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A REVIEW OF FLUCONAZOLE LOADED TRANSETHOSOMAL GEL FOR CANDIDIASIS

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ABSTRACT

Candidiasis is one of the most common fungal infections. For the treatment, antifungal therapy is used. Fluconazole is considered as most effective as compared to other antifungal drugs. Various disadvantages occur when the drug is administered as conventional form. In this review dealing with the latest form of vesicular system like transethosome. When the drug is incorporated in the form of transethosome which nullify the all the disadvantages when it is formulated in any other conventional systems and there by provide stable and more effective formulation, and also having high patient compliance. Transethosome containing high concentration of ethanol along with edge activator which provide high penetration to the skin and leads to better therapeutic action.

KEYWORDS: Candidiasis, Transethosomal gel, antifungal, bioavailability, chitin, Edge activator.

INTRODUCTION

The fungal infection caused by *Candida* species is known as Candidiasis. In a year worldwide, it affects over 4 billion people. The infection is technically referred to as oidiomycosis, candidosis as well as moniliasis and also commonly called as yeast infection.[1,2] The Candida species belongs to the kingdom Fungi, the phylum Ascomycota, subphylum Mscomycotina, class Ascomycetes, order Saccharomycetales, and lastly the family Saccharomycetaceae.[3] There are more than 150 known Candida species; however, only 15 of those species are of clinical importance: Medically significant *Candida* species

include: *Candida albicans, Candida krusei, Candida tropicalis,Candida glabrata, Candida inconspicua, Candida kefyr, Candida norvegensis, Candida parapsilosis, Candida guilliermondii, Candida lusitaniae, Candida dubliniensis, Candida pelliculosa, Candida lipolytica, Candida rugosa, and Candida famata.*[4]

Humans naturally have small amounts of Candida that live in the vagina, mouth, and stomach and are free from any infections. When there's an overgrowth of the fungus occur which leads to Candidiasis. Among these 90% of the candidiasis is caused by species Candida albicans. Candidiasis, infectious disease produced by the yeast-like fungus Candida albicans and closely related species.[5] Some evidence shows that prolonged treatment with broad-spectrum antibiotics, such as tetracyclines and the chloramphenicol, may predispose to the development of candidiasis, perhaps by killing off normal microbial antagonists to the fungus. Candida is a common organism present in the gastrointestinal mucosa and reproductive system and can be isolated from the oral cavity and hence up to 80% of the healthy population is found to be prone to the most common fungal infections such as candidiasis. Candida species produce infections which ranging from non-life threatening infection such as mucocutaneous to invasive conditions which may leads to life threatening problem and affect vital organs in our body.[6]

The genus Candida has 163 acknowledged anamorphic species, present on the different habitat. The Candida have been discovered primarily in association with human and animals and causes infection in humans which are comparatively restricted natural distribution. Candida albicans are most important species and it is responsible for oral candidiasis, Candidemia and candiduria frequently seen in patients and it is also responsible to cause vaginal thrush in girls at pubeteric age group.[7] In human beings, normal flora is the common sites where the Candida species found. Other sites are skin, gastrointestinal tract and female genital tract particularly higher in vagina during pregnancy. Many times it is reported that the commensally Candida is causes endogenous infections. Many predisposing factors are seen in superficial as well as systemic candidiasis.[8]

Candida may be transmitted by nosocomial i.e. from hospital acquired infection or vertical i.e. from maternal vaginal infection. Candida colonizes of health care workers i.e. 30%. Site of colonization is usually use of broad spectrum or multiple antibiotics, immature immunity, gastrointestinal tract, parenteral alimentation and intravenous fat emulsion, central venous,

catheters colonization with Candida and prolonged urinary catheterization are the predisposing factors for candidiasis in infants.[9]

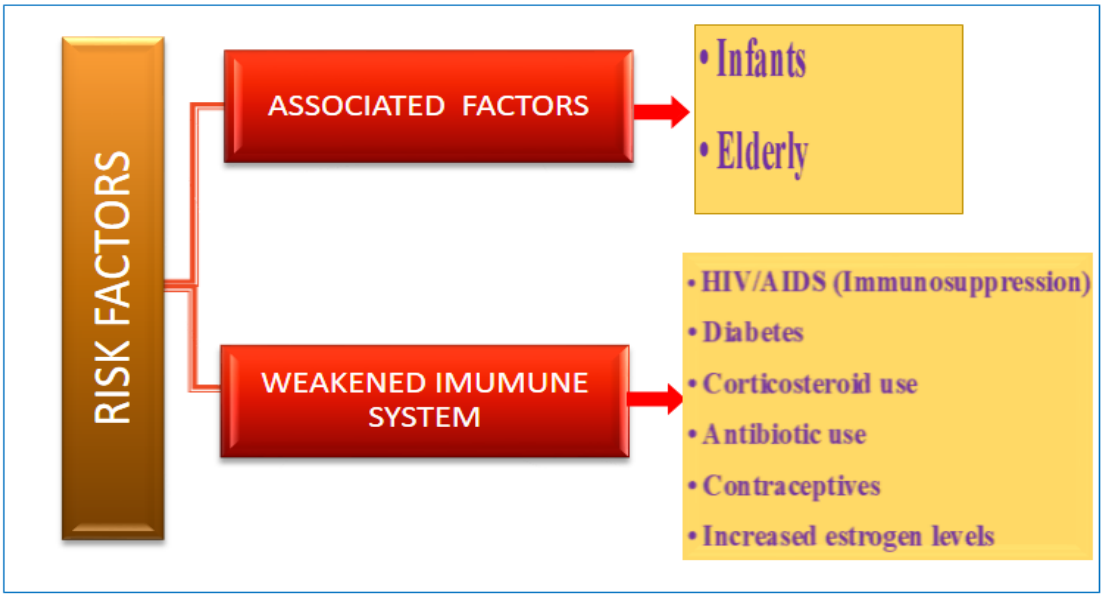

Figure 1: Risk factors of candidiasis.

Morphology

Candida albicans appears in several morphological forms (yeast, pseudohyphae, and hyphae). The morphological transitions from yeast to pseudohyphae and hyphae are reversible. The main difference between yeast and hyphae composition is that the hypha cell wall has slightly more content of chitin than yeast.[10]

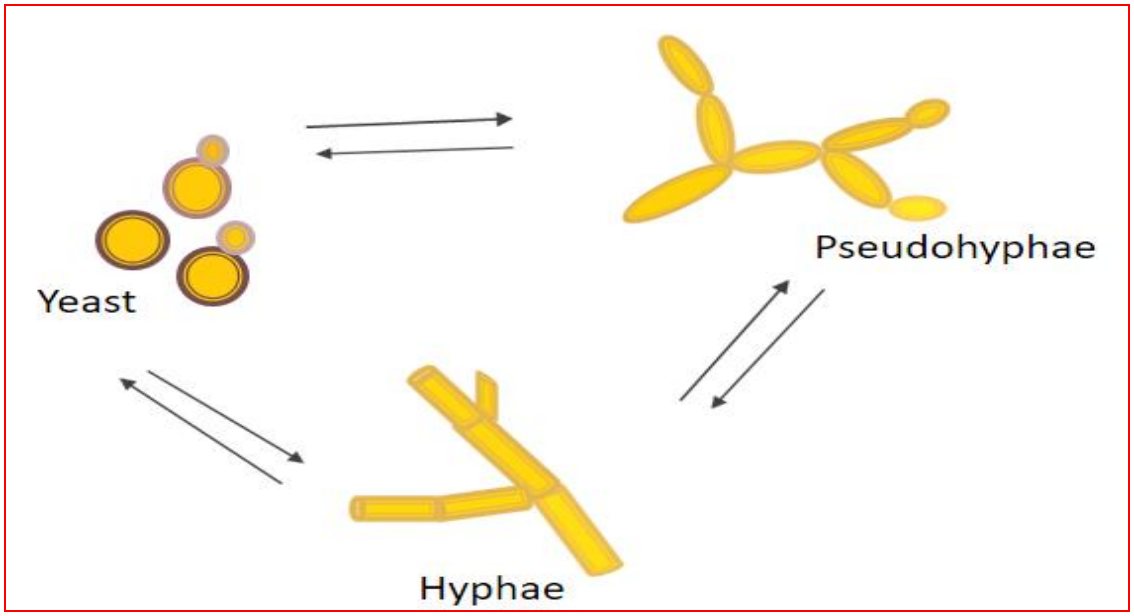

Figure 2: Different forms of candida (Yeast, Pseudohyphae & Hyphae respectively).

Pathogenesis

The term 'Microbiota'means, ecological communities of commensal, symbiotic and pathogenic microorganism found in and on all multicellular organisms. Candida species belongs to microbiota.[11] The mode of transmission is two way. The former one is Endogenous candidaemia in which *Candida* that constitute the microbiota of various anatomical sites under conditions of host weakness behave as opportunistic pathogens. The later one is exogenous, which occurs mainly through the hands of health care professionals. Rare, transmission through person to person can occur between family members or between patients. Other spread of infection are healthcare materials, such as contaminated catheters and intravenous solutions. Being immunocompromised, extreme age, pregnancy, diabetes mellitus, receiving prolonged antibacterial and aggressive cancer chemotherapy or undergoing invasive surgical procedures and organ transplantation are the major risk factors for candidiasis.[12]

C. albicans is an example of dimorphic fungus: it can exist in two form, the ovoid-shaped budding yeast form, which transitions to the branching filamentous hyphae form. To infect its host, C. albicans yeast cells adhere to the host cell using adhesins, the best studied of which are the agglutinin-like sequence proteins and Hwp1. After initial adherence, contact with the host cell there is a transition from the yeast to hypha, directed growth of the hypha occurs through thigmotropism. Invasion into the host cell is then facilitated by adhesion, invasins, and physical forces, and occurs via active penetration or endocytosis. There is a strong correlation between adherence to the host and ability to colonize and cause disease. C. albicans is highly adherent and causes a wide range of diseases.[13]

Virulence factors[14,15]

C. albicans is the most important species among the genus Candida. C. albicans containing various known virulence factors which helps in the spreading of infections in human beings and favours its pathogenicity. The ability of *C. albicans* to infect such diverse host is supported by a wide range of factors known as virulence factors. The virulence factors of the C. albicans have the great role in the pseudohyphae formation by attached with epithelial cells (in respiratory tract), endothelial cells (in blood vessels), hyphal switching, phenotypic switching, surface recognition molecules, and extracellular hydrolytic enzyme i.e. phospholipase and proteinase and production have been suggested to be virulence attributes for Candida.

1. Polymorphism

C. albicans is a polymorphic fungus. That can grow either as round ovoid-shaped budding yeast, or as parallel-walled true hyphae. In between these two there exist another form known as pseudohyphae and are elongated ellipsoid cells with constrictions at the septa. At high pH (> 7) *C. albicans* cells predominantly grow in the hyphal form, while at a low pH (< 6) yeast form is induced. Conditions like the presence of serum or N-acetylglucosamine, starvation, physiological temperature and CO_2 promote the formation of hyphae.

2. Biofilms formation

A further important virulence factor of *C. albicans* is its ability to form biofilms on biotic or abiotic surfaces. Biotic surface include mucosal cell surfaces whereas abiotic surface includes (Catheters, dentures). If the biofilms are mature which cause much more resistant to antimicrobial agents and host immune factors in comparison to planktonic cells. The factors responsible for strong resistance includes, increased expression of drug efflux pumps, the biofilm matrix, complex architecture of biofilms and metabolic plasticity.

3. Secretion of hydrolytic enzymes

Extracellular hydrolytic enzymes appear to play an important role in candidal overgrowth, as these enzymes facilitate adherence and tissue penetration and hence invasion and destruction of the host tissue. Among the most important hydrolytic enzymes produced by Candida are phospholipases, secreted aspartyl proteinases, proteases and lipases. Another most common virulence factor is haemolysin which contributes to candidal pathogenesis.

The secreted aspartic proteases (Saps) is an enzyme secreted by *C. albicans.* There are ten members in the family. Ranging from Sap1–10. Members of Sap1–8 are secreted and released to the surrounding medium, whereas Sap9 and Sap10 remain bound to the surface of cell. Saps 1–3 have been shown to be required for damage of reconstituted human epithelium in vitro, and for virulence in a mouse model of systemic infection.

Phospholipase is another enzyme secreted by *C. albicans*. Seven phospholipase genes have been identified (PLA, PLB1, PLB2, PLC1, PLC2, PLC3 and PLD1); however, the role of the enzymes encoded by these remains unclear.

4. Phenotypic switching

The term dimorphism means the transition between yeast and hyphal growth form. And it has been revealed that both growth forms are important for pathogenicity. As compared to yeast form the hyphal form has been shown to be more invasive and plays an important role in tissue invasion and resistance to phagocytosis. On the other hand the smaller yeast form is believed to represent the form primarily involved in dissemination.

5. Host defects[16]

Defects of host also play a significant role in the development of candidal infections. There exist a host defense mechanisms against *Candida* infection and their associated defects that allow infection include:

- **Cell-mediated immunity:** Chronic mucocutaneous candidiasis, diabetes mellitus, HIV infection, cyclosporine A, corticosteroids.
- **Mucocutaneous protective bacterial flora:** Broad-spectrum antibiotics.
- **Complement:** Hypocomplementemia.
- **Polymorphonuclear leukocytes:** Chronic granulomatous disease.
- **Phagocytic cells:** Granulocytopenia.
- Hypogammaglobulinemia.
- **Monocytic cells:** Myeloperoxidase deficiency.
- **Intact mucocutaneous barriers:** Wounds, intravenous catheters, burns, ulcerations.
- **Monocytic cells:** Myeloperoxidase deficiency.
- Immunoglobulins.

6. Invasion

To invade into host cells *Candida albicans* can utilize two different mechanisms, they are induced endocytosis and active penetration. For induced endocytosis, a specialized proteins is expresses on the cell surface (invasins) by the fungus, that triggering engulfment of the fungal cell into the host cell. It is still unclear exactly which factors mediate this second route of invasion into host cells. Fungal adhesion along with physical forces are believed to be crucial. The enzyme Secreted aspartic proteases (Saps) have also been proposed to contribute to active penetration.

7. Adherence to host surfaces

Adherence to host surfaces is the primary factor in the fungal colonization of human tissues.

There are several cell signaling cascades in both the fungus to control this process. And the environment. In addition, *Candida* can also adhere to the surfaces of medical devices and form and form biofilms. The adhesion phenomenon is exhibited by specialized surface proteins, called adhesins (agglutinin-like sequences), that specifically bind to sugars and amino acids on the surface of other cells or support adherence to abiotic surfaces.

8. Immunity to *candida albicans*

Candida albicans cause severe systemic candidiasis in immunocompromised patients. To activate the innate immune system, it includes various virulence factors. *C. albicans* induces pro-inflammatory cytokine production in various cell types *via* many receptors, and is recognized by this receptors including Toll-like receptors (TLRs) and C-type lectin receptors (CLRs). Toll-like receptors for *Candida albicans* is a transcription factor, which is required for pro-inflammatory cytokine production C-type lectin receptors and can induce pro-inflammatory cytokine and chemokine production in various cell types including epithelial cells, which serve as barriers to oral candidiasis. This microorganism also support phagocytosis *via* CLRs on macrophages.

In case of innate immunity Phagocytosis is one of the first processes. Neutrophils, macrophages, neutrophils, and dendritic cells engulf *C. albicans*. The cell wall components of *C. albicans* (chitins, mannans and glucans) are virulence factors and leads to the activation of phagocytosis.

Classification of candidiasis[17,18]

Candida show a wide spectrum of clinical features and can be classified as superficial, mucosal and invasive candidiasis. *Candida albicans* is an important human yeast pathogen that accounts for the majority of superficial and systemic infections caused by the *Candida* genus.

1. Superficial candidiasis

a) Cutaneous candidiasis

Secondary infection of skin and nail in predisposed patients is known as cutaneous candidiasis. Disease involvement may be generalized or localized in to the skin or nails. Diaper rash, otomycosis, intertrigo candidiasis, candida folliculitis, onychia and paronychia are the spectrum of cutaneous candidiasis. It usually occurs in axillary folds, inguinal or intergluteal areas because of moist, warm and creased condition, and usually leads to

maceration and trauma in skin. It is commonly found in obese and diabetics patients. Other predisposing factors are using oral contraceptives and improper use of antibiotics.

2. Mucosal candidiasis

a) Oropharyngeal candidiasis (OPC)[19]

Also known as 'oral candidiasis or 'oral thrush'. Organisms grow in mucus membranes in the mouth. when other organisms become depleted, The yeasts are able to out compete for the limited resources, and *Candida* takes over in the mouth or throat, it is often called 'thrush' and causes a sore throat along with a white coating in the tongue and mouth. Clinically evident oral candidiasis can be categorized in to three general factors; oral mucosal environment, immune status of host and particular strain of *C. albicans* (hyphal form is usually associated with pathogenic infection) Oropharyngeal candidiasis is one of the most common, oral mucosal infections seen in persons with Human Immunodeficiency Virus (HIV). Predisposing conditions includes epithelial changes, reduced saliva secretion, high carbohydrate diet, changes in commensal flora and local mucosal diseases.

The different types of oropharyngeal candidiasis includes,

- Acute pseudomembranous
- Acute atrophic
- Chronic hyper-plastic
- Chronic atrophic
- Median rhomboid glossitis
- Denture stomatitis
- Angular cheilitis

b) Vulvovaginal candidiasis

Candidiasis in the vagina is commonly called 'Vaginal candidiasis', 'vaginal yeast infection', 'vulvovaginal candidiasis, or 'candidal vaginitis. Vaginal thrush is a yeast infection of the vagina and tissues at the opening of the vagina. This type of yeast infection is caused by the fungus Candida. All women normally have Candida in the vagina without having any symptoms. Sometimes Candida can multiply and cause an infection if the environment inside the vagina changes in a way that encourages its growth. And cause burning sensations along with extreme itching with white discharge.

3. Invasive or systemic candidiasis

Here the infection reaches the blood stream, and also affect vital organ in our body. Severe organ invasive or systemic hematogenously disseminated candidiasis is characterized by spreading of the *candida* cells into almost the entire body with a tendency to create abscesses in vitally important organs inducing their failure which leads to mortality. Hyper- and/or hypothermia, hypotension, tachycardia, high white blood cell counts are the clinical signs of ongoing systemic candidiasis. Consequence of some invasive medical procedures, Immunosuppressive therapy and aging are the other sign.

Prevention of candidiasis[20]

- Keep skin clean and dry.
- Adjusting food preference.
- Avoiding frequent use of antibacterial soaps.
- Take medications as directed by a doctor.
- And follow a healthy lifestyle.
- Antifungal Therapy.

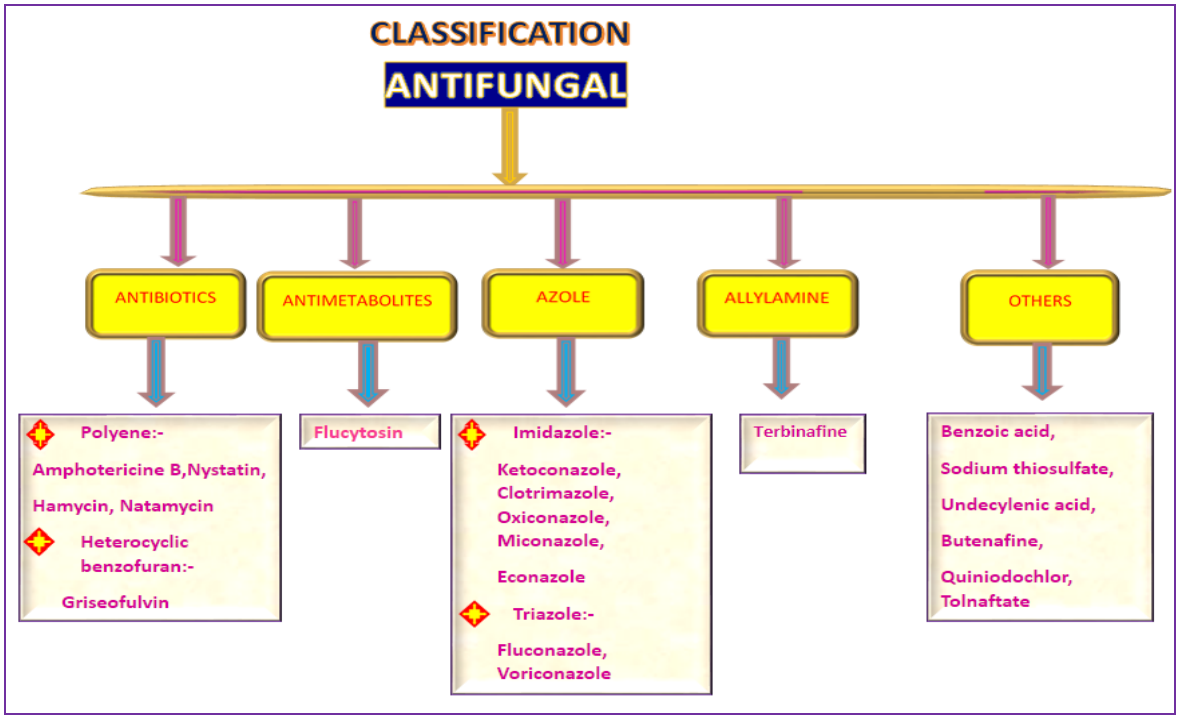

Figure 3: Classification of antifungal drugs.

From the given Antifungal class of drug we can say that Fluconazole is more effective for the treatment of candidiasis, since it have less side effect as compared to any other antifungal

class of drug. Fluconazole is chemically 2-(2, 4-difluorophenyl)-1, 3-bis (1H-1, 2, 4-triazol-1-yl)-2-propanol, a synthetic triazole derivative antifungal agent that has been shown to be effective against a wide range of fungal infections like superficial and systemic, following both oral and intravenous administration.[21] For the treatment of Candidiasis, Fluconazole remain one of the most frequent prescribed triazole because of its excellent bioavailability, readily absorbed, tolerability, less endocrine effect, good brain as well as CSF(Cerebro Spinal Fluid)penetration, absorption does not affected by food, pH or disease state and having excellent tissue penetration. It is new existing drug.[22]

Mechanism of action

Fluconazole is an oral synthetic bis-triazole compound that inhibits the cytochrome P_{450}-dependent enzyme 14α alpha-demethylase step in the formation of ergosterol. This leads to disruption in a number of membrane-associated cell functions. This enzyme necessary for the convertion of lanosterol in to ergosterol.[23]

- ✓ Interept the synthesis
- ✓ Depletion of ergosterol
- ✓ Increased membrane permeability
- ✓ Inhibit the fungal growth[24]

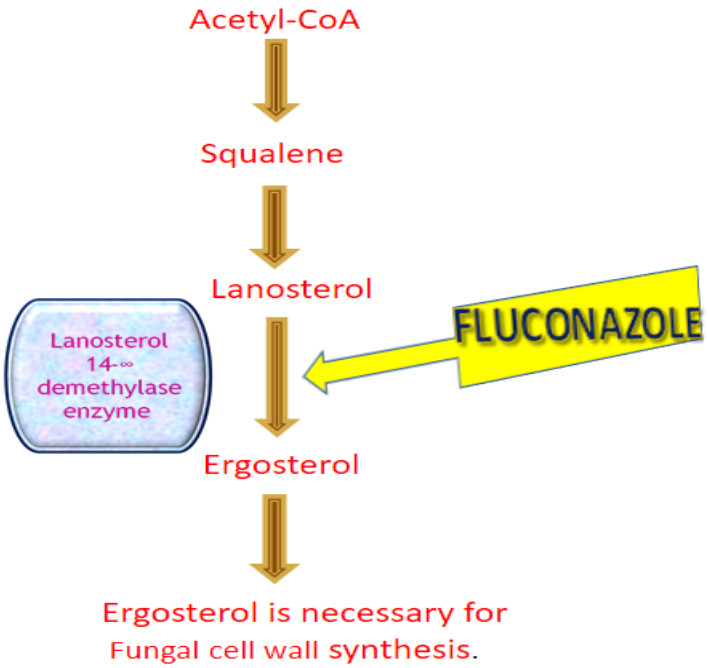

Figure 4: Mechanism of action of fluconazole on candida.

However the major demerit of fluconazole is, it is not recommended in pregnant ladies & lactating mothers. Other demerit include the drug cause side effect like nausea, vomiting, abdominal pain, rash, headache, kidney damage and liver damage. Incidence and severity of these side effect depend on dose and duration of therapy.[25] So that oral delivery is not preferred. Transdermal drug delivery is one of the attractive route for drug delivery due its easy accessibility.one of the advantage over oral form is lower fluctuation in plasma drug level. The major disadvantages of transdermal delivery is low permeability of skin limit number of drug which can be delivered in this manner.[26] Novel drug delivery is newer method for the delivery of molecules. Here the medicaments is selectively targeted or delivered only to its site of action other than non-target area. There is an increase in concentration of the medication in some parts of the body compared to other. Conventional liposome do not penetrate deep into skin but remain accumulate to the upper layer of the strateum corneum. They show inability to cross the SC. To overcome the stratum corneum barrier of skin, for the passage of drugs, a new drug delivery system has to be used.[27]

Hence new class of lipid carrier such as ethosome and transferosome were developed to enhance the delivery of drug molecules. Ultra deformable vesicles (UDV) have recently become a promising tool for the development of improved and innovative dermal and transdermal therapies. Deformable vesicles like transethosomes present the advantages of being nontoxic, biocompatible, biodegradable and thermodynamically more stable formulations. They have been used for dermal and transdermal delivery of many molecules including proteins and peptides. In addition, their production is relatively simple and easy to scale up. Compared to conventional liposomes, deformable vesicles have higher entrapment efficiency and higher potential in skin penetration. These are bilayer biocompatible vesicular drug delivery systems that are used for many drugs for their biochemical, cosmetic, veterinary and therapeutic purposes. The first group consists of penetration enhancer containing vesicles ethosomes. The second group comprised of deformable vesicles, such as transfersomes and non-ionic surfactant–based flexible vesicles.[28]

The term transethosomes and the underlying concept were introduced by Song et al., in 2012, and are characterized by having a high content of ethanol (30% to 40%) together with an edge activator, the backbone of the transethosome. Transethosomes may contain advantages of both transfersomes and ethosome. The mechanism of skin penetration might be a fusion of both mechanisms. Thansethosomes shows the presence of phospholipid like

phophatidylcholine, high amount of ethanol, permeation enhance or edge activator. Vesicles have irregular spherical shape. Depending upon the drug their size lies between 40 nm to 200 nm.[29]

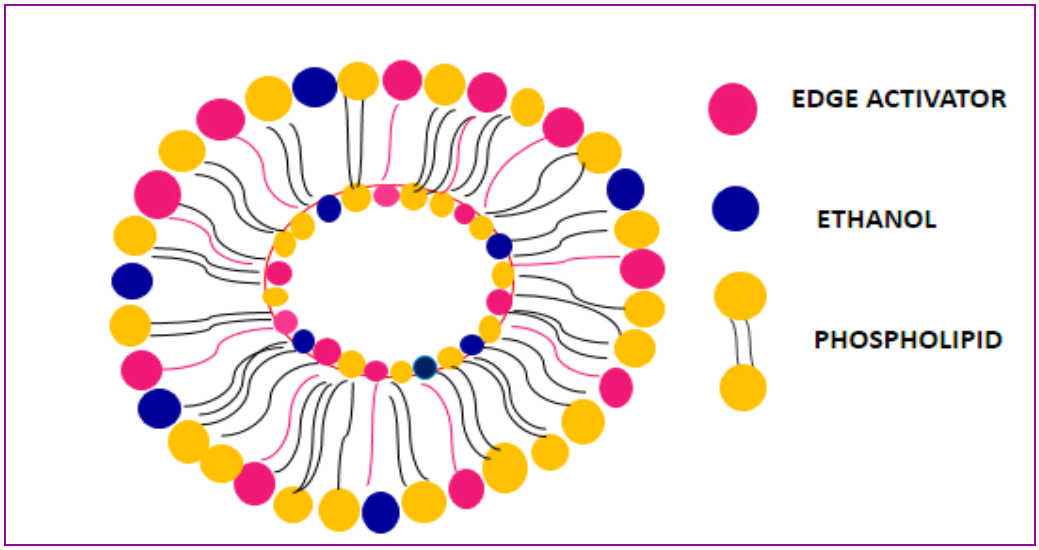

Figure 5: Structure of transethosome.

Advantages of transethosome[30,31]

- The raw materials used in the formulation are non-toxic in nature.
- Passive, non-invasive and is available for immediate commercialization.
- Avoidance of first pass effect.
- The transethosomal drug is administrated in a semisolid dosage form.
- It enhance drug permeation through skin for transdermal drug delivery.
- This drug delivery system shows better stability as compared to other conventional vesicles forms.
- Transethosomal drug delivery can be applied to many fields including cosmetic and veterinary fields.
- It shows high patient compliance as it is administered in semisolid form like gel or cream.
- As compared to liposomes, transethosomes improve skin delivery of drugs both under occlusive and non occlusive condition.
- Simple method of drug delivery as compared to sonication, iontophoresis, laser surgery, cryo surgery and other complicated methods.
- Direct entry of bioactive molecules into systemic circulation.

Disadvantages of transethosome

- Adequate solubility of the drug in both aqueous environments and lipophilic medium to reach dermal microcirculation and gain access to the systemic circulation.
- Sometimes cause skin irritation or allergic reaction on contact dermatitis.
- Formation of unsuccessful vesicles can coalesce Transethosome.
- Product loss during transfer from organic and water media.

Salient features of transethosomes[32,33]

- Easy to prepare, does not involve tedious process and also avoid the unnecessary use of pharmaceutical additives, can be used for both topical as well as systemic delivery.
- They are highly flexible so have higher flux rate across skin and higher rate of skin penetration as comparison to other vesicular systems.
- Encapsulated drug is protected from the degradation as due to which they release their content slowly and gradually.
- The entrapment efficiency is high, as they are biodegradable and biocompatible in nature.
- The drug having high molecular and low molecular weight can be entrapped.

Mechanism of transethosome

The drug absorption through transethosome probably occurs in following two phases.

- Ethanol effect.
- Transethosome effect.
- Ethanol effect

The high concentration of ethanol (30-40%) present in the transethosomes, this ethanol penetrates into the lipids present in the intracellular space of the skin and decreases its density and make it flexible. When the concentration of the ethanol is reduced from 20% may lead to increase in the size of vesicle.

- Transethosome effect

Permeation enhancer (like tween 20, tween 60, tween 80, span 60, span 65, span 80, sodium cholate, sodium deoxy cholate etc.) present in the transethosome which disrupt the intracellular lipids from stratum corneum. When the intracellular lipids disrupt pores of the skin becomes wider and facilitates the permeation of system across the skin.

The penetration of the transethosomes mechanisms can be described in 3 way

- ♠ There occur an interaction between hydrophilic lipid and water which makes the polar lipid to attract water molecules induce hydration, then the lipid vesicles moved to the site where there is a higher water concentration, the difference in water contents across skin stratum and epidermis develops transdermal osmotic gradients that leads to penetration of transethosomes across skin.
- ♠ Transethosomes induce hydration which leads to widen pores due to it there is gradual release of drug occurs that binds to targeted organs.
- ♠ Transethosomes act as penetration enhancer which disrupt the intercellular lipid, which results in widen of pores and increase the permeation of system through skin.

Application[34,35]

1. Delivery of Antifungal Drugs: Transethosomes containing amphotericin B, terbinafine, ketoconazole showed enhanced permeation. Also voriconazole transethosomes showed skin permeation and deposition as compared to that of conventional liposomes, deformable liposomes and ethosome.
2. Delivery of Non-steroidal Anti-inflammatory Drugs (NSAIDs): Oral administration of NSAIDs are associated with various GI side effects. Hence transdermal delivery system using ultradeformable vesicles is preferred. Transethosomes containing ketorolac tromethamine show better penetration than drug containing ethosomes. Garg V et al., recently proved that piroxicam transethosomal gel was found to be superior in all aspects as compared to other vesicular form with highest elasticity and improved stability.
3. Delivery of Anticancer Drugs: Imiquimod was investigated using transethosome technology. The results were found to be favourable and provided a new approach for skin cancer treatment. Transethosomes showed better penetration and increased transdermal flux due to high elasticity. Transethosomes retained its penetration power even after storage.
4. Issues and Future Progress Related to Ethanol Based Vesicles for Transdermal Drug Delivery: Most of the active molecules do not pass through stratum corneum due to barrier. Ethanol based carriers have opened a new window to deliver various bioactive molecules transdermally as they have ability to fluidize and disturb the rigid lipid system of stratum corneum. These systems represent non-invasive and efficient drug delivery approach for large and medium sized bioactive molecules along with high patient compliance and low cost treatment. However, effective clinical exploration of the ethanol

based nanocarrier system is still a challenge. It is very necessary to evaluate them clinically to check their potency. Ethanol based carriers need safety exploration in some specific clinical conditions like their application to open areas of eczema as ethanol show irritant effect to skin. So, further research in this field will promote effective drug release.

5. Better permeation for anti-inflammatory drug activity.
6. Improved Transdermal flux.
7. Increase penetration across skin.
8. For Transdermal immunization.
9. Increase entrapment efficiency and skin permeation.
10. Ethosomes are used in pilosabeceous targeting.
11. Transdermal Delivery of Hormones.
12. Delivery of Anti-Arthritis Drugs.
13. Delivery of Antibiotics.
14. In the treatment herpetic infection.
15. Transcellular Delivery.

CONCLUSION

For the treatment of fungal infections like candidiasis, antifungal class of drug is used. As compared to other drug, fluconazole having less side effect and excellent pharmacokinetic profile. Oral form may show various disadvantages. Therefore, the development of a novel carrier system for transdermal delivery is required to minimize these disadvantages. The fluconazole- loaded transethosomes showed high stability, prolonged release of the drug, and excellent in-vitro skin permeation to the deeper skin layers. Based on this it can be considered that transethosomal gel may be a promising carrier to deliver drug through transdermal route.

They provide safety, efficacy and more patient compliance hence are more superior to any other vesicular system. Transethosomes have become promising carriers not only for topical treatment of local but also for systemic disorders. They can be explored in the future for delivery of various drugs through transdermal delivery. Formulation of transethosome in the form of vesicles in gel may improve their viscosity and hence increase their residence time on the site of action.

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