme is called, 14a-demethylase.An accumulation of C14 methylated sterols which likely disrupt membrane structure Inhibition of this enzyme by azoles causes. The another second mechanism is decreased drug accumulation, it mediated by either increased efflux of the drug or diminished uptake *C. krusei* for the determination if fluconazole resistance in *C. krusei* is mediated by one or more of these mechanisms, In addition, fluconazole uptake and cytochrome P-450 content of these organisms were measured. Fluconazole resistance is a 14a-demethylase.

## CONCLUSION

The drug more efficiently to skin tissue such as the epidermis, stratum corneum and dermis when topical formulation of Fluconazole was demonstrated to be able to deliver. Therefore, the topical formulation of fluconazole is promising for the treatment of cutaneous mycoses caused by dermatophytes and other dermatophytosis, Candida krusei, Candida glabrata *etc*.

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