REVIEW ARTICLE

Transethosomes a Novel Transdermal Drug Delivery System for Antifungal Drugs

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ABSTRACT

The skin, particularly the stratum corneum considered a barrier to the entry of drugs, antifungal drugs, are widely used for the treatment of fungal infections and they are given either systemically or topically. Antifungal drugs are not fully effective due to many factors like poor skin penetration, inability to reach target sites, short residence time, systemic side effects, and low bioavailability due to hepatic metabolism which in turn require high or frequent dosing and decrease the compliance of the patients, Hence approaches have recently been focused on a novel transdermal drug delivery of antifungal drugs, one such approach are vesicular nano-carrier delivery systems these systems can produce sustained release of the drug, which minimizes the side effects, The frequency of dosing and increase patient compliance. Transethosomes as a novel vesicular carrier system introduced to minimize these drawbacks of antifungal drugs. Transethosomes increase the stability and solubility of antifungal drugs and hence increasing their efficacy in eliminating the infection. The drug is given as a semisolid dosage form lead to increase patient compliance.

Keywords: Antifungal, Drug Delivery, Transethosomes, Transdermal, Vesicular Delivery.

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INTRODUCTION

Fungal infections can affect skin and mucous membrane. It can lead to the production of systemic infections of different internal organs. Skin fungal infections (SFI) can be grouped into three categories, i.e., superficial, cutaneous, and subcutaneous, according to the scale of tissue damage.[1] Figure 1 gives a summary of SFI.

Antifungal drugs are used to treat and stop the development of skin fungal diseases (SFD). These drugs discovered over the years do not significantly affect drug resistance, inability to reach target sites, short residence time, poor bioavailability, lack of penetration, etc. So to overcome these challenges, novel delivery systems are being explored for effective delivery of these drugs. Vesicular nano-carrier delivery systems (VNCDS) is one of such methods; these include liposomes, niosomes, ethosomes, transferosomes, transethosomes, etc.[2] Topical therapy is the most common and used to manage mucosal and cutaneous fungal diseases this provides advantages including the delivery of drugs to the site of infection and decreasing the side effects of drugs. However, in some issues, topical therapy decreases patient adherence to the therapy due to the side effects produced by these antifungals like redness, burning, or swelling of the skin. Furthermore, candidiasis fungal infections are difficult to be treated due to the insufficient and low penetration ability of the drug to reaches the infected site and inadequate deposition in the skin, producing limited topical bioavailability. Noticeably, most of the currently available antifungal agents are highly lipophilic, and with poor aqueous solubility, this will lead to a low release rate of drugs into the skin.[3] Vesicular delivery systems (VDS) can produce the drug's sustained release, minimizing the side effects, the frequency

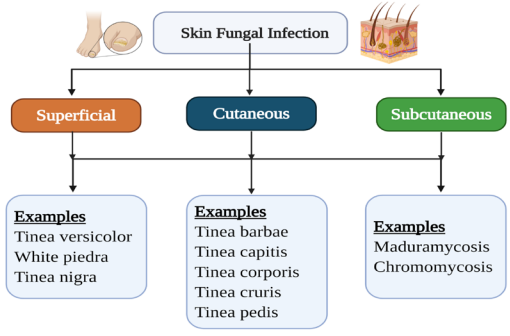

Figure 1: Skin fungal infections according to the site of penetration of fungus into the skin. Created with biorender.com (Source: Personal collection).

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of dosing, and increasing patient compliance.[4] Figure 2 shows the advantages of VDS for topical delivery.

So in this review, the aim was to show the utility of transethosomes as a novel vesicular delivery system for effective and safe treatment of fungal skin infections.

STRUCTURE OF THE SKIN

The stratum corneum is farthest layer of the epidermis. It is composed of 10–25 of highly keratinized layers of longitudinal, dead corneocytes; these layers are anchored in the lipid bilayers matrix. It has been explored that the stratum corneum is the main barrier of the skin that prevents permeation. When a topical formulation is applied to skin, the active drug has to enter through the stratum corneum. The factor that restricts these processes is the slow diffusion of the material through the dead horny layer of skin. The stratum corneum acts as a hydrophobic membrane. The passage rate of low and high molecular weight organic non-electrolytes is generally determined within the stratum corneum.[5] Figure 3 represents the structure of the skin.

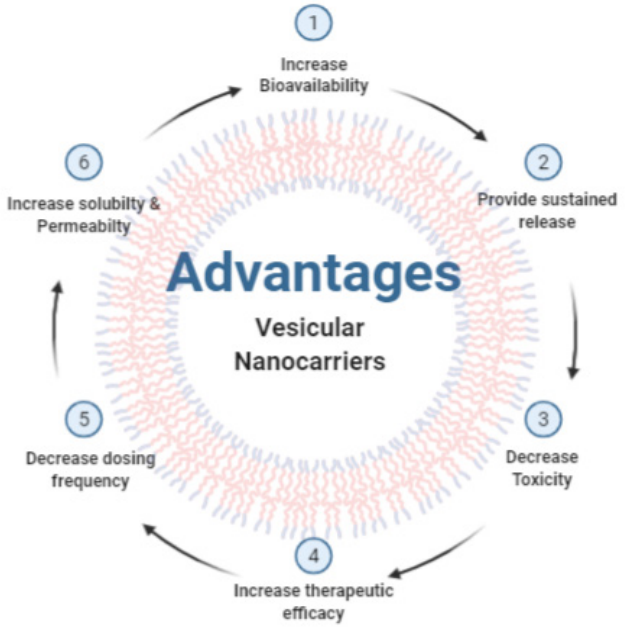

Figure. 2: Advantages of VDS for topical delivery "Created with BioRender.com"(Source: Personal collection)

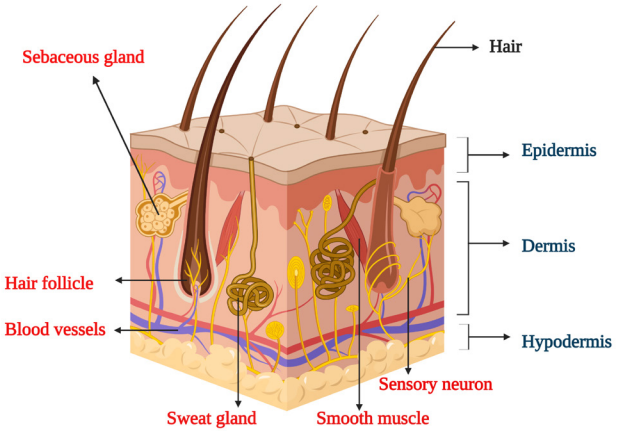

Figure 3: The structure of the skin "Created with BioRender.com" (Source: Personal collection)

NOVEL VESICULAR NANOCARRIER SYSTEMS

Numerous approaches have been used to facilitate the passage through the skin's stratum corneum (SC) barrier.[6] Stratum corneum or horny layer of the skin represents the challenging barrier that does not permit the crossing of most of the drugs, except lipophilic drugs and those with low molecular weight. Vesicular nano-carrier or ultra-deformable vesicles (UDV) recently represent a promising approach for the advanced and improved transdermal delivery of drugs. Deformable vesicles like transethosomal formulations show the advantages of being nontoxic and stable thermodynamically. Deformable vesicles have been used as a tool for dermal and transdermal delivery of many substances like peptides and proteins. Also, their production is very simple and easy to scale up.[7] Figure 4 represents the vesicular nano-carriers.

The exact theory of transethosomal permeation and penetration through the skin is not fully clear. The combination of phospholipids and the ethanolic effect is believed to be responsible for the distribution of the drug deeper and passage into the skin layers.[6] Transethosomes are irregular and spherical and have higher skin permeation/penetration as well as higher elasticity studies. This is due to the combination of ethanolic effect and edge activator or surfactant that makes a change in the lipid bilayer of these vesicles.[8] The extent of flexibility and partition coefficient are the major determinants that define the movement of transethosomes across the cutaneous layer. Transethosomes movement through the stratum corneum layer is facilitated by hydration force. Because another three layers are greater than Stratum corneum fluid content, due to which fluid gradient created. The passage through skin by osmotic strength theory has been explained by Cevc *et al.*[9] The drug can be easily released in the stratum corneum, pass through the different layers of skin, and reach systemic circulation. Transethosomes are deforming themselves to enter through the intercellular space of stratum corneum. Ethanol and edge

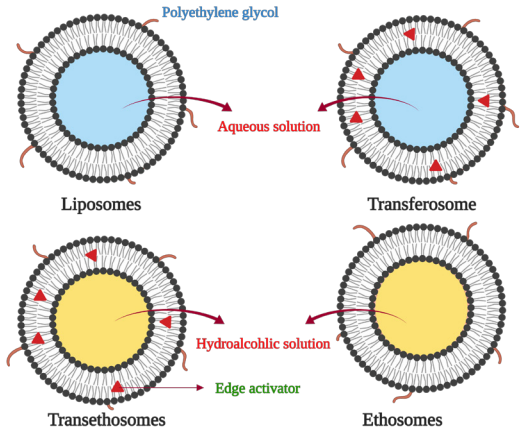

Figure 4: Vesicular nano-carriers used for topical antifungal drug delivery "Created with BioRender.com" (Source: Personal collection)

activator in vesicles enhance the flexibility and fluidity and due to the elastic nature of the vesicles that can easily move through the narrow intercellular spaces.[9] The penetration mechanism of transethosomes is shown in Figure 5.[10]

TYPES OF ETHOSOMAL SYSTEM

Classical Ethosomes

They are a new generation of conventional liposomes, ethanol of concentration up to 45% w/w, phospholipids, and water are the main ingredients of them. Classical ethosomes, according to the reports, were more effective than classical liposomes because they were small in size and had negative ζ-potential and the higher ability for drug entrapment, and these are very important in transdermal delivery. Furthermore, skin penetration and stability profiles are higher compared to classical liposomes.[11,12]

Binary Ethosomes

They were presented by Zhou *et al*.[13] using a different type of alcohol like propylene glycol added to the classical ethosomes introduces the binary ethosomes. Alcohols used commonly in binary ethosomes are isopropyl alcohol (IPA) and propylene glycol (PG).[14]

Transethosomes

Transethosomes are recent vesicular nano-carrier systems that have the advantages of both transfersomes and ethosomes.[15]

Transethosomes are recently discovered ethosomal systems and considered a new generation and were first reported by Song *et al*. in 2012.[16] these vesicles were designed to share the benefits of both classical ethosomes and deformable lip (transfersomes) to introduce transethosomes.[17] Edge activators and permeability enhancers of different types have been used to produce transethosomal systems with better features. According to the reports, drugs of molecular weights of 130.077 Da to 200–325 kDa can be entrapped with transethosomes.[17] Figure 6 shows the three types of ethosomal systems, according to their compositions.

ADVANTAGES OF TRANSETHOSOMES[7,18]

- Increased drug permeation through the skin for transdermal drug delivery (TDD).
- Nontoxic raw material
- Higher stability
- Transethosomal drug administrated in a semisolid dosage form.
- Bypass first-pass metabolism effect of the liver.
- Biocompatible and biodegradable

DISADVANTAGES OF TRANSETHOSOMES

- Loss of product during the transfer from alcoholic and water media.[18]
- Skin irritation or allergic reaction on so it's not suitable for patients with allergic dermatitis.[18]
- Coalescence leads to unsuccessful vesicle formation.[18]
- The drug should be of a reasonable molecular size to be absorbed percutaneously.[9]

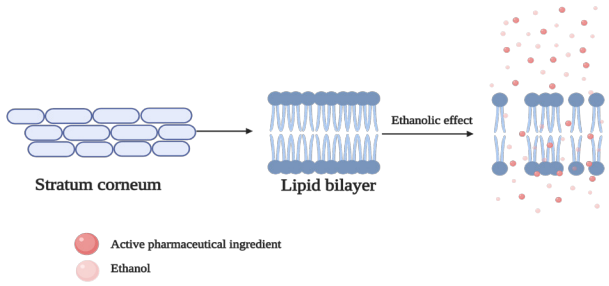

Figure 5: The penetration mechanism of transethosomes "Created with BioRender.com" (Source: Personal collection)

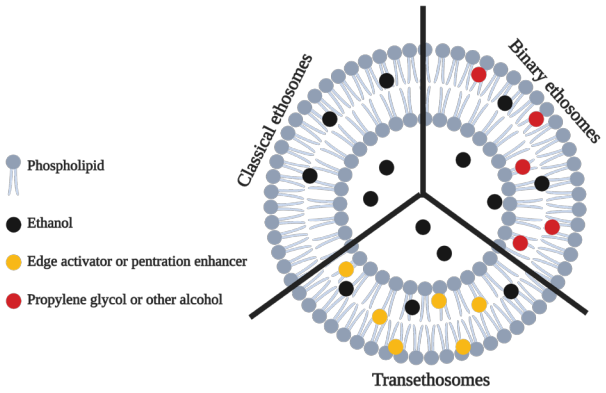

Figure 6: The different types of ethosomal systems "Created with BioRender.com" (Source: Personal collection)

Table 1: The comparison between ethosomes and transethosomes[17]

Parameter	*Binary ethosomes*	*Transethosomes*
Ingredient	1. Phospholipids 2. Ethanol 3. Propylene glycol or other alcohol 4. Charge inducer 5. Water 6. Drug	1. Phospholipids 2. Ethanol 3. Edge activator (surfactant) or penetration enhancer 4. Charge inducer 5. Water 6. Drug
Shape	Spherical	Regular or irregular spherical shape
Entrapment efficiency	Higher than classical ethosomes	Higher than classical ethosomes
Skin permeation	Typically equal to or higher than classical ethosomes	Higher than classical ethosomes
Size	equal to or smaller than classical ethosomes	depending on type and concentration of permeability enhancer or edge activator used
Stability	Stable than classical ethosomes	No particular trend determined

- Information about the toxicological profile of transethosomes is not known.[10]
- Sensitivity to light leads to degradation, so, antioxidants such as α-tocopherol are added to the formulation.[7]
- Safety examination for ethanol-based nano-carriers needed in some specific conditions like their application to open areas of eczema and dermatitis since ethanol can irritate the skin.[7]

METHODS OF PREPARATION

Transethosomes are prepared by using cold technique and hot technique**.**

Cold Method

This technique is the most commonly used for transethosomes production. This method includes dissolving lipids in ethanol with continuous stirring at room temperature followed by the addition of edge activator and heating the mixture up to 30°C with vigorous agitation. Then stirring of the mixture is for 5 minutes in an enclosed vessel. Water is heated up to 30ºC in a separate container and added to the alcoholic mixture gradually in a fine stream. Also, sonication is done to reduce the size of transethosomes.[7,19,20] Finally, the formulation is kept under refrigeration.[11] The cold method has been shown in Figure 7.

Hot Method

Phospholipid dispersed in water and heated in a water bath up to 40ºC to get a colloidal solution. Ethanol and glycol mixture maintained at temperature 40ºC. The phase that contains ethanol and glycol is added to the aqueous phase—stirring for 7–10 minutes. According to the hydrophilic or hydrophobic properties, the drug can be dissolved in water/ethanol. Temperature is kept at 40ºC throughout the procedure. The size of the transethosomes is reduced by sonication.[15] Figure 8 represents the hot method technique.

Mechanical Dispersion Method

Lipid and surfactant are taken in a clean, dry, round bottom flask, and the mixture is dissolved in ethanol. This method was enhanced by combined hydration of the thin-film and ultrasound homogenization. A thin lipid film is produced using a rotary evaporator above the lipid transition temperature. The excess organic solvent is removed by keeping it overnight under

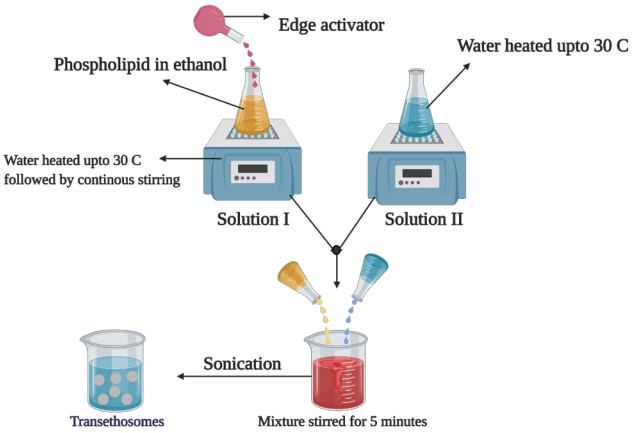

Figure 7: Preparation of transethosomes using the cold method "Created with BioRender.com" (Source: Personal collection)

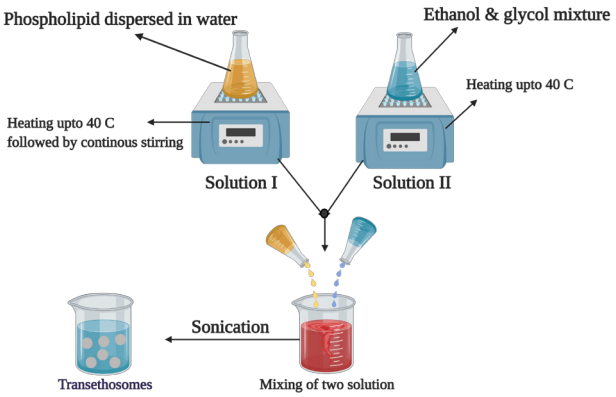

Figure 8: Preparation of transethosomes using hot method "Created with BioRender.com" (Source: Personal collection)

MATERIALS COMMONLY USED IN PREPARATION OF TRANSETHOSOMES

Table 2: Materials used in transethosomes[7]

Class	*Examples*	*Role*
Phospholipid	Egg phosphatidylcholine Hydrogenated soy Phosphatidylcholine Soya phosphatidylcholine Distearyl phosphatidylcholine	Vesicle forming unit
Alcohol	Ethanol	Imparts softness and act as a penetration enhancer
Surfactant	Sodium deoxycholate Sodium cholate Span 80 Tween 80	Flexibility to the vesicles
Dye	Rhodamine 123 Fluorescein-DHPE Rhodamine-DHPE Nile-red	Characterization
Buffering agent	Saline phosphate buffer pH 6.4	As a hydrating agent

Table 3: List of recently reported literature for various types of transethosomes used for delivery of antifungal

Drug	*Study finding*	*Year*	*Reference*
Ketoconazole	The study showed that the novel vesicular system consisted of a high concentration of ethanol or edge activator, significantly increased the skin retention of ketoconazole compared to classical liposomes	2015	[24]
Voriconazole	Transethosomes were better than other vesicular carriers in improving the skin permeation and skin deposition of voriconazole in the dermis/epidermis site.	2016	[26]
Econazole	Transethosomes loaded econazole nitrate are adequate to deliver the drug transdermally in a controlled manner for effective treatment of cutaneous infections	2018	[23]
Terbinafine	Transethosomes that contain edge activators (e.g., surfactants) or penetration enhancers change the drug thermodynamic activity and increase the drug penetration by solubilizing it in the subcutaneous lipids.	2020	[25]

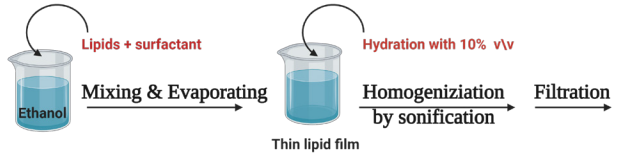

Figure 9: Preparation of transethosomes using Mechanical Dispersion Method
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a vacuum. Hydration of the film is with 10 % v/v ethanol in phosphate buffer pH 6.5 by rotation at 60 rpm. The drug is then added to the formulation.

The transethosomes are sonicated to reduce their size.[7] Homogenization of the transethosomes for 5 minutes by sonification. Next, filtering off using a 0.22 µm filter.[10]

CHARACTERIZATION PARAMETERS OF TRANSETHOSOMES

Morphology of Transethosomes

Using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), visual imaging of transethosomes can be done. Transethosome under electron microscopy shows that a formulation has a 300–400 nm vesicular size in diameter. Vesicles obtained are flexible because of their improper round shape.[22]

Vesicle size and Zeta potential

Particle size and zeta potential can be measures using dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).[20]

Entrapment Efficiency

The efficiency of the transethosomes to entrap the drug can be measured using the ultracentrifugation method. Transethosomes will be centrifuged at high speeds and the free drug present in the supernatant layer will be measured using a suitable analytical technique[22]

Transition Temperature

The transition temperature of transethosomes can be measured by using differential scanning calorimetry (DSC).[7]

Drug Content

UV spectrophotometer can be used to measure the drug content of transethosomes. This can also be measured quantitatively by a modified high-performance liquid chromatographic method (HPLC.[7]

Vesicle Stability

The stability of the transethosomes vesicles can be detected by assessing the vesicle size and structure periodically after a while using DLS and TEM. [10]

Skin Permeation Determinations

The ability of the transethosomes to penetrate the layers of the skin can be determined by using confocal laser scanning microscopy (CLSM).[22]

In-vitro Drug Release

Permeation rate is determined. To optimize the formulation before the more expensive in-vivo studies are done, the time required to establish steady-state permeation and the permeation flux at steady-state and the information obtained from in-vitro studies are used.7

CONCLUSION

The therapeutic efficacy of antifungals is limited due to unfavorable physicochemical properties and their toxicity profiles. Transethosomes as a novel carrier utilize their unique properties like high biocompatibility, ease of surface alteration, and smaller size to minimize these antifungal drugs' disadvantages. The stability profile, solubility profile, and targeting power of antifungals to the infected tissues can be improved using transethosomes and then increasing their efficacy. Increased patient compliance is achieved since the drug is given as a semisolid dosage form. Transethosomes are not restricted only to the topical treatment of local diseases; they are becoming a promising approach for systemic diseases.

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