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A REVIEW ON: TRANSETHOSOMES AS NOVEL VESICULAR CARRIERS FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin which is the largest and most accessible organ of human body through its layers to the circulatory system. Transdermal drug delivery offers many advantages over conventional injection and oral methods but the skin, particularly stratum corneum acts as a barrier to most drug absorption, so novel vesicular drug delivery systems such as liposomes, niosomes, ethosomes, transferosomes and transethosomes has been developed to overcome this limitations and to improve the transport of drugs through the skin. Transethosomes are the attempt to combine the advantages of classical ethosomes with deformable liposomes (Transferosomes) in one formula. Transethosomes are composed of phospholipids, ethanol, penetration enhancer or an edge activator and water. The penetration rate of the skin is increased by ethanol and the drug is delivered into the deeper layers of skin. These transethosomal systems are more efficient in drug delivery when compare to other vesicular systems and these vesicles can be used for transdermal delivery of various classes of drugs; transethosomes are simple to prepare and safe to use. The purpose of

this review is to focus on various aspects of transethosomes including their mechanism of penetration, preparation, composition and characterization.

KEYWORDS: Transethosomes, Transdermal drug delivery, vesicular drug delivery, Ethanol, Phospholipids.

INTRODUCTION

Drug delivery systems (DDS) are used to transport therapeutic drugs in to the body as required to attain the desired therapeutic effects, which are usually designed to improve aqueous solubility of drugs, chemical stability of active agents, increase pharmacological activity, and reduce side effects.[1] A drug's efficacy can be impacted significantly by the way in which it is delivered, Drugs can be introduced into the body by different routes of drug delivery such as buccal drug delivery, nasal drug delivery, ocular drug delivery, oral drug delivery, pulmonary drug delivery, parenteral drug delivery, sublingual drug delivery, vaginal drug delivery, anal drug delivery and transdermal drug delivery.[2]

Transdermal drug delivery system

In the area of drug delivery, innovations are taking place at a much quicker pace. Improved patient compliance and effectiveness are inseparable characteristics of new drug delivery systems. A more radical approach has been to explore newer interfaces on the body for introducing therapeutics one such approach is transdermal drug delivery.[3]

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin which is the largest and most accessible organ of human body through its layers to the circulatory system. TDDS offers many advantages over conventional injection and oral methods.[4]

It comprises list of advantages over conventional routes such as.

- The first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects can be avoided by transdermal delivery.
- Easy to use and non-invasive.
- Drug input can be stopped at any point after removal of the medicament from the site.
- Increases compliance and reduces medical costs.
- Suitable route for unconscious or vomiting patient and best route for paediatrics patients.
- Lesser chances of overdose and easy detection of drug.[5]

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, by the hair follicles and sebaceous glands i.e. collectively called the shunt or appendageal route or directly across the stratum corneum.[6]

The human skin

Human skin, the integument of humans has a valuable role. One of the most important functions is its ability to act as a protective barrier against the ingress of foreign material and the loss of excessive endogenous material such as water. The barrier function of the skin is thus reflected in its multi-layered structure. Each layer is known to represent different levels of cellular or epidermal differentiation.[7]

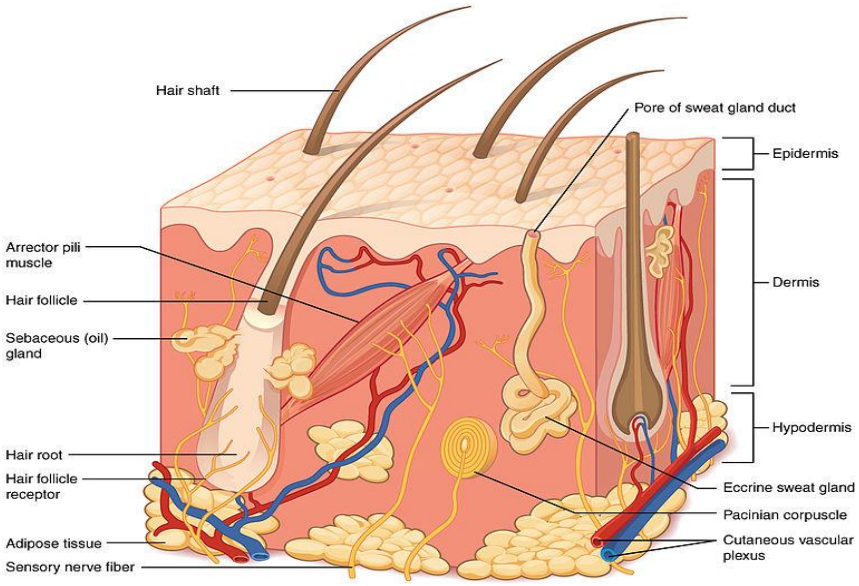

Figure 1: Structure of skin.

Human skin comprises of three distinct but mutually dependent tissues, namely: The stratified, a vascular, cellular epidermis; underlying dermis of connective tissues and; Hypodermis.

Epidermis

The multi-layered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8mm on palms and soles down to 0.06mm on the eyelids. The major area of skin is covered by stratum corneum and the remainder of the epidermis, also called viable epidermis.

Stratum Corneum

This is the outermost layer of skin, also known as horny layer. It is around 10mm thick when dry but swells to several times this thickness when fully hydrated. It accommodates 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. When it comes to the penetration, stratum corneum acts as the principal barrier.

Viable Epidermis

It is located beneath the stratum corneum and differs in thickness from 0.06mm on the eyelids to 0.8mm on the palms. While moving inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basale.

Dermis

Dermis is a 3 to 5mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels and nerves. In the regulation of body temperature continuous blood supply has an essential function. Capillaries reach to within 0.2mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus maintains the dermal concentration of permeate very low and the resulting concentration difference across the epidermis gives the required driving force for transdermal permeation.

Hypodermis

The dermis and epidermis is supported by the hypodermis or subcutaneous fat tissue. It serves as a fat storage area. This layer help out to regulate temperature, provides nutritional support, mechanic protection and it carries principal blood vessels, nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers to reach into systemic circulation.[8]

Transdermal drug delivery has become an alternative to the traditional oral drug delivery route of administration because of numerous benefits in comparison to oral drug delivery. Technological advancements and novel drug delivery systems have led to the successful development of drugs with adequate molecular dimensions or delivery systems for efficient transdermal drug delivery.[9]

From the past years, novel drug delivery systems such as vesicular drug delivery system have been developed to improve physicochemical characteristics of drugs, pharmacokinetic/ pharmacodynamics properties of drugs and transport of drugs through the skin.[10]

Transethosomes

Transethosomes are the lipid based vesicles which includes the basic components of classical ethosomes and an additional compound such as a penetration enhancer or an edge activator (surfactant) in its formula. These are the latest generation of ethosomal systems and were first recorded in 2012 by Song *et al.*

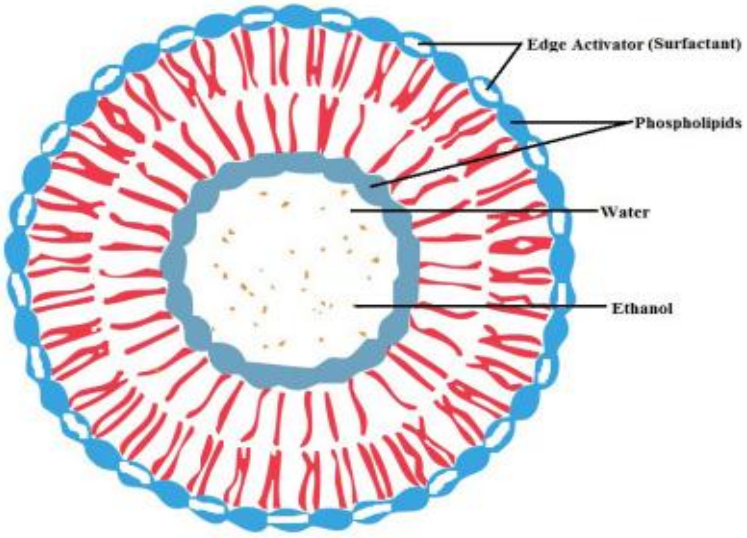

Figure 2: Structure of transethosome.

In an attempt to combine the advantages of classical ethosomes with deformable liposomes (Transferosomes) in one formula, these novel vesicles were formed. Many research scholars have proclaimed superior transethosomal properties over traditional ethosomes. Divergent forms of edge activators and penetration enhancers were investigated for the sake of better characteristic ethosomal systems. According to the reports, drugs of molecular weights of 130.077Da to 200–325kDa can be entrapped with Transethosomes.[11]

In these lipid based vesicles, phospholipids (or non-ionic surfactants) play the role of carrier for delivering drug molecules into the skin. They can easily interact with stratum corneum, improve tissue hydration and merge with lipids of the stratum corneum. They contain a hydrophilic (polar) head as well as hydrophobic (non-polar) tail. Edge activator (biocompatible surfactant) is a bilayer softening agent. It is usually added to improve flexibility and permeability. Alcohol is a primary character of the transethosomal system

which gives an unusual identity to it as a vesicular system. Ethanol deforms the layer of skin and leads to malleability and flexibility of these vesicular systems enabling them to penetrate inside stratum corneum through tiny openings due to fluidization. Water is the important constituent as it helps to form bilayer when phospholipids are added and help in flexibility of system. When ethanol and edge activator are incorporated, it leads to rearrangement of lipid bilayer and it becomes more deformable in such a way that it can penetrate deeper into the dermis.

Advantages of transethosomal drug delivery

- It shows high patient compliance as it is administered in semisolid gel or cream form.
- Contrary to deformable liposomes, transethosomes improve skin delivery of drugs both under occlusive and non-occlusive condition.
- Transethosomal drug delivery can be applied to several fields like veterinary and cosmetic fields.
- The Transethosomal system is passive, non-invasive and is accessible for immediate commercialization.
- Simple method of drug delivery as compared to iontophoresis, laser surgery, cryosurgery and other complicated methods.
- Sustain release and control release can be attainable with transethosomes as a drug can be entrapped into it.

Disadvantages of transethosomal drug delivery

- The molecular size of the drug should be appropriate that it should be absorbed percutaneously.
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and acquire access to the systemic circulation.
- When there is an incomplete formation of vesicles it can lead to coalescence of transethosomes.
- Skin irritation, an allergic reaction and also dermatitis can be seen due to the usage of ethanol in formulation.

Comparison between ethosomes and transethosomes

Table 1: Comparison between ethosomes and transethosomes.

Parameter	Ethosomes	Transethosomes
Composition	1. Phospholipids 2. Ethanol 3. Propylene glycol or other alcohol 4. Charge inducer 5. Water	1. Phospholipids 2. Ethanol 3.Edge activator (surfactant) or penetration enhancer 4. Charge inducer 5. Water
Morphology	Spherical	Regular or irregular spherical shape
Entrapment Efficiency	Higher than classical Ethosomes	Higher than Ethosomes
Skin Permeation	Typically equal to or higher than classical Ethosomes	Higher than Ethosomes
Size	Equal to or smaller than classical Ethosomes	Size based on type and concentration of penetration enhancer or edge activator used
Stability	Stable than classical Ethosomes	Stable than Ethosomes

Mechanism of drug permeation

Major barrier for drug absorption is stratum corneum. Transport of drug through stratum corneum can be carried out by transferring the drug through three pathways namely intracellular, intercellular and follicular pathways. The Transethosomes can cross stratum corneum by following two pathways.

1. Ethanol

When ethanol comes in touch with stratum corneum it disrupts the phospholipids and fluidizes lipid layer which is located in stratum corneum. It increases the intracellular space connecting the corneocytes which in turn increases the permeation and slowly release of the therapeutic agent into skin layers.

2. Edge activator

It generates disruption of intercellular lipids and widens the hydrophilic pores of the skin, through these pores the drug is released gradually. This causes molecular interaction which then increases skin penetration. Many studies recorded that edge activators alone are incapable to penetrate into lower layers of skin.

Fluidity and elasticity of transethosomes is increased due to presence of both ethanol and edge activator. As fluidity of lipid layer increases, there is deduction in its size. Because of

elastic behaviour, the shape can be altered so that it can pass through the narrow regions of intercellular pathway. After passing through stratum corneum, it passes through viable epidermis and reaches the dermis.[12, 13]

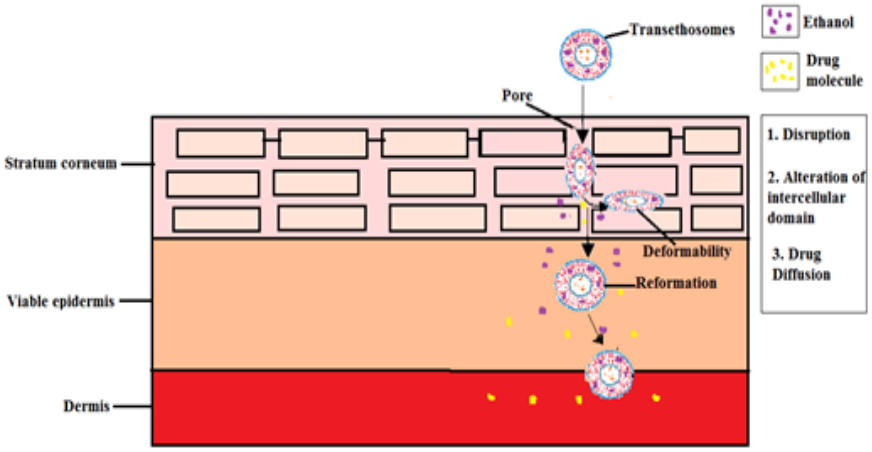

Figure 3: Mechanism of drug permeation of transethosomes.

Method of preparation

The different methods for preparation of transethosomes are as follows.

Preparation by 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. Finally the formulation is kept under refrigeration.

Preparation by 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 and stirring is done 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.[11,14]

Characterization parameters of transethosomes

Morphology of transethosomes[15]

Using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), visual imaging of transethosomes can be done. Vesicles obtained are flexible because of their improper round shape.

Vesicle size and zeta potential[16]

Particle size of the transethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

Entrapment efficiency[15]

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. %EE can be expressed as.

%EE= [Qt–Qs/Qt] ×100

Where, Qt = total theoretical amount of drug added and

Qs = amount of drug found in supernatant

Transition temperature[17]

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

Stability studies[18]

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. It means size is measured by DLS and a structural change is observed by TEM.

Skin permeation determinations[19, 20]

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

***In-vitro* drug release study and drug deposition study**[15]

In-vitro drug release study and drug deposition can be performed by Franz diffusion cell with artificial or biological membrane and Dialysis bag diffusion.

CONCLUSION

The review presented here is an overview on one of the current novel drug delivery system named as vesicular carrier i.e. transethosomes. In the field of transdermal drug delivery, technological advancements and novel drug delivery systems have led to the successful development of drugs with adequate molecular dimensions or delivery systems for efficient drug delivery. Transethosomes are the attempt to combine the advantages of classical ethosomes with deformable liposomes (Transferosomes) in one formula. Transethosomes have been reported to entrap the drugs which have various physicochemical characteristics, i.e. hydrophilic, lipophilic or amphiphilic. Further incorporation of the transethosomal system in a suitable vehicle for dermal or transdermal delivery has some advantages like preventing ethanol evaporation, prolonging contact time with the skin, enhancing the therapeutic efficacy of the entrapped drug, patient compliance, improving stability and shelf life of the final dosage form. Thus transethosomes possess promising future in effective transdermal delivery of drugs.

CONFLICT OF INTEREST: None.

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